A mesoscale model of DNA interaction with functionalized nanopore

Yaling Liu and Samir M. Iqbal

Citation: *Appl. Phys. Lett.* **95**, 223701 (2009); doi: 10.1063/1.3240400

View online: <http://dx.doi.org/10.1063/1.3240400>

View Table of Contents: <http://apl.aip.org/resource/1/APPLAB/v95/i22>

Published by the American Institute of Physics.

Related Articles

Nanoscale structure of protamine/DNA complexes for gene delivery

Appl. Phys. Lett. **102**, 053703 (2013)

Perspective: Nanomotors without moving parts that propel themselves in solution

J. Chem. Phys. **138**, 020901 (2013)

Micro-/nanofluidics based cell electroporation

Biomicrofluidics **7**, 011301 (2013)

Amplified spontaneous emission of Rhodamine 6G embedded in pure deoxyribonucleic acid

Appl. Phys. Lett. **101**, 171113 (2012)

Single particle demultiplexer based on domain wall conduits

Appl. Phys. Lett. **101**, 142405 (2012)

Additional information on Appl. Phys. Lett.

Journal Homepage: <http://apl.aip.org/>

Journal Information: http://apl.aip.org/about/about_the_journal

Top downloads: http://apl.aip.org/features/most_downloaded

Information for Authors: <http://apl.aip.org/authors>

ADVERTISEMENT

AIP | Applied Physics
Letters

**EXPLORE WHAT'S
NEW IN APL**

SUBMIT YOUR PAPER NOW!

**SURFACES AND
INTERFACES**

Focusing on physical, chemical, biological, structural, optical, magnetic and electrical properties of surfaces and interfaces, and more...

**ENERGY CONVERSION
AND STORAGE**

Focusing on all aspects of static and dynamic energy conversion, energy storage, photovoltaics, solar fuels, batteries, capacitors, thermoelectrics, and more...

A mesoscale model of DNA interaction with functionalized nanopore

Yaling Liu^{1,2,a)} and Samir M. Iqbal^{2,3,4}

¹Department of Mechanical and Aerospace Engineering, The University of Texas at Arlington, Arlington, Texas 76019, USA

²Joint Graduate Committee of Biomedical Engineering Program, University of Texas at Arlington and University of Texas Southwestern Medical Center at Dallas, Arlington, Texas 76019, USA

³Department of Electrical Engineering, University of Texas at Arlington, Arlington, Texas 76019, USA

⁴Nanotechnology Research and Teaching Facility, University of Texas at Arlington, Arlington, Texas 76019, USA

(Received 15 March 2009; accepted 28 August 2009; published online 30 November 2009)

Functionalized nanopores have been used recently for the detection of specific DNA. The interactions between the DNA and the nanopore are not well understood due to the small size of DNA/nanopore and dynamic translocation process. Various chemical modifications have also been applied on nanopore surfaces for improved signal yield and selective detection. This paper develops an understanding of the interactions between translocating DNA and chemically modified nanopore surfaces. An energy-based mesoscale computational model is used to elucidate critical interrelationships between physical properties of the nanopore, electric field strength, and translocation kinetics. We report a nonlinear increase in DNA translocation speed with increasing electric field strength. The model predicts a transition in translocation from hybridization-driven to electric field-driven, in agreement with experimental data. This work advances the molecule-level understanding of the DNA-nanopore interface, and can help in designing optimized lab-on-chip devices for molecule based diagnosis. © 2009 American Institute of Physics.

[doi:10.1063/1.3240400]

Microfabrication technology has made possible biological/chemical analysis of various molecular 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 an important topic for biomolecular analysis. However, the interactions between DNA and nanopore are not well understood due to the small size of DNA/nanopore and dynamic translocation process. Studies on electrophoretic transport of DNA in nanochannels¹ have revealed significant contributions from DNA-channel surface interactions, which lead 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 Coating nanopores with organic molecules such as silanes can change the surface charges, hydrophobicity of the nanopore channels, provide chemical functionality, and make the surface biologically friendly. In particular, solid-state nanopore channels with DNA selectivity have been reported recently where the nanopore channel was coated with hairpin DNA molecules.⁶ Such functionalized nanopores were shown to selectively transport short lengths of “target” single stranded DNA (ssDNA) that were complementary to the probe. Even a single base mismatch between the probe and the target resulted in longer translocation time and a significantly reduced number of translocation events. Such functionalization schemes are expected to be used for a variety of ligand-receptor combinations, and the solid-state functionalized nanopores can serve as next generation of sequencing tools.

It is thus important to characterize the interaction between DNA and chemically modified nanopores. In this paper, we develop a mesoscale model of DNA translocation through hairpin-loop (HPL) coated nanopore with DNA selectivity. Similar modeling approach can be extended to describe other types of biomolecule-functionalized nanochannel interactions.

A schematic of DNA translocation through HPL-functionalized nanopore is illustrated in Fig. 1. The basic idea of the translocation experiment lies in the fact that DNA molecules are highly charged. Under an applied electric field, a DNA molecule can be driven through the nanopore in a linear head-to-tail fashion. This movement, called translocation, is seen as a pulse as DNA mechanically blocks/replaces certain volume of ionic species. A perfect complementary (PC) ssDNA hybridizes with matching HPL-DNA sequen-

FIG. 1. (Color online) (a) Schematic of a functionalized nanopore. The chemical modification reduced the nanopore diameter. (b) Molecular structure of an HPL-DNA. (c) Schematic depicting current trace trends for PC (blue/left) and MM (red/right) DNA data, shown side by side for clarity. Reprinted by permission from Macmillan Publishers Ltd: Nature Nanotechnology, (Ref. 6) copyright (2007).

^{a)}Author to whom correspondence should be addressed. Electronic mail: yaling.liu@uta.edu. Tel.: +1-817-272-1256. FAX: +1-817-272-5010.

FIG. 2. (Color online) Model of DNA translocation in hairpin modified nanopore. (a) Each hairpin site is modeled as a potential well; (b) Hybridization leads to localized reduction of energy barrier.

tially, 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 PC and mismatched (MM) targets. Statistical analysis of the pulses yields trends that are used to sort the DNA. 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_h). The free energy difference between the two states ΔG largely influences the DNA translocation speed in functionalized nanopore. The free energy contributions ΔG for a duplex with mismatches are well-documented in literature. For example, a MM $G \cdot T$ base interaction with a 20 bases HPL (as the whole loop and stem form the duplex) under 0.1M KCl leads to $\Delta G_{MM} = 0.93$ kcal/mol.^{6,7} The positive contribution to ΔG_{MM} from the MM $G \cdot T$ pairing means, to a first order approximation, that immobilized HPL-DNA provides a repulsive potential to the MM-DNA target that tries to interact with it. For a PC-DNA under the same condition, $\Delta G_{PC} = -0.6$ kcal/mol. The negative contribution to ΔG lowers the energy state, thus facilitates target DNA travel.

To model the sequential translocation of DNA through nanopores coated with HPL-DNA, each hairpin is modeled as an independent potential well (Fig. 2). The depth of the MM well is equal to $k_0 = \Delta G_{MM}$. For a MM-DNA, the potential well is a constant. However, a perfectly matched DNA hybridizes with HPL-DNA and lowers the potential well depth by $\Delta k = \Delta G_{MM} - \Delta G_{PC} = 1.53$ kcal/mol.⁶ The hybridization process is thus modeled as a reaction process with association rate k_h , with the potential well depth dropping when a PC-DNA enters interaction regions:

$$k = \begin{cases} (\Delta k) \exp(-k_h \Delta t) + (k_0 - \Delta k), & \text{if } i\lambda/2 < x < (i+1)\lambda/2, \\ k_0, & \text{otherwise,} \end{cases} \quad (1)$$

where x is the distance DNA travels inside a nanopore and Δt is the time duration that the DNA interacts with an HPL site.

The coated nanopore surface is modeled as a series of functional sites with spacing λ . The potential φ above the functional sites can be written as a Fourier series, which after truncating the first two terms, yields $\varphi = k(1 - \cos 2\pi x/\lambda)$. The electrostatic force applied on the DNA is Eq , with q being the total effective charge on the DNA. The momentum transfer from the surrounding fluids and nanopore are modeled as a friction term with friction coefficient ξ . The equation of motion for the DNA can be written based on the HPL potentials, a friction term, an electrostatic term, and a Brownian term as:

FIG. 3. PC-DNA translocating speeds at different k_h . Inset shows PC-DNA translocation time history at different hybridization rates k_h .

$$m\ddot{x} = -k \frac{2\pi}{\lambda} \sin\left(\frac{2\pi}{\lambda}x\right) + Eq - \xi\dot{x} + F_B, \quad (2)$$

where the last term is a Brownian term coming from the fluid and wall.

Since the DNA is translocating in a narrowly confined nanopore, which is an over-damped system, Eq. (2) can be simplified as

$$\dot{x} = -k \frac{2\pi}{\lambda} \sin\left(\frac{2\pi}{\lambda}x\right) / \xi + Eq / \xi + \sqrt{2k_B T / \delta t} \xi R. \quad (3)$$

Theoretically, DNA is a charged polyelectrolyte with $2e^-$ charge per base. However, each base would have maximum 66% of its charge shielded with counter-ion condensation.⁸ To match with experimental configuration,⁶ we assume a 15 base ssDNA with 50% of net charge. The electric fields considered range between 50 and 300 mV, which are applied on a nanopore of 40 nm in length. The friction coefficient is estimated to be 2.7×10^{-8} N s/m. A time step of 0.005 ms is used in the simulations. The HPL density is assumed to be $10^{12}/\text{cm}^2$,⁹ thus $\lambda \approx 10$ nm and four HPL sites along the nanopore length are considered. To better reveal the characteristics of the translocation process, we neglect the random noise term and solve Eq. (3) numerically. The influences of hybridization time, electric field strength, and DNA matching property on DNA translocation kinetics are depicted in subsequent figures.

Figure 3 shows the DNA translocation distance time history and translocation speed at different DNA hybridization rates k_h under a 200 mV field. Each periodic pattern represents the DNA passage through an HPL site. The translocation speed increase as k_h increases, which indicates that faster hybridization accelerates the translocation process. However, when the hybridization is fast enough, the translocation speed reaches a plateau and the translocation speed is independent of the HPL potentials. The inset of Fig. 3 shows the translocation time history, which clearly shows faster translocation process with higher hybridization rate. According to Ref. 10 DNA hybridization rate is ~ 10 s⁻¹ for diffusion limited 16 base ssDNA. For ssDNA confined in nanopore, a higher hybridization rate of 50 s⁻¹ is chosen for all cases later.

The translocation kinetics also largely depends on the applied external electric field strength. At low electric field, the electric force itself is not enough to drive a PC-DNA

FIG. 4. PC-DNA translocation through a nanopore at increasing electric field strength. The translocation speed is a function of electric field strength. The circles are simulation predictions and the stars are empirical data from Ref. 6. The inset shows distance time history.

through and the DNA needs to hybridize with HPL in order to pass each HPL site, as shown in Fig. 4. However, when the electric field is strong enough, a DNA can directly pass through the nanopore without interacting with HPL. Accordingly, the translocation speed shows two linear regimes, indicating a change in dominant translocation mechanism from hybridization-dominant to be electrical force-dominant. The simulated translocation speeds are compared with empirical data from Ref. 6 which shows good consistency despite the complex factors such as temperature and pH that might have influenced experimental results. Only two voltages (100 and 200 mV) were reported in the selective DNA transport experiments. The larger translocation speed at higher E -field strength, in our simulations, is also consistent with the experimental data of Ref. 6. It does show a nonlinear increase of translocation time with E -field strength increase. The simulated mean free passage time ratio $\tau_{100 \text{ mV}} / \tau_{200 \text{ mV}} = 3.06$ agrees with the experimental measurements with $\tau_{100 \text{ mV}} / \tau_{200 \text{ mV}} = 3.56$.

For a MM-DNA, due to the all-or-none selectivity of HPL-DNA, the potential well depth remains constant during translocation. Under such circumstances, the HPL coated nanopore behaves like a bare nanopore with a blocking or passing property. The resulting translocation speeds at different E -field strengths are plotted in Fig. 5. The predicted translocation speeds agree well with empirical data at high E -field of 200 mV (inset to Fig. 5), but have significant difference at low E -field of 100 mV. This indicates that interactions other than hybridization and electrical force dominate translocation at the low voltage regimes.

Comparing Figs. 4 and 5, it should be noted that a particular range of E -field exists for best signal distinction between PC-DNA and MM-DNA. At very low E -field, though the translocation speed of PC-DNA is much larger than MM-DNA, the signal strength would be weak. At very high E -field, there would be no significant speed difference. The upper limit of applied E -field is determined by the ratio $\beta = Eq / (k_0 2\pi / \lambda)$. If $\beta \gg 1$, even MM-DNA can easily pass through HPL sites which leads to small translocation velocity

FIG. 5. MM-DNA is blocked in nanopore under low E -field while a direct pass through happens at high E -field. The dots are simulation predictions and the stars are empirical data from Ref. 6.

difference between MM-DNA and PC-DNA. The critical condition $\beta = 1$ corresponds to an applied E -field of 5 mV/nm. Ideally, a voltage range between 2.5 and 5 mV/nm should be applied to achieve a strong and distinctive signal for PC-DNA and MM-DNA.

In summary, we have developed an energy-based mesoscale model for DNA translocation in a functionalized nanopore. The model predicts a nonlinear relationship between PC-DNA translocation speed and electric field strengths, which is consistent with experimental observations. For MM-DNA, a blocking or direct-pass behavior is observed, which is determined by critical electric field strength. Such mesoscale model can serve as a predictive tool for determining optimized operational parameters such as electric field strength, nanopore size, surface properties etc., for DNA-nanopore devices.

This work was supported in part by University of Texas at Arlington Research Enhancement Program (to Y. L. and S. M. I.), the Oak Ridge Associated Universities (Ralph E. Powe Award to Y. L.), the National Science Foundation Tera-Grid resources (Startup allocation to Y.L.), and a grant by the Metroplex Research Consortium for Electronic Devices and Materials, Dallas, Texas (to S. M. I.). The authors thank Diane Manry from The Oakridge School, Arlington, Texas for the cover artwork. The authors contributed equally to this work.

¹J. D. Cross, E. A. Strychalski, and H. G. Craighead, *J. Appl. Phys.* **102**, 024701 (2007).

²A. J. Han and Y. Qiao, *Langmuir* **23**, 11396 (2007).

³Y. R. Kim, J. Min, I. H. Lee, S. Kim, A. G. Kim, K. Kim, K. Namkoong, and C. Ko, *Biosens. Bioelectron.* **22**, 2926 (2006).

⁴O. Schepelina and I. Zharov, *Langmuir* **22**, 10523 (2006).

⁵G. L. Wang, B. Zhang, J. R. Waymunt, J. M. Harris, and H. S. White, *J. Am. Chem. Soc.* **128**, 7679 (2006).

⁶S. M. Iqbal, D. Akin, and R. Bashir, *Nat. Nanotechnol.* **2**, 243 (2007).

⁷H. T. Allawi and J. SantaLucia, *Biochemistry* **36**, 10581 (1997).

⁸H. Chang, B. M. Venkatesan, S. M. Iqbal, G. Andreadakis, F. Kosari, G. Vasmatzis, D. Peroulis, and R. Bashir, *Biomed. Microdevices* **8**, 263 (2006).

⁹H. Du, C. M. Strohsahl, J. Camera, B. L. Miller, and T. D. Krauss, *J. Am. Chem. Soc.* **127**, 7932 (2005).

¹⁰P. V. Riccelli, F. Merante, K. T. Leung, S. Bortolin, R. L. Zastawny, R. Janeczko, and A. S. Benight, *Nucleic Acids Res.* **29**, 996 (2001).