A MESOSCALE MODEL FOR MOLECULAR INTERACTION IN FUNCTIONALIZED NANOPORES

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ABSTRACT
Nanopores have been used to detect DNA translocation and gene detection. However, the interaction between DNA and nanopore is still not well understood due to the small size of DNA/nanopore and dynamic translocation process. Very recently, various chemical modifications have been applied on nanopore surface for improved signal yield and selective detection. Thus, it is important to characterize the interaction between DNA and chemically modified nanopores. This paper intends to develop an understanding of the interaction between DNA and chemically modified nanopore surface and the translocation process of DNA by probing the DNA-nanopore interaction mechanisms through computational modeling. The DNA-nanopore interaction will be explored through a model that links atomistic DNA-nanopore interaction to meso-scale particle dynamics. Critical interrelationships between physical properties of the nanopore (surface properties, sizes, roughness etc.), electric field strength, and translocation kinetics will be established. This research not only advances the molecular-level understanding of the DNA-nanopore interface, but would also help design lab-on-chip devices for molecule based diagnosis.

INTRODUCTION
Microfabrication technology nowadays has made possible bio-/chemical analysis of very minute samples through micro- and nanofluidic devices. The rapid stretching and sequencing of single DNA molecules in nanopores is of practical importance in genetic detection, analysis and discovery. The dynamics of DNA in nanopores has become a crucial topic toward the development of lab-on-chip devices for biomolecular analysis. However, the interaction between DNA and nanopore is still not well understood due to the small size of DNA/nanopore and dynamic translocation process. Studies on electrophoretic transportation of DNA in nanochannels [1] have revealed significant contribution of DNA-channel surface interaction, which leads to a diffusion rate much lower than that predicted by traditional diffusion theory. Moreover, various chemical modifications are applied on nanopore surface for improved signal yield [2-5]. In particular, solid-state nanopore channels with DNA selectivity have been reported recently where the nanopore channel was coated with hairpins [6]. This coating made the nanopores selective towards single strand DNA (ssDNA). Such functionalized nanopores were shown to selectively transport short lengths of 'target' ssDNA that were complementary to the probe. Even a single base mismatch between the probe and the target resulted in longer translocation pulses and a significantly reduced...
number of translocation events. Coating nanopores with DNA or other organic molecules like silanes can make these more biologically friendly. Such coatings can change the surface charges, hydrophobicity of the nanopore channels, and provide chemical functionality. Such functionalization schemes are expected to be used for a variety of ligand-receptor combinations of significant importance, and the solid-state functionalized nanopore can serve as next generation of sequencing tools, whereas a pore functionalized with specific probe can indicate the presence of target biomolecules up to single nucleotide mismatch sensitivity. Thus, it is important to characterize the interaction between DNA and chemically modified nanopores. In this paper, we develop a meso-scale model of DNA translocation through hairpin loop coated nanopore with DNA selectivity. This work may not only advance the molecular-level understanding of the DNA-nanopore interface, but also help design lab-on-chip devices for molecular transportation and diagnosis.

METHOD

A meso-scale model of the DNA translocation through hairpin-functionalized nanopore is developed. A ss-DNA is transported through nanopore by electrophoresis. A perfect complementary (PC) ss-DNA hybridizes with matching hairpin-loop (HPL) DNA sequentially, which facilitates the translocation process. Under optimal conditions in solution, the HPL-DNA has been shown to demonstrate an all-or-none selectivity down to single-base mismatch sensitivity between perfect complementary (PC) and mismatched (MM) targets. The ssDNA-hairpin hybridization kinetics is modeled as a reaction process. Before hybridization occurs in the interaction region, ssDNA and hairpin have a free energy $G_0$. Hybridization results in a lower energy state (hybridized free energy $G_2$). The free energy difference between the two states $\Delta G$ largely influences the DNA translocation speed in functionalized nanopore.

Figure. 2. Model of DNA translocation in hairpin modified nanopore. Each hairpin site is modeled as a potential well.

To model the sequential translocation of DNA through nanopores coated with HPL-DNA, each hairpin is modeled as an independent potential well. The depth of the well is equal to the interaction potential energy between the HPL and DNA. For a mismatched DNA, the potential well is a constant. However, a perfectly matched DNA hybridizes with HPL-DNA and lowers the potential well depth by hybridization energy $\Delta k$. The hybridization process is modeled as a reaction process with association rate $k_a$, thus the potential well depth drops when DNA enters interaction regions:

$$k = \begin{cases} (k_0 - \Delta k) \exp(-k_a \Delta t) + \Delta k, & \text{if } 0 < x < \lambda/2 \\ k_0, & \text{otherwise} \end{cases}$$

The coated nanopore surface is modeled as a series of functional sites with spacing $\lambda$. The potential above the functional sites can be written as a Fourier series, which we truncate after the first two terms, yielding $\varphi = k(1 - \cos 2\pi x / \lambda)$. The momentum transfer from the surrounding fluids and nanopore are modeled as a friction term with friction coefficient $\eta$. From the potentials, friction terms, and the electric force terms, the equation of motion for the DNA can be written as:

$$m\ddot{x} = -k \sin(2\pi x / \lambda) + Eq - \eta \dot{x} + f^B,$$  \hspace{1cm} (2)

Where $f^B$ is a Gaussian random noise term. We solve (2) numerically through the Verlet algorithm to find the position of the DNA as a function of time.
RESULTS

As a first attempt, we neglect the random noise term and assume that there are four hairpin sites within the nanopore. Our preliminary results illustrate the influence of hybridization time, electric field strength, and DNA matching property on DNA translocation kinetics. Fig. 2 shows a DNA translocation distance time history and translocation speed at different DNA hybridization rates $k_h$ (which can be determined from MD simulation in the future work). Each periodic pattern represents that the DNA passed through a HPL-DNA site. The translocation speed increases as $k_h$ increases, which indicates that fast hybridization with larger $k_h$ accelerates the translocation process.

For a mismatched DNA, due to the all-or-none selectivity of HPL-DNA, the potential well depth remains constant during translocation. Under such circumstance, the HPL-DNA coated nanopore behaves like a bare nanopore with a blocking or passing property. Under low electric field, DNA is totally blocked. Fig. 3 shows the distance over time profiles for MM-DNA translocation under different potential well depths $k$.

The translocation kinetics also largely depends on the applied external electric field. At normal electric field, the electric force itself is not enough to drive DNA through, thus, DNA needs to hybridize with HPL-DNA and translocate through each HPL-DNA sites in sequence, as shown in Fig. 2. However, when the electric field is strong enough, DNA can directly pass through the nanopore without interacting with HPL-DNA. The electric strength dependent translocation kinetics will be explored in our future work.

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REFERENCE