Some aspects of a two-pore translocation problem

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Abstract. We report Brownian dynamics (BD) simulation results for a coarse-grained (CG) model semi-flexible polymer threading through two nanopores. Particularly we study a “tug-of-war” situation where equal and opposite forces are applied on each pore to avoid folds for the polymer segment in between the pores. We calculate mean first passage times (MFPT) through the left and the right pores and show how the MFPT decays as a function of the off-set voltage between the pores. We present results for several bias voltages and chain stiffness. Our BD simulation results validate recent experimental results and offer avenues to further explore various aspects of multi-pore translocation problem using BD simulation strategies which we believe will provide insights to design new experiments.

1. Introduction
In a series of experiments [1]-[4] where single-stranded DNA (ss-DNA) were allowed to translocate through an α-hemolysin protein pore by applying a voltage across the pore, it was observed that the histogram of the mean first passage time (MFPT) are very different for different ss-DNA. This lead to the idea that characteristics of translocation through a nano-pore can be used for DNA sequencing. Since then polymer translocation (PT) problem [5] has remained an active field for both fundamental and experimental research. The original aim and scope of rapid and cheap sequencing of human genome without amplification has broadened to analyze other important biopolymers. Technological advancement made it possible to prepare synthetic nano-pores including single layer of graphene nanopores, where the pore diameter and width can be controlled. One of the hallmarks of PT problem is the theoretical and simulation studies of the first passage time problem [5] where ordinary and partial Fokker-Planck equations are used [8, 9] to predict the translocation exponent α for a polymer chain of length $N$ characterized by $\langle \tau \rangle = AN^\alpha$, originally proposed by Kantor and Kardar [10]. For the driven translocation problem the tension propagation (TP) theory of Sakaue [11] captured the nonequilibrium aspects of the translocation manifested in cis-trans asymmetry [12, 13, 14]. Sakaue’s TP theory was subsequently translated into a Brownian dynamics tension propagation (BDTP) scheme [15, 16] and it was possible to carry out simulation of very large polymer chains which validated the scaling theory of driven polymer translocation [17]. It was shown that the finite chain length effects are strong, and it is only in the very large chain limit one observes the asymptotic Kantor-Kardar limit, namely, $\langle \tau \rangle = AN^{1+\nu}$, where $\nu$ is the Flory exponent [18].

While single-pore translocation paved the way to do new science with nano-pores and nano-channels, recently it has been realized that instead of a single pore, a ssDNA co-captured in a multiple-nano-pore system with automatic feed-back loop to monitor the speed will provide better control on the polymer segments in between the successive nano-pores [18]. It has been
recently reported that by applying an equal and opposite bias at the left and right pores of a two-pore system to create a “tug-of-war” situation one can reduce the diffusion of the chain segment and reduce the probability of occurrence of folds which hinders the analyses of the segment [18].

To design such an experiment, where a DNA segment is co-captured in two pores, is a significant challenge. Furthermore, direct observation of physical quantities become very limited due to resolution issues making “seeing” in nano-meter length scales extremely hard. Recently we demonstrated that BD simulation of CG models can provide detail picture of evolution of polymer conformations inside nanochannels [20] which are of considerable help to experimentalists to understand their data with reference to a specific model. In this paper we demonstrate that BD simulation results on a CG model mimicking the two-pore experiment qualitatively captures the experimental results. In the next two sections we briefly describe the model and present preliminary results. We then conclude with a few remark about future work on two-nano-pore systems.

2. The Two-NanoPore Model and BD simulation
We have implemented BD simulation scheme in two dimensions (2D) whose schematics are shown in Fig. 1 for a chain of length \( N = 16 \) although the simulation is carried out for the chain length \( N = 64 \). We start with the situation where the polymer segment is co-captured in both the pores. The origin of the coordinate system is chosen at the symmetric location equidistant from the two pores. Initially a straight polymer chain is placed symmetrically with respect to the origin so that the equal straight segments lie at the left of the left pore and right of the right pore. In this paper we kept the distance between the pores \( N_0 = 20 \) the same, so that at \( t = 0 \) the beads with indices 23 and 42 are located inside the right and the left pore, beads with indices 1-22 and 43-64 are located at the left and right side of the left and right pore respectively. The beads with indices 24-41 are inside the two pores. The initial straight chain is then equilibrated with BD simulation time about 5 times the Rouse relaxation time \( \tau_{eq} \propto N^{1+2\nu} \) keeping the beads located inside each pore clamped. To model the polymer chain, the immobile
wall which contains the nanopore, we have used Lennard-Jones (LJ) and anharmonic spring potentials, and a three body bond-bending potential as in Eqns. 1-3, described in detail in our recent publication [20]. The excluded volume interaction between any two monomers is given by a short range Lennard-Jones (LJ) potential.

\[ U_{\text{LJ}}(r) = 4\varepsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^{6} \right] + \varepsilon, \quad \text{for} \quad r \leq 2^{1/6}\sigma; \]

\[ = 0, \quad \text{for} \quad r > 2^{1/6}\sigma \]

(1)

Here, \( \sigma \) is the effective diameter of a monomer, and \( \varepsilon \) is the strength of the potential. The connectivity between neighboring monomers is modeled as a Finite Extension Nonlinear Elastic (FENE) spring with

\[ U_{\text{FENE}}(r) = -\frac{1}{2}kR_{0}^{2}\ln \left( 1 - r^{2}/R_{0}^{2} \right) \]

(2)

where \( r \) is the distance between the consecutive monomers, \( k \) is the spring constant and \( R_{0} \) is the maximum allowed separation between connected monomers. The chain stiffness is introduced by adding an angle dependent three body interaction term between successive bonds as

\[ U_{\text{bend}}(\theta_{i}) = \kappa(1 - \cos \theta_{i}) \]

(3)

Here \( \theta_{i} \) is the angle between the bond vectors \( \vec{b}_{i-1} = \vec{r}_{i} - \vec{r}_{i-1} \) and \( \vec{b}_{i} = \vec{r}_{i+1} - \vec{r}_{i} \), respectively. The parameter \( \kappa = k_{B}T\ell_{p} \), where \( \ell_{p} \) is the persistence length of the chain, \( k_{B} \) and \( T \) are the Boltzmann constant and the temperature respectively. The values of the parameters and the BD scheme are the same as described in [20].

After the polymer chain is equilibrated with beads inside the left and right pores at clamped position, the chain is allowed to translocate with biases applied at the left and the right pores as shown in Fig. 1. We consider both the cases \(-f_{L} = f_{R} \) and \(|f_{L}| - |f_{R}| \neq 0 \). The simulation results are averaged over 1000 initial conditions. We have checked in few cases that a choice of initial configuration of the chain as an off-lattice self-avoiding random walk does not affect the final results.

3. Results

We show BD simulation results for a chain length of \( N = 64 \) for several biases and chain persistence length, and make comparison with the experimental results reported by Reisner and coworkers [18]. First we show the plot of \( \langle \tau_{R} \rangle \) versus \( \langle \tau_{L} \rangle \) in a “tug-of-war” in Fig. 2. The graph shows that most of the points lie on the straight line \( \langle \tau_{R} \rangle = \langle \tau_{L} \rangle \). The same behavior has been observed by Reisner and coworkers. However, there are scattered points above the line \( \langle \tau_{R} \rangle = \langle \tau_{L} \rangle \). These points correspond to those events where the chain spends different time in between the pores after finishing translocation through the left pore, and before the final exit through the right pore. We have shown results for two different “tug-of-war” situation; (i) \(-f_{L} = f_{R} = 1.0 \) corresponds to the low bias case when \(|f_{L}|\sigma = |f_{R}|\sigma \simeq k_{B}T \) and (ii) the other for higher bias \(|f_{L}|\sigma = |f_{R}|\sigma \simeq 5k_{B}T \). In the former case the MFPT is longer resulting the distribution of points to be qualitatively different than the case for \(|f_{L}|\sigma = |f_{R}|\sigma \simeq 5k_{B}T \) analyzed further in the context of MFPT in Figs. 3(c) and 4(c). The histograms of the MFPT for the case when the external biases \(-f_{L} = f_{R} \simeq k_{B}T \) and \(-f_{L} = f_{R} \simeq 5k_{B}T \) are shown in Figs. 3 and 4. The MFPT through the left pore \( \langle \tau_{L} \rangle \) (Figs. 3(a) Figs. 4(a)) and through the right pore (Figs. 3(b) Figs. 4(b)) are qualitatively similar in each case for low and high biases. This is due to the fact that almost 90% of the translocation time is spent before the chain translocates through the left pore (please see the numbers for \( \langle \tau_{L} \rangle \) and \( \langle \tau_{R} \rangle \) in Figs. 3 and 4) when the chain
experiences a tug-of-war situation with net zero force. It is only after the translocation through the left pore the chain experiences the driving force from the right pore only. This explains the qualitative differences in Fig. 3(c) and Fig. 4(c) which corresponds to the scattered points in Fig. 2(a) and 2(b) respectively. The distribution of delay time $|f_L| - |f_R|$ in Fig. 4(c) is narrower than that of in Fig. 3(c), as in the former case the chain experiences a larger net larger force after translocating through the left pore.

Finally, we show the result how $\langle \tau_R \rangle$ depends on the offset bias ($|f_R| - |f_L| > 0$). Evidently one would expect that $\langle \tau_R \rangle$ will be maximum when $\Delta f_{LR} = |f_R| - |f_L| = 0$ and will decay as $\Delta f_{LR}$ is increased. This is shown in Fig. 5 for two different chain stiffness $\kappa = 16$ and 64. This is in accord with our previous work that a stiffer chain takes longer time to translocate [21]. When we normalize the translocation time by the maximum value in each case, the scaled plots in Fig. 6 collapse onto the same master curve. The general shape of the collapsed curve is the same as observed experimentally [18].

4. Summary and conclusion

In summary, motivated by recent experimental work we have carried out BD simulation to study translocation and eventual escape of a model semi-flexible polymer initially captured by two nanopores. BD simulation on the same model polymer for a single nano-pore translocation have been very successful in explaining a variety of translocation phenomena and played a major role to validate the scaling theories and tension propagation theory of polymer translocation. Therefore, it is no surprise that for the two-pore translocation problem we observe that the simulation strategy is capable of reproducing the experimental results and thus can provide further details not captured in the experiments. To the best of our knowledge this is the first simulation study of the two-pore translocation problem. But the preliminary results are
Figure 5. $\langle \tau_R \rangle$ as a function of $\Delta f_{LR}$ for two values of chain stiffness parameter $\kappa = 16.0$ (black circles) and $\kappa = 64.0$ (red squares) respectively.

Figure 6. Normalized $\langle \tau_R \rangle$ as a function of $\Delta f_{LR}$ for two values of chain stiffness parameter $\kappa = 16.0$ (black circles) and $\kappa = 64.0$ (red squares) respectively.

reassuring enough to explore in detail for a larger parameter space for much longer chains which will enable us to watch folds during the translocation process. We also plan to introduce a self-feedback mechanism to slow down the diffusion of the chain which will help to design new experimental strategies to control biomolecules.

5. Acknowledgement
The author thanks Prof. Walter Reisner for various discussions.

[1] J. J. Kasianowicz, E. Brandin, D. Branton and D. W. Deamer, Proc. Natl. Acad. Sci. U.S.A. 93, 13770 (1996).
[2] A. Meller, L. Nivon, E. Brandin, J. A. Golovchenko, and D. Branton, Proc. Natl. Acad. Sci. U.S.A. 97, 1079 (2000).
[3] A. Meller, L. Nivon, and D. Branton, Phys. Rev. Lett. 86, 3435 (2001).
[4] A. Meller and D. Branton, Electrophoresis 23, 2583 (2002).
[5] For recent reviews in the field please see M. Muthukumar Polymer Translocation (CRC Press, Boca Raton, 2011); Vladimir V. Palyulin, Tapio Ala-Nissila, and Ralf Metzler, Soft Matter, 10, 9016 (2014).
[6] W. Sung and P. J. Park, Phys. Rev. Lett. 77, 783 (1996).
[7] M. Muthukumar, J. Chem. Phys. 111, 10371 (1999).
[8] J. L. A. Dubbeldam, A. Milchev, V.G. Rostiashvili, and T.A. Vilgis, Phys. Rev. E 76, 010801(R) (2007).
[9] J. L. A. Dubbeldam, A. Milchev, V.G. Rostiashvili, and T.A. Vilgis, Europhys. Lett. 79, 18002 (2007).
[10] Y. Kantor and M. Kardar, Phys. Rev. E 69 021806 (2004).
[11] Sakaue, T Phys. Rev. E 76 021803 (2007).
[12] Lehtola V. V. Kaski K. and Linna R. P Phys. Rev. E82 031908 (2009).
[13] Bhattacharya A and Binder K Phys. Rev. E81 041804 (2010).
[14] A. Bhattacharya, Computer Simulation Studies in Condensed Matter Physics XXII, Eds. D. P. Landau, S. P. Lewis, and H. B. Schuttler, Elsevier, Physics Proceedia 3, 1411 (2010).
[15] Ikonen T. , Bhattacharya A., Ala-Nissila T. and Sung W. J. Chem. Phys.137 085101 (2012).
[16] T. Ikonen, A. Bhattacharya, T. Ala-Nissila and W. Sung, Phys. Rev. E 85, 051803 (2012).
[17] Ikonen T, Bhattacharya A, Ala-Nissila T, and Sung W EPL103 38001 (2013).
[18] Controlling DNA Tug-of-War in a Dual Nanopore Device, Xu Liu, Yuning Zhang, Roland Nagel, Walter Reisner, William B. Dunbar, arXiv:1811.11015
[19] Grest, G.S.; Kremer, K. Molecular dynamics simulation for polymers in the presence of a heat bath. Phys. Rev. A 1986, 33, 3628(R) (1986).
[20] Bernier S, Huang A, Reisner W, and Bhattacharya A Macromolecules 51 4012 (2018).
[21] Adhikari R. and Bhattacharya A. J. Chem. Phys. 138 204909 (2013).