Modeling DNA Translocation Kinetics in Nanopores with Selectivity

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ABSTRACT

The development in nanotechnology has made fabrication of solid-state nanopores with 20nm diameter possible. These nanopores have found a variety of applications, with the foremost one being sensing of the biological molecules. To achieve molecular sensing, a major requirement of these solid-state nanopores is molecular selectivity. This paper focuses on modeling the DNA translocation in functionalized nanopore with application on gene sequencing.

INTRODUCTION

As a DNA is translocating through a nanopore, free ion flux inside the nanopore is blocked, causing a dip in the electric current measured. The duration of dip in current is proportional to the time the DNA remains inside the pore, ideally proportional to the DNA length. Process to impart selectivity to these nanopores has been demonstrated by Iqbal et. al.\(^1\) by coating a nanopore with hairpin loop DNAs (HPL, see figure 1c) thereby making it a functionalized nanopore as shown in figure 1a.

![Figure 1](image)

Figure1.(a) Schematic of the bio-functionalized system (First appeared in Iqbal et. al.\(^1\)) (b) Schematic to show selectivity achieved due to the difference in duration of translocation times measured using the dip in ionic current of matched and mismatched DNA. (c) HPL DNA structure.

The molecular selectivity of the nanopore lies on the fact that tethered HPL opens up and hybridizes with a perfectly matched translocating DNA and facilitates its translocation. While even for a single base mismatch, the HPL won't open and thus increase the translocation time of the mismatch DNA as shown in figure 1b. DNA translocation kinetics in bare nanopores has been studied with molecular dynamics simulations in our previous work\(^2\). However, the dynamics of such translocation process in a functionalized nanopore is still not clear. The focus of our research work is to characterize the DNA translocation in the functionalized nanopores using Coarse-Grained Molecular Dynamics (CGMD) simulation.

METHOD

The timescale step for full atomistic scale molecular dynamics simulation is usually fs. The time required for the simulation scales with the number of atoms in the system, making the simulation of a large system such as surface-coated nanopore computational challenging. To eliminate this limitation, a coarse grain model of bio-functionalized nanopore-DNA system with stochastic dynamics is used for this study. The simulations are run in Gromacs and visualized using VMD (Visual Molecular Dynamics).

![Figure 2](image)

Figure2: Study of atomistic model interaction to get the Lennard-Jones potential for the coarse-grained DNA-nanopore interaction.

A two-site coarse-grained DNA model is built where a nucleotide of DNA is represented using two atoms: one for backbone and one for base atoms\(^3\). The coordinates of coarse-grained atoms are built using MATLAB. The Lennard-Jones potentials for the coarse-grained DNA and nanopore interaction are determined by characterizing the interaction between the full-atomistic nucleotide and the pore as shown in figure 2.

RESULTS

To understand the effect of bio-functionalization on the nanopore, the following parameters are analyzed: the type of coating, density of the coating, applied bias voltage, and the
effective pore diameter. Since the coatings possess a charge of their own, they reorient themselves under the applied bias voltage and lead to an effective pore diameter (epd) instead of the original bare pore diameter.

The types of coatings considered are HPL and single strand DNA (ssDNA). The result in figure 3 indicates the different effective pore diameters obtained for the respective coatings under various electric field strengths. The HPL coatings are more rigid compared to the ssDNA, thereby the effective pore diameter obtained by the HPL coating are lesser than that for the ssDNA. The result also indicates that when HPLs open into ssDNAs, the effective pore diameter increases, thus eases the translocation of the matched DNA. While for even a single base mismatch, the HPL maintains in loop form, thus the effective pore diameter is comparatively lesser, causing it to take longer time to translate through the bio-functionalized nanopore.

Density of the coatings is another essential parameter to determine the effective pore diameter. Two configurations are considered for both the HPL and ssDNA coatings: four and eight coating molecules in one circumferential layer respectively, as shown in figure 4a and figure 4b. In addition, the ssDNA coatings will be modulated in axial direction of the pore with a distance of 1nm or 2nm as shown in figure 4c and figure 4d.

Our future work is to understand the effect of the bias voltage applied and the effective pore diameter on the DNA translocation process. As shown in figure 5, a ssDNA translocates through a four layers ssDNA coated bio-functionalized nanopore with an effective pore diameter of 1nm and an electric bias of 0.1V/nm.

REFERENCES