# New and Notable

## DNA Capture and Translocation through Nanoscale Pores—a Fine Balance of Electrophoresis and Electroosmosis

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Nanopores are probably the simplest single molecule sensors ever developed, yet they exhibit surprisingly complex behavior. Because virtually all nucleic acids and proteins carry a native electrical charge, an electric field may be used to attract, thread, and translocate biopolymers to and through a simple nanometer-scale hole in a thin membrane or film. When a nanopore is made small enough that its diameter is only slightly larger than an analyte's cross section, the biopolymer must unfold upon entry to the pore and translocate through it in a single-file manner, scanning the full contour length of the molecule as it progresses through the nanopore. During translocation, the biopolymer physically blocks a fraction of the ion current flowing through the pore, permitting straightforward resistive sensing of these analytes.

The ability to discriminate molecular size and charge, and furthermore to detect local variation in these properties along the length of an analyte, has led to a multitude of potential sensing applications, among which nucleic acid sequencing has garnered particular interest (1). Since the first report of nucleic acid sensing using nanopores in 1996 (2), scientists have developed biopolymer sensors capable of detecting nucleic acids employing both membrane-embedded protein pores (i.e., the staphylococcal toxin $\alpha$-hemolysin (1,3) and the mycobacterial porin MspA (4)) as well as synthetically fabricated nanopores crafted in thin inorganic films of silicon compounds (5) or graphene (6–8).

Two challenges are common to all nanopore types and sensing platforms: First, biopolymer capture into the nanopore must be optimized for high detection efficiency. Second, sensing resolution along the length of the analyte must be maximized within the practical bandwidth limitations of instrumentation, which means that slower translocation speeds are highly desirable. Nanomolar double-stranded DNA is typically captured into a small solid-state nanopore at a rate of approximately one event per second at a 300-mV applied bias, for which translocation speeds can exceed tens of base-pairs per microsecond (9). Thus, these two challenges are of particular concern for the development of nanopore DNA sequencing approaches, which seek to sequence far smaller quantities (and hence smaller concentrations) of DNA with single base resolution (1). Moreover, potential solutions must address both challenges simultaneously. Recent experimental reports have shown that the application of a salt gradient across a nanopore fabricated in a thin film of silicon nitride both enhances the capture rate of DNA molecules into the pore and reduces their translocation speed by more than an order of magnitude. The effects of these two seemingly contradictory observations were found to increase with the magnitude of salt gradient and appear to be determined by a fine balance between the electrophoretic and electroosmotic forces in the vicinity of or inside the nanopore (9). However, until now no unified theory had been described to quantitatively account for both DNA capture rate and translocation speed, specifically in the case where the electroosmotic flow in the nanopore opposes the translocation direction (10–12).

In this issue of *Biophysical Journal*, He et al. (13) describe a numerical simulation study of DNA capture and translocation processes in nanopores. They find that a salt gradient applied to the system with higher concentration on the *trans* side of the membrane (by convention, DNA molecules translocate from the *cis* to the *trans* side) induces the accumulation of positive net charge near the entrance to the nanopore, which enhances capture of the negatively charged DNA. Interestingly, the same positive charge also induces cationic electroosmotic flow through the nanopore, which moves in opposition to the DNA, retarding the motion of the anionic DNA. These competing effects dominate in different regimes: During the initial trapping stage, electrophoretic forces overwhelm the electroosmotic flow that might otherwise keep DNA from entering the pore. Consequently, DNA capture is enhanced by the presence of the accumulated positive charge at the mouth of the pore. Upon DNA threading, the electroosmotic forces effectively counter the electrophoretic driving force, resulting in retardation of DNA translocation speed. The numerical simulations further predict that as the magnitude of the salt gradient increases, the retardation factor (a ratio of DNA translocation time with and without salt gradient) exceeds 30-fold, and could be further increased by applying even larger salt gradients.

This theoretical description not only quantitatively agrees with the original experimental observations, but may even suggest that salt gradients are a more powerful means of controlling translocation speed than previously thought. One implication of their proposed mechanism is that the application of a salt gradient to a nanopore system might be orthogonal to—and therefore applicable in combination with—other techniques for slowing DNA translocation through a

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nanopore, such as altering the buffer, changing pore geometry and charge, or chemically coating the nanopore. This work also imposes theoretical limitations on the degree to which salt gradients alone can influence DNA translocation speed, and establishes that the effects on capture rate cannot be decoupled from the change in translocation speed, nor would they be easily tunable or switchable in real-time. But with this new description of a potential mechanism for salt gradient-enhanced capture and translocation retardation in nanopores, He et al. (13) have provided the nanopore community with a framework for future experimental and theoretical exploration.

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