Translocation of a Semiflexible Polymer Through a Nanopore

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TRANSLOCATION OF A SEMIFLEXIBLE POLYMER THROUGH A NANOPORE

by

Ramesh Adhikari
B.S. Physics, Tribhuvan University, Kathmandu, Nepal, 2001
M.S. Physics, The University of Southern Mississippi, Hattiesburg, MS, 2009

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Major Professor: Aniket Bhattacharya
ABSTRACT

The transport of a biomolecule through a nanopore occurs in many biological functions such as, DNA or RNA transport across nuclear pores and the translocation of proteins across the eukaryotic endoplasmic reticulum. In addition to the biological processes, it has potential applications in technology such as, drug delivery, gene therapy and single molecule sensing. The DNA translocation through a synthetic nanopore device is considered as the basis for cheap and fast sequencing technology. Motivated by the experimental advances, many theoretical models have been developed. In this thesis, we explore the dynamics of driven translocation of a semiflexible polymer through a nanopore in two dimensions (2D) using Langevin dynamics (LD) simulation. By carrying out extensive simulation as a function of different parameters such as, driving force, length and rigidity of the chain, viscosity of the solvent, and diameter of the nanopore, we provide a detailed description of the translocation process.

Polymer translocation through a nanopore is a stochastic process. The statistical average of the time period and its distribution while the first monomer enters the pore from the cis side until the last monomer exits towards the trans side is called the mean first passage time (MFPT) or simply the translocation time $\langle \tau \rangle$ that explains the dynamics of polymer translocation. We found the power law scaling of the MFPT with the chain rigidity. We
explain this scaling law using the non-equilibrium tension propagation (TP) theory proposed by Sakaue [Phys. Rev. E 76, 021803 (2007)] and its modifications to Brownian dynamics tension propagation (BDTP) theory [Phys. Rev. E 85 051803 (2012)], originally developed for a fully flexible polymer. The BDTP theory, using the residence time of each monomer at the pore, introduced a time scale on which the tension front propagates along the chain backbone and hits the last monomer in the cis compartment, a tension propagation time $t_{tp}$. Our simulation data for $t_{tp}$ obtained by monitoring the dynamics of last monomer validate the TP theory for a semiflexible polymer [J. Chem. Phys. 138, 204909 (2013)]. We have showed that the $t_{tp}$ increases (decreases) as a function of chain rigidity (driving force) but the ratio $t_{tp}/\langle \tau \rangle$ decreases (remains independent).

We have also studied the translocation of a heterogeneous chain mimicking a rod-coil conformation (as often occurs in partially melted dsDNA or proteins). Specifically, we studied dependence of MFPT on the free parameters of the chain such as, alternate blocks of stiff and flexible segments of size $m$ and $n$, bending rigidity, the spring constant ($k_F$) which controls the bond elastic potential between the successive monomers and the repeat unit $p$ (such that $N = m_p n_p$). We demonstrate that due to the change in entropic barrier and the inhomogeneous viscous drag on the chain backbone a variety of scenarios are possible amply manifested in the waiting time distribution of the translocating chain. These information can be deconvoluted to extract the mechanical properties of the chain at various length scales and thus can be used to nanopore based methods to probe bio-molecules, such as partially melted DNA, and proteins.
To explore the effect of solvent on the translocation process, we have calculated the MFPT as a function of the solvent viscosity. At low solvent-viscosity, a stiffer chain translocates faster than a flexible chain of the same length but the order of translocation speed is reversed in the high viscosity regime. We observe a non-monotonic dependence of \( \langle \tau \rangle \) on \( \gamma \) in the low viscosity regime. The scaling laws developed for the translocation at high viscosity do not fit for the system consisting the solvent of low viscosity. However, we have observed that the translocation time at low solvent-viscosity still remains sensitive to the parameters such as, \( \kappa_b \), \( N \), \( F \) and \( P_d \).

Attractive binding particles (BPs) present in the *trans* compartment accelerate the threading process in two ways: (i) reducing the back-sliding of the translocated monomer and (ii) providing the pulling force towards the translocation direction. We observe that for certain binding strength and concentration of the BPs, the translocation is faster than the ideal ratcheting condition as elucidated by Simon, Peskin, and Oster [Proc. Natl. Acad. Sci. U.S.A. 89, 3770 (1992)]. The asymmetry produced by the BPs at the *trans* side leads to similarities of this process to that of a driven translocation with an applied force inside the pore manifested in various physical quantities. We provide scaling relations for the force experienced by the translocating chain as well as for the scaled MFPT. Based on the analysis of our simulation data we provide plausible arguments how scaling theory of driven translocation can be generalized for such directed diffusion process by replacing the externally applied force with an effective force.
We believe the information gained from these studies will be useful for designing nanopore based devices of sequencing as well as understanding the physics of biomolecular transport in various cases.
To my parents for their amazing love and support
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CHAPTER 1
INTRODUCTION

Theoretical understanding of biological phenomena requires modeling and simulations at various time and length scales. One can model the system based on all particle interactions which requires large computational effort. The other way is to carry out simulation at larger scales which includes the effective interactions between the collective units or groups, a coarse-grained method. We have studied the conformation and dynamics of biomolecules using the coarse-grained approach. In particular, we have studied the translocation dynamics of a semiflexible polymer through nanopore using Brownian dynamics (BD) simulation.

The polymer translocation is ubiquitous in biological processes [1], such as DNA and RNA translocation across nuclear pores, protein transport through membrane channels, virus injection [2]. The polymer translocation is also important in the technological applications, such as rapid DNA sequencing [3], gene therapy and controlled drug delivery [4]. Therefore, the study of polymer translocation through a nanopore has remained an active topic for the last two decades [1, 5–7]. A large fraction of theoretical and simulation studies have been devoted to the study of translocation dynamics of a fully flexible chain. But, most of the biopolymers such as dsDNA, proteins, actin and microtubules exist in the semiflexible form. Thus the study of polymer translocation needs to be extended to semiflexible chains. Before we introduce the translocation problem, it is important to analyze some equilibrium
properties and dynamics of the semiflexible polymer in the bulk. Although the main objective of this thesis is to study the translocation of a semiflexible polymer through a nanopore, we also present a brief discussion about the conformation and dynamics of a semiflexible polymer in the bulk (detailed explanation can be found in our publication II) [8].

1.1 Conformation and dynamics of semiflexible polymer

Exact analytical results for polymer chains can be theoretically obtained in two extreme cases, namely for the fully flexible or rod-like polymers. While most of the physical quantities can be extracted analytically by using such models; nonetheless, these limits do not provide the complete description of the polymers which exist in between these extreme cases (semiflexible). Therefore, different models and theories have been developed to illustrate the physical behavior of semiflexible polymer [9]. Worm like chain (WLC) model, suggested by Kratky and Porod in 1949, provides a powerful theoretical description of the semiflexible polymer [10]. Various studies have been carried out extensively [11] and various moments of the conformational distribution have been calculated [12]. According to the WLC model, the Hamiltonian for the chain is given by [9]

\[ H = 0.5\kappa_b \int_0^L \left( \frac{\partial^2 r(s)}{\partial s^2} \right)^2 ds, \]  \hspace{1cm} (1.1)

where, \( \kappa_b \) is the bending rigidity (a measure of stiffness), \( L \) is the contour length and the integration is carried along the contour \( s \). In the discrete form, we can rewrite the WLC
equation (Eq. 1.1) as [9]:

$$\mathcal{H} = \sum_{i=1}^{N-2} \kappa_b \langle [1 - \cos \theta_i] \rangle,$$

(1.2)

where, $\theta_i$ is the angle at the $i$th monomer made by the adjacent bond vectors. as in Fig. 1.3.

### 1.1.1 Chain conformation

The conformation of a semiflexible polymer is characterized by its physical properties such as, persistence length $l_p$ and the end-to-end distance $R_N$. The persistence length is a characteristic length scale for the semiflexible polymer. Experimental values of the persistence lengths for biopolymers vary from $\sim 50$nm for dsDNA to $\sim 10\mu m$ for actin filaments and few millimeters for microtubules [13, 14]. Theoretical calculation of the persistence length is based on exponential decay of the two-point correlation function between unit tangent vectors $\mathbf{u}(s)$ along the polymer, i.e., $\langle \mathbf{u}(s) \cdot \mathbf{u}(0) \rangle = \exp(-s/l_p)$ [9]. We can rewrite this expression for the persistence length as $l_p = -1/\ln \langle \cos \theta \rangle$; where $\theta$ is an angle between the consecutive bond vectors of the chain. From the Eq. 1.1, the persistence length can be expressed as [15]: $l_p = 2\kappa_b/(d - 1)k_BT$; with $d$, $k_B$, and $T$ are physical dimension, Boltzmann constant and the absolute temperature, respectively. In one of our publications [8], we have shown (Fig. 1.1(a)) that both of these methods are consistent with each other for the calculation of persistence length.
Figure 1.1: (a) Comparison of persistence lengths calculated by two different methods: 
\[ l_p = -1 / \ln(\langle \cos \theta \rangle) \] and \[ l_p = 2 \kappa_b / k_B T. \] (b) Plot of \[ \sqrt{\langle R^2 \rangle / l_{p,25}^2} \] as a function of \[ N^{0.75Z}. \] The solid line is a fit to a straight line. \( \kappa \) in the key of the figures are same as \( \kappa_b \).

The mean square end-to-end distance for the WLC model is given by [9]

\[ \langle R_N^2 \rangle = \frac{2L^2}{n_p} \left( 1 - \frac{1}{n_p} [1 - \exp(-n_p)] \right), \quad (1.3) \]

where, \( L = (N-1)b_l \) is the contour length with the bond-length \( b_l \) and \( n_p = L/l_p \). For \( l_p \ll L \), the chain behaves like Gaussian coil with \( \langle R_N^2 \rangle = 2l_pL \) and for \( l_p \gg L \), the chain behaves as a rod with \( \langle R_N^2 \rangle = L^2 \). Most of the predictions based on the WLC model are consistent with some of the experimental results. But, it fails to explain some aspects caused by excluded volume (EV) effects [16] in the limit \( L \gg l_p \). This incompleteness of the model has also been pointed out in the experimental [17] studies. Atomic force microscopy (AFM) imaging
experiments also found some deviations from WLC expectations [17]. From the on-lattice simulation carried out by Hsu et al. [18, 19], they showed that the Gaussian regime (WLC) crosses over to self-avoiding walk at $\langle R^2 \rangle \sim l_p^3$ in three dimension but the Gaussian regime is completely absent in two dimension (2D). Using off-lattice BD simulation, we also found that the Gaussian regime is completely absent in 2D. The scaling theory explains the important aspects of EV, where, the chain statistics in $d$-dimension satisfies the relation [20, 21]

$$\sqrt{\langle R^2_N \rangle} \sim N^{\nu} l_p^{1/d+2} b_{d+1/d+2}. \quad (1.4)$$

Where, $N$ is the total number of monomers in a chain and $\nu$ is the Flory exponent ($\sim 0.59$ for 3D and 0.75 for 2D). Using simulation data, we have verified the Eq. 1.4 for all values of $L/l_p$ (Fig. 1.1(b)).

1.1.2 Dynamics

The dynamics of the polymer chain can be analyzed by calculating the mean square displacement (MSD) of various monomers along the chain. The MSD for a center of mass and middle monomer of the chain can be calculated as [22]

$$g_1(t) = \langle (r_{N/2}(t) - r_{N/2}(0))^2 \rangle \quad (1.5)$$

$$g_3(t) = \langle (r_{CM}(t) - r_{CM}(0))^2 \rangle \quad (1.6)$$
and the fluctuation of the position of the middle monomer with respect to the center mass is given by [22]

$$g_2(t) = \langle \left((\mathbf{r}_{N/2}(t) - \mathbf{r}_{CM}(0)) - (\mathbf{r}_{N/2}(t) - \mathbf{r}_{CM}(0))\right)^2 \rangle$$  (1.7)

where, $\mathbf{r}_{N/2}$ and $\mathbf{r}_{CM}$ are the position vectors of the middle monomer and the center of mass of the chain, respectively. The middle monomer advances with two crossovers separating the early sub-diffusive ($g_1(t) \sim t^{0.75}$), regime of monomer dynamics of the flexible chain ($g_1(t) \sim t^{2\nu/(1+2\nu)}$), and finally the diffusive regime ($g_1(t) = g_3(t) \sim t$) where it follows the dynamics of the center of mass of the entire chain [8]. The crossover points depend on the chain stiffness. When the fluctuation of the monomer reaches to the value of the order of $l_p$, the monomer dynamics behaves like the flexible chain until the time when it again crosses over to the regime where the monomer diffuses as a center of mass of the entire chain. This double crossover phenomena was first properly formulated in terms of scaling theory by us [8].

From the study of dynamics in the bulk, we realize the importance of the EV effect on the semiflexible polymer. WLC chain model which neglects the EV interaction does not contain this dynamics of all value of $L/l_p$. Since the translocation of the polymer is followed by the relaxation in the cis compartment, the study of the conformation and dynamics of the chain in the bulk is equally important in the study of the polymer translocation.
1.2 Polymer translocation through a nanopore

1.2.1 Nanopore

Initially, the application of microscopic hole was proposed by Wallace Coulter in 1940s to count blood cells [23]. Coulter’s holes were roughly 10µm, slightly larger than the size of the cell. As time passed, smaller and smaller holes were possible due the development of the fabrication technology. In the last two decades, the concept of threading through the hole is elucidated with the hole of size of the order of few nanometers which named as ‘nanopore’. The application expanded from cellular scale to the molecular scale. The macromolecules such as DNA and proteins can be transported through the nanopore connecting two compartments \(\text{cis}\) and \(\text{trans}\) filled with solvents. When the polymers pass through the nanopore, it blocks the ionic current. Thus the polymer structure can be analyzed by observing the patterns of the blockade of ionic current through the pore [24, 25].

One of the potential applications of the nanopore device is the DNA sequencing. The conventional sequencing method [26, 27] is expensive and takes too long. The nanopore sequencing provide high speed and low cost which can be done at the single-molecule level [23]. Due to the biological importance and technological applications, a variety of nanopores have been developed [28].

Initial macromolecular sensing experiments used the biological nanopore. The most popular biological nanopore is \(\alpha\)-hemolysin produced by the bacterium \(Staphylococcus\ \text{aureus}\) [29]. Biochemists have discovered many more biological nanopores such as the protein
MspA produced by *Mycobacterial* [30], and ClyA produced by *Escherichia coli* [31]. The novel biological nanopores have several advantages over the α-hemolysin pore. The most important advantage is the reduced barrel length of the narrow portion of the device, *e.g.*, the narrowest portion of the MspA can accommodate only three nucleotide whereas α-hemolysin has 10-12 nucleotide long β-barrel. The narrower depth of the nanopore produces the better resolution and throughput.

Over a decade ago, several research groups [3,32], fabricated solid state nanopore by drilling a hole into a thin insulating membrane (*e.g.*, silicon nitride, silicon oxide, aluminum oxide). Recently, the two dimensional layered material such as graphene and molybdenum disulfide are also used as a membrane for the solid state nanopore. More recently, the third category of the nanopores, hybrid nanopores, have been developed. The first hybrid nanopores were developed by capturing the α-hemolysin proteins in SiN pores [33]. The huge scientific effort has been used for modifying the nanopore to generate high resolution and throughput at low cost [34].

### 1.2.2 Brownian dynamics and polymer translocation

The motion of a Brownian particle is determined by the random collisions of the particle with its surrounding particles. The motion can be explained by solving the Fokker-Planck equation (Eq. 1.8) or the Langevin equation (Eq. 1.9).
Fokker-Planck equation gives the time evolution of a probability density of the system.

The one-dimensional Fokker-Planck equation can be expressed as [1]:

\[
\frac{\partial P(x, t)}{\partial t} = -\frac{\partial}{\partial x} [A(x, t)P(x, t)] + \frac{\partial^2}{\partial x^2} [B(x, t)P(x, t)],
\]

(1.8)

where, \(P(x, t)\) is a probability of finding a particle at position \(x\) and time \(t\), and \(A(x, t)\) & \(B(x, t)\) are the coefficients. Solving the second order partial differential equation with unknown coefficients is, in general, difficult and needs the boundary conditions. On the other hand, Langevin equation (which contains an explicit stochastic force term) provides an easier way to solve the Brownian dynamics. Mathematically, the Langevin equation can be expressed as a stochastic differential equation [35]:

\[
m_i \frac{d^2 \vec{r}_i(t)}{dt^2} = -\gamma_i \vec{v}_i(t) + \vec{F}_i(r(t)) + \vec{\chi}_i(t),
\]

(1.9)

where \(F_i(r(t))\), \(\gamma_i\) and \(\vec{\chi}_i(t)\) the total force caused by the different potentials, the friction coefficient and the stochastic force, respectively. \(\vec{\chi}_i(t)\) is the stochastic force which satisfies the fluctuation-dissipation theory [36]

\[
\langle \vec{\chi}_i(t) \rangle = 0; \text{ and } \langle \vec{\chi}_i(t) \cdot \vec{\chi}_i(t_0) \rangle = 2dk_BT\gamma_i\delta(t - t_0)
\]

(1.10)

The diffusion of a Brownian particle in the presence of constraints is significantly different from the diffusion of a free particle. Various interaction potentials (constraints) make the motion of the polymer more complex than the free particle. Brownian dynamics is important to study the structure and dynamics of the complex fluids. Therefore, the translocation dynamics of a polymer through a nanopore can be studied using BD approach.
The pioneering theoretical works [37, 38], considering the polymer translocation as one dimensional barrier crossing problem on the translocation coordinate $s$ (Fig. 1.2) and using the Fokker-Planck formalism, introduced the BD to study the polymer translocation. In general, the Brownian particles are considered moving in the overdamped condition, i.e., inertial term on the left side of Eq. 1.9 is neglected. The Langevin equation for the polymer translocation in the overdamped limit is:

$$\gamma \frac{d}{dt}s = F(t) + \chi(t). \quad (1.11)$$

Where, $F(t)$ represents the sum of the entropic force and the other interactions (such as excluded volume, bond harmonic, bond bending and pore-polymer interaction) and the applied bias at the pore and $s$ represents the length of the translocated segment at the trans side. Eq. 1.11 is equivalent to the Fokker-Planck equation (Eq. 1.8) when the system is close to the equilibrium. This condition is not satisfied for the driven translocation which requires separate theory.

1.2.3 Tension propagation (TP) and Brownian dynamics tension propagation (BDTP) theory

For a driven translocation, only a domain of the subchain in the cis side (Fig. 1.2) close to the pore remains mobile. Therefore, Eq. 1.11 which assumes that all the monomers move with same velocity, can not explain the driven translocation. Tension propagation theory proposed by Sakaue [39] is able to explain the nonequilibrium driven translocation.
Figure 1.2: Minimalist view of a polymer chain translocating through an ideal pore in a thin wall from cis to trans side in terms of the translocation ($s$) coordinate. The picture shows an instant of translocation when $s$ segments are at the trans side with remaining $N - s$ segments at the cis side of a chain of length $N$.

This theory implements the local force balance formula, $f_0 = 6\pi \eta r v(t)$; where $\eta$ is solvent viscosity, $r$ is the effective radius of the chain monomer, $v(t)$ is velocity and $f_0$ is the net driving force. According to the TP theory, if the driving force is substantially large, it propagates along the chain backbone which causes the non-trivial time dependent drag on the chain monomers. It introduces two processes namely tension propagation and tail retraction. The phenomenon when the tension propagates on the chain backbone in the cis compartment until it hits at the last monomer is called the “tension propagation” and the corresponding time duration is referred as the tension propagation time. Once the TP hits the last monomer, the remaining chain at the cis side translocates rather fast and this phenomenon is referred as “tail retraction”. One of the contributions of the TP theory is to look at the entire
translocation process as pre and post translocation events whose natures are qualitatively different [39].

Applying the time dependent friction $\gamma(t)$, Ikonen et al. [40] modified Eq. 1.11 as $\gamma(t) \frac{ds}{dt} = F_{\text{driving}}(t) + \chi(t)$ which is so called Brownian dynamics tension propagation (BDTP) theory. It introduces the tension propagation time as a characteristic parameter to describe the translocation process. This theory successfully describes the wide range of the translocation exponent $\alpha$ observed by previous experiments and simulations as a finite chain effect. The exponent for the infinite chain obtained from the TP theory $\alpha \sim 1 + \nu$ acts as the upper limit for the exponent according to BDTP theory. This theory developed a method (namely ‘waiting time distribution’) to calculate the tension propagation time $t_{tp}$. The $s$ coordinate corresponding to the peak on the nonmonotonic waiting time distribution represents the end of the tension propagation process. Using the Langevin dynamics simulation in two dimension, we have validated the BDTP theory for the semiflexible polymer. We have shown that the TP time for the finite chain using the waiting time distribution is consistent with that calculated by direct observation of the last monomer. In this thesis, we present the simulation results of the driven translocation at various conditions of chain and its surroundings such as solvent, wall and pore, and the binding particles. We demonstrate the validity of the TP theory for all the situations we concerned.
1.3 Simulation of polymer translocation

Computational studies provide valuable insights and physics to design better nanopore devices. One of the techniques to perform the simulation of biopolymers is an all atom molecular dynamics (AAMD) technique [41]. The all atom model keeps the chemical details of the system but is limited to very short time scale. Using all atom model, the study of physical behavior in the physically observable length and time scale is almost impossible for the DNA translocation problem. Therefore, to study the behavior of macromolecules in the larger length and time scales coarse grained (CG) models are important. The CG models consider a group of atoms as a single particle. Using appropriate interactions between such particles, one can attain the physical properties in the physical time and length scales. In our simulation studies, we have used the ‘bead-spring model’ (Fig. 1.3) proposed by G. Grest and K. Kremer [42] in 1986. Each bead on the chain represents a group of molecules, such as, a nucleotide in a dsDNA. A spring connecting two consecutive beads mimics the bond between the respective groups. The size and mass of such bead in a polymer are $\sigma \sim 0.34\text{nm}$ and $m \sim 321 \text{ amu}$, respectively. Various interaction potentials can be imposed depending on the model of the polymer. In the following paragraphs, we explain few interactions which are common to most of the polymer models.
1.3.1 Bonded and Non-bonded interaction

As in the original bead spring model by Grest and Kremer [42], we have used finite extensible non-linear elastic (FENE) potential as the bonded interaction because it provides a nearly constant contour length of the chain. For example, in our simulation, the bond length remains constant at $b_l \simeq (1.000 \pm 0.001)\sigma$. This potential can be expressed mathematically as:

$$U_{\text{FENE}}(r) = -\frac{1}{2}k_F R_0^2 \ln(1 - r^2 / R_0^2)$$

(1.12)

where $k_F$ and $R_0$ are the strength of the spring and the limit of the chain extensibility, respectively. The strength of the bond is controlled by spring constant $k_F$. The minimum value is chosen so that it prevents the chain crossing. If the value of $k_F$ is too large, due to the large FENE energy, the long time simulation is unfavorable. Therefore, the choice of $k_F$ should be within a certain range which prevents the chain crossing and also provide the convergence of the simulation for reasonably long MD simulation time.

![Figure 1.3: Bead-spring model of a polymer chain with bending angle $\theta_i$ subtended by the vectors $\vec{b}_i = \vec{r}_i - \vec{r}_{i-1}$ and $\vec{b}_{i+1} = \vec{r}_{i+1} - \vec{r}_i$.](image)


The flexibility of a polymer can be expressed by the angle dependent ‘bending potential’ as

\[ U_{\text{bend}}(\theta_i) = \kappa_b (1 - \cos \theta_i). \]  

\[ (1.13) \]

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, as shown in Fig. 1.3. The strength of the interaction is characterized by the bending rigidity \( \kappa_b \).

Lennard Jones (LJ) potential represents non-bonded interaction between every pair of the CG particles. The potential is repulsive and attractive at short and long length scales as described by

\[ U_{\text{LJ}}(r) = 4\epsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^6 \right] + \epsilon; \text{ for } r \leq r_c \]

\[ = 0; \text{ for } r > r_c. \quad (1.14) \]

To save the computational time, the long-range interaction is calculated only for the pair which are within a fixed distance, namely a cut-off distance \( r_c \). The strength of the attractive LJ potential \( \epsilon \) also depends on the solvent condition. The solvents which are responsible for the negligible attractive LJ interaction are considered as the good solvents. In such condition, the non-bonded pairwise interaction is given by the repulsive part with cut-off distance \( r_c = 2^{1/6} \sigma \). The attractive part of the potential is completely omitted by choosing the cut-off \( r_c \) which represents the EV effect. The potential is shifted (Eq. 1.14) to remove the discontinuities in the interaction energy. The chain monomers also interact with the wall particles with the LJ potential. In our simulation, we apply a purely repulsive LJ potential.
between the wall particles and chain monomers.

\[
U_W(r) = 4\epsilon_c \left[ \left( \frac{\sigma_{\text{eff}}}{r} \right)^{12} \right] + \epsilon, \quad \text{for } r \leq 2^{1/6}\sigma_{\text{eff}};
\]

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

(1.15)

\(\sigma_{\text{eff}}\) is the Van der Waals radius for the pair of wall particle and chain monomer. Typically, this can be expressed as an average \(\sigma_{\text{eff}} = (\sigma + \sigma_w)/2\), where \(\sigma_w\) is the size of the wall particles.

### 1.3.2 Integration scheme for Langevin equation

We can rewrite the Langevin equation Eq. 1.9 in terms of the total interaction potential \(U = U_{\text{LJ}} + U_{\text{FENE}} + U_{\text{bend}} + \cdots\) as

\[
m_i \ddot{r}_i(t) = -m\gamma' \ddot{v}_i(t) + \vec{F}_i(t) + \vec{\chi}_i(t),
\]  

(1.16)

where, the Gaussian white noise term \(\chi_i(t)\) follows the fluctuation-dissipation relation Eq. 1.10. The systematic force \(F_i(t)\) can be found from the potential \(U\), and \(\gamma' = \gamma/m\). We integrate this differential equation by using the algorithm proposed by Gunsteren and Berendsen [43].

According to the algorithm, Eq. 1.16 can be integrated (where the systematic force is expanded as: \(F(t) = F(t_n) + \dot{F}(t_n)(t - t_n) + O[(t - t_n)^2]\) with \(\dot{F}(t) = [F(t_n) - F(t_{n-1})]/\Delta t)\)
and discretized as [43]:

\[
x(t_n + \Delta t) = x(t_n) [1 + \exp (-\gamma' \Delta t)] - x(t_n - \Delta t) \exp (-\gamma' \Delta t) \\
+ m^{-1} F(t_n)(\Delta t)^2(\gamma' \Delta t)^{-1} [1 - \exp (-\gamma' \Delta t)] \\
+ m^{-1} \dot{F}(t_n)(\Delta t)^3(\gamma' \Delta t)^{-2} \left[ \frac{1}{2} \gamma' \Delta t [1 + \exp (-\gamma' \Delta t)] - [1 - \exp (-\gamma' \Delta t)] \right] \\
+ X_n(\Delta t) + \exp(-\gamma' \Delta t)X_n(-\Delta t) + O(\Delta t^4)
\]

(1.17)

where, \(X_n(\Delta t)\) and \(X_n(-\Delta t)\) are random variables defined as [43]:

\[
X_n(\Delta t) = (m \gamma'^{-1}) \int_{t_n}^{t_n + \Delta t} [1 - \exp (-\gamma'(t_n + \Delta t - t))] \chi(t)dt,
\]

(1.18)

and

\[
X_n(-\Delta t) = (m \gamma'^{-1}) \int_{t_{n-1}}^{t_{n-1} + \Delta t} [\exp (-\gamma'(t_{n-1} - t)) - 1] \chi(t)dt.
\]

(1.19)

\(X_n(-\Delta t)\) and \(X_{n-1}(\Delta t)\) are correlated since they are different integrals over the same interval, they obey a bivariate Gaussian distribution [44]. The parameters of the distribution can be determined by evaluating the various correlation functions using Eqs. 1.10, 1.18 and 1.19, for example:

\[
\langle X_{n-1}^2(\Delta t) \rangle = \frac{k_B T}{m \gamma'^2} [2\gamma' \Delta t - 3 + 4 \exp (-\gamma' \Delta t) - \exp (-2\gamma' \Delta t)]
\]

(1.20)

\[
\langle X_n^2(-\Delta t) \rangle = -\frac{k_B T}{m \gamma'^2} [-2\gamma' \Delta t - 3 + 4 \exp (\gamma' \Delta t) - \exp (2\gamma' \Delta t)]
\]

(1.21)

\[
\langle X_{n-1}(\Delta t)X_n(-\Delta t) \rangle = \frac{k_B T}{m \gamma'^2} [\exp (\gamma' \Delta t) - \exp (-\gamma' \Delta t) - 2\gamma' \Delta t].
\]

(1.22)

Although BD formalism can be implemented using various updating schemes, the algorithm as described by Eq. 1.17 is proven to be extremely stable for larger time steps \(\Delta t\).
1.4 A brief history of polymer translocation

A lot of experimental and theoretical studies have been carried out on the topic of translocation of a polymer through a nanopore in the last two decades [6,28]. Here, we note the works which are considered as breakthroughs in the history of polymer translocation.

→ Experiment: The concept of translocation was initiated from the Wallace Coulter’s experiment to count the blood cells passing through the hole in 1940. After a half century, in 1994 the, Bezrukov et al. [24] used Alamethicin channel to count the polyethylene oxide (PEO) molecule. In 1996, Kasianowicz, Brandin, Branton, and Deamer [45] used an α-hemolysin channel and showed that the sequence of nucleotide in RNA can be identified by observing the ionic current across the channel. They also were able to distinguish different units of block copolymers by observing the amplitude and duration of the signals. In 2001, Li et al. [32] developed the ion-beam sculpting technique and produced a solid-state nanopore. They used it to detect the passage of DNA. In 2005, Dekker’s group measured the translocation time of long DNA (up to 97000 base pairs) and found the power law relation between the translocation time and the length of polymer [3]. To control the speed of translocation through the solid-state nanopore, Keyser et al. (in 2006) [46], Movileanu’s group (in 2008) [47] and Pedone et al. (in 2010) [48] used optical tweezers, electrostatic trapping and the pore-cavity-pore complex, respectively. Recently, scientists have concentrated their attention to develop the more complex biomimetic nanopores. Dekker’s group (in 2010) [33] demonstrated the
functionality of the hybrid nanopore by inserting α-hemolysin protein into a graphene nanopore. Most recently, Wei Guo et al. [49] have developed the biomimetic gatekeepers of living cells by the self-assembly of the cross-linked DNA oligomers inside the solid-state nanopore. During last two decades, many other experimentalists performed numerous experiments to analyze structures and dynamics of the polymers translocating through the nanopore.

→ **Theory and simulation**: During last two decades, a lot of theoretical (analytical or computational) studies have been performed for both biased and unbiased translocation.

Sung and Park, in 1996 [37], started the theoretical effort to study the unbiased polymer translocation. Assuming the polymer as a Gaussian chain, they studied the unforced translocation in the equilibrium limit. They predicted that the translocation time scales as $\tau \sim N^3$ and $\sim N^{2.5}$ in Rouse and Zimm dynamics, respectively. Muthukumar [38] in 1999, found that translocation time for a self avoiding chain scales as $\tau \sim N^2$. Both of these two studies considered the translocation as a diffusion across an entropic barrier, one assume the diffusion of center of mass while the other considered the diffusion of monomers under the local interaction with the pore. Chuang et al. in 2001 [50], argued that the translocation time can not be smaller than Rouse equilibration time ($\tau_R = N^{1+2\nu}$) where, $\nu$ is a Flory exponent ($\nu_{3D} = 0.58$ and $\nu_{2D} = 0.75$). Performing Monte Carlo (MC) simulation, they showed that $\tau$ scales as $\tau \sim N^{1+2\nu}$.

Other researchers who performed their research on the unbiased translocation also
found that the translocation time scales as \( \langle \tau \rangle \sim AN^\alpha \), where \( \alpha \leq 1 + 2\nu \) is a translocation exponent and \( A \) is a prefactor that depends on other parameters such as, the solvent viscosity [51] and size of the pore [52–56].

The scaling analysis of the translocation time for the driven translocation includes two major parameters, the chain length \( N \) and the applied external force \( F \). Most of the experiments considered an external electric field as the driving force. Some of the studies used the bias due to the interaction of the polymer with the attractive particles in the \textit{trans} side. But most of the theoretical studies have used a constant force at the pore disregarding the source of it.

In 2004, Kantor and Kardar [57], assuming a virtual membrane at one end of a polymer, found the lower limit of the translocation time scales as \( \tau \sim N^\alpha / F \) with \( \alpha = 1 + \nu \). Luo \textit{et al.} [58] found the possibility of crossover for the exponent depending on the chain length, applied bias and the solvent conditions. Gauthier and Slater [59, 60] found the same exponent found by Kantor and Kardar. Luo \textit{et al.} [61], In 2009, carried out simulation in two distinct limiting regimes for slow and fast translocation and found \( \alpha = 1 + \nu \) for slow process. All of them found the same inverse-force scaling for \( \tau \).

The large variation of scaling exponents obtained from various works indicates that the driven translocation may represent the nonequilibrium process. To solve the translocation in the nonequilibrium limit, Sakaue, in 2007 [39], proposed a TP theory. Lehtola \textit{et al.} [62] and Bhattacharya \textit{et al.} [63] verified the driven translocation of polymers through a nanopore as a nonequilibrium process which made the use of TP theory
relevant. Sakaue’s TP theory was modified by Rowghanian and Grosberg [64], in 2012, by introducing the ‘iso-flux trumpet’ approach. Dubbeldam et al. [65], considering three different force regimes, found the different scaling exponents for each regimes. Ikonen and coworkers [40,66,67] combining the TP idea with the Brownian dynamics developed the BDTP theory. This assured that the scattered values of $\alpha$ for the driven translocation obtained from previous works were due to the finite chain effect. According to their results, for all the chains that can be taken in experiment or simulation, the exponent is less than the asymptotic value $1 + \nu$. Although the scaling relation for the translocation of fully flexible polymer is settled after the BDTP model, none of the previous works considered the chain rigidity of the semiflexible polymer. Therefore, in 2013, we developed [68] the scaling relation of the translocation time with the chain rigidity which we present in chapter 2 of this thesis.

Study of heterogeneous polymer translocation was proposed by Muthukumar in 2002 [69]. Kafri et al. [70], Mirigan et al. [71], Gauthier et al. [59,60] and Luo et al. [72,73] studied the effect of chain heterogeneity on polymer translocation. The heterogeneity was based on the effective pore polymer interaction. The chain heterogeneity based on the chain rigidity was introduced by de Haan et al. [74] in 2013. They simulated a short chain in the quasi-static limit (pore-friction dominated translocation) and showed that the stiff segment translocates faster than the flexible segment. But, at high viscosity (beyond the threshold of quasi-static limit), we have found that the stiffer segments translocate slower than the adjacent flexible segments. We have presented a detailed
explanation of the translocation of heterogeneous flexible/rigid chain in chapter 3 of this thesis. The effect of the solvent-viscosity on the translocation time for a homopolymer in the two different regimes (pore-friction and solvent-friction dominated) has been presented in chapter 4 of this thesis.

In 1992, Simon, Peskin and Oster [75] explained the protein translocation through membrane pore according to the Brownian ratchet mechanism caused by the chaperonin proteins present in the trans compartment. In 2003, Zandi et al. [76] found that the translocation of rodlike polymer in the presence of chaperonin proteins in the trans side is not only by the Brownian ratchet mechanism but also driven by a net pulling force due to the interaction between the polymer and the chaperonin particles. Ambjornsson et al. [77, 78] and Abdolbahav et al. [79–81] also studied the polymer translocation in presence of the binding particles. Yu et al. extended the Ref. [76] for longer flexible [82], one dimensional compressible rod [83] and for semiflexible polymer [84]. In chapter 5, we provide a far more comprehensive picture of the translocation dynamics by suggesting scaling relation for the MFPT on various factors which are then further justified in the context of TP theory.

1.5 Goals of the thesis

The overall goal of this thesis is to explore the dynamics of driven translocation of a semiflexible polymer through a nanopore using computer simulation method augmented by
theory in two dimension. In particular, we aim to study the polymer translocation under the influence of various factors such as, applied external force, solvent viscosity, size of the pore and presence of other particles in the surroundings. We will provide the important scaling laws abstracted from the simulation results which will be helpful to design the experiments for translocation of a semiflexible polymer through a nanopore. Detailed explanation of the goals of this thesis are as follows:

• First, we investigate the variation of the translocation time for semiflexible polymers with different bending rigidity and establish the scaling laws. We explain our findings using TP or BDTP theory. We calculate the tension propagation time for the translocating chain from the direct observation of dynamics of last monomer and validate the method (waiting time distribution) used by the BDTP scheme. This provides a clear and straightforward demonstration of Sakaue’s TP picture, i.e., the polymer translocation can be looked as a pre and post translocation process.

• Second, we explain the driven translocation of a single chain which consists of segments of different flexibility which mimics the real biopolymers such as partially melted DNA or secondary structured proteins. We expect the waiting time distribution for such chain will end up with the fringelike spectrum where the maxima and minima correspond to the stiff and flexible segments. By observing the number of maxima and minima on the distribution, we can find the flexible and stiff segments on the polymer of interest.
• Third, we state the effect of solvent viscosity for a semiflexible polymer translocating through a nanopore. At low viscosity the pore-friction dominates the system and the translocation can be described as the entropic barrier crossing problem. But, at the high solvent viscosity and for the longer chains, the viscous drag from the bulk in the \textit{cis} compartment dominates the system and the translocation can be described by using nonequilibrium TP theory. We aim to provide the relation between the translocation dynamics and the solvent viscosity in the two regimes (pore-friction and solvent-friction dominating).

• The fourth objective of thesis is to study the directed diffusion of a semiflexible polymer through a nanopore in the presence of attractive binding particles in the \textit{trans} compartment. The force exerted by the binding particles on the translocated segment of the chain depends on the concentrations and strengths of binding particles and rigidity of the polymer. Therefore, the translocation time also depends on these parameters. We compare the translocation of semiflexible polymer driven by forces, applied at the pore from external agency and exerted by the biological components present in the \textit{trans} side of the system. Here also we analyze and reconcile our findings in terms of TP theory.
1.6 Organization of thesis

The thesis is organized as follows. Chapter 2 is focused on the simulation of semiflexible polymer translocating through a nanopore. In this chapter, we have explained about the validation of tension propagation theory by direct observation of dynamics of the last monomer of the chain during the translocation. We have presented the effect of chain heterogeneity on translocation dynamics in chapter 3. Chapter 4 is presented with the study of effect of the solvent viscosity (which is accounted implicitly via Langevin equation) on translocation. In this chapter, we discuss about the two different regimes where the translocation speed of flexible and stiff chain overturn. The translocation of a polymer chain due to the binding and unbinding of binding particles present in the trans compartment has been explained in the chapter 5. We conclude the thesis by providing the overall summary in chapter 6.

Here, we provide a list of publications and unpublished manuscripts resulting from the work presented in this thesis as [8, 68, 85, 86]:


CHAPTER 2
DRIVEN TRANSLOCATION OF SEMIFLEXIBLE POLYMER THROUGH A NANOPORE: A BROWNIAN DYNAMICS STUDY

2.1 Introduction

Polymer translocation is of particular interest in the context of biopolymers as translocation is an important ubiquitous process in molecular biology [1, 5–7]. Translocation of DNA and RNA across nuclear pores, protein transport through membrane channels, and virus injection are examples of such processes [2]. Naturally, a microscopic and fundamental understanding of the polymer translocation process in living organisms is essential in health related issues. Understanding this process is also immensely important for making fast, efficient, and low cost single molecule analysis devices. In a series of pioneering experiments using single stranded as well as double stranded DNA translocating through α-hemolysin protein pore and synthetic nanopores [3, 25, 32, 45, 87], where the histogram of the MFPT was obtained by measuring the fluctuation in the channel current, it was demonstrated that a nanopore can be used to determine sequences of a heteropolymer. Recently “nanopore” based techniques have been commercialized and are being used to detect sequences [88]. Significant advancement has been made to fabricate uniformly sized nanopores and nanopore arrays for fast parallel high throughput DNA analysis [89, 90].
These exciting experiments have provided enough enthusiasm to develop a proper theoretical framework for polymer translocation through a nanopore. Sung and Park [37] and Muthukumar [38] considered translocation as a one dimensional barrier crossing problem and derived expression for the translocation exponent $\alpha (\langle \tau \rangle \sim N^\alpha)$ using a free energy expression for a polymer threaded through the pore (Fig. 1.2). These initial predictions were followed by many others [39,40,50,53,57,65,66,91–98] using back of the envelope estimates and dynamical scaling arguments [50,57], analyzing folds of the chains [65], incorporation of memory effects [53,93,94], mass and energy conservations [39,95–97], and tension propagation along the chain backbone [39]. The TP theory captures the true nonequilibrium aspects for the case of driven translocation. The original theory, which was introduced for an infinite chain has been further refined by Ikonen et al. [40,66] and Dubbeldam et al. [98] to study the TP in a finite chain. Ikonen et al. extended the TP theory to a Brownian dynamics scheme (BDTP) and emphasized the role of non-negligible pore friction for finite chains which introduces correction to scaling in the translocation exponent [40]. BDTP theory explains scattered values of the translocation exponent $\alpha$ and provides a unifying picture of driven translocation using the TP idea. These experimental and theoretical developments have been supplemented by a large number of simulation studies which played crucial role in the theoretical developments in the field [40,51,54–56,58–63,66,67,72,73,99–111]. Along with simulation studies of coarse-grained model ab initio and atomic resolution Brownian dynamics have been carried out to predict the DNA sequence dependence on ion current [112, 113].
Almost all of the aforementioned theoretical and simulation studies have been addressed in the context of a fully flexible chain. However, in order to capture some realistic aspects of a translocating of a DNA through a nanopore one needs to consider the chain stiffness. The purpose of this chapter is twofold. First to extend the simulation studies of polymer translocation for a semi-flexible chain. Secondly, use the simulation results to validate some aspects of the tension propagation phenomenon which has been very useful to explain apparent discrepancies of the simulation studies for finite chains. We find that many aspects of the TP picture, which has been developed for a fully flexible chain remain valid for semi-flexible chains as well. By monitoring the dynamics of the monomers as a function of the the chain length, chain stiffness, and the driving force, we have been able to obtain a complete picture of the translocation process. One of the salient aspects of this study is that our simulation results provide direct demonstration of the TP along the chain backbone and by comparing the tension propagation time $t_{tp}$ obtained (i) from the time dependence of the last monomer and (ii) from the peak position of the residence time $W(s)$ our studies validate the theoretical prediction of time dependent drag on the translocating chain.

2.2 Simulation details

We have used a bead spring model [42] of a polymer chain with excluded volume, spring and bending potentials. The excluded volume interaction between any two monomers is given by short range LJ potential $U_{LJ}$ (Eq. 1.14). The connectivity between neighboring
monomers is modeled as a FENE spring (Eq. 1.12). The chain stiffness is introduced by adding an angle dependent interaction $U_{\text{bend}}$ between successive bonds (Eq. 1.13). The strengths of the LJ, FENE and bending interactions are characterized by the depth $\epsilon$ of the LJ interaction, FENE constant $k_F$ and bending rigidity $\kappa_b$, respectively.

Figure 2.1: Representation of the $s$-coordinate ($s$-th) monomer inside the pore in the bead-spring model of a translocating chain used in our simulation. The figure shows a $N = 13$ chain having the 7-th monomer ($s = 7$) inside the pore and the remaining $N - s = 6$ monomers at the cis side. The springs joining the monomers are not shown in Fig. 2.1. Translocation occurs from the cis to the trans side.

The purely repulsive wall consists of one monolayer (line) of immobile LJ particles of diameter $\sigma$ along the $y$-axis at $x = 0$. The pore is created by removing two particles at the center (Fig. 2.1). Inside the pore, the polymer beads experience a constant external force $F$ such that $-Fx = U_{\text{ext}}$ and a repulsive potential from the inside wall of the pore. We use the
Langevin dynamics (Eq. 1.16) with the total interaction $U = (U_{\text{LJ}} + U_{\text{FENE}} + U_{\text{bend}} + U_{\text{W}} + U_{\text{ext}})$ for the $i^{th}$ monomer, where $U_{\text{FENE}}, U_{\text{bend}}, U_{\text{LJ}}$ and $U_{\text{W}}$ are given by Eqs. 1.12, 1.13, 1.14 and 1.15, respectively. The reduced units of length, time and temperature are chosen to be $\sigma$, $\sigma\sqrt{m/\epsilon}$, and $\epsilon/k_B$, respectively. For the spring potential we have chosen $k_F = 30\epsilon/\sigma^2$ and $R_0 = 1.5\sigma$, the friction coefficient $\gamma = 0.7\sqrt{m\epsilon/\sigma^2}$, the temperature is kept at $1.2\epsilon/k_B$. The value of this external force is kept at $F\sigma/\epsilon = 5.0$ throughout the simulation. The choice of the FENE potential along with the LJ interaction parameters ensures that the average bond-length in the bulk $\langle b_l \rangle = 0.971\sigma$. With the choice of these parameters probability of chain crossing is very low. These parameters have been chosen to be the same as in recent studies [40, 66, 72, 73] of polymer translocation of flexible chains for ready comparison of results. We also find that the average bond-length $\langle b_l \rangle$ is almost independent of the range of chain stiffness parameter ($\kappa_b = 0 - 32\epsilon$) used in our simulation. The equation of motion is integrated with the reduced time step $\Delta t = 0.01$ following the algorithm proposed by van Gunsteren and Berendsen [43].

### 2.3 Results and discussions

We have studied 5 different chain lengths $N = 16, 32, 64, 128$ and 256 for several different values of the bending constant $\kappa_b = 0 - 32$. However, for clarity we present only a limited set of data. First we equilibrated the polymer chain by placing the first monomer at the center of the pore. We then allow the polymer to translocate driven by the bias present
uniformly inside the pore. For the translocation related properties we have taken statistics from at least 2000-5000 independent runs, as needed to obtain good statistics. We present all quantities in terms of reduced LJ units unless otherwise specified.

2.3.1 First passage time and its distribution

We first studied how the MFPT varies with the chain stiffness leaving everything else the same. We find that the MFPT monotonically increases with the chain stiffness as shown in Fig. 2.2(a). Here we provide a plausible physical argument for this increase in MFPT combining TP idea with the Kantor and Kardar estimate of MFPT [57] which is given by

$$\langle \tau \rangle \sim \langle R_g \rangle / \langle v_{CM} \rangle,$$

(2.1)

where $\langle R_g \rangle$ and $\langle v_{CM} \rangle$ correspond to the average root mean square radius of gyration and the average velocity of the center of mass of the chain, respectively. According to Eq. 2.1 the MFPT $\langle \tau \rangle$ will increase provided $\langle R_g \rangle$ increases and $\langle v_{CM} \rangle$ either decreases, or stays constant. In Fig. 2.2(b) and Fig. 2.2(c), we show how these two quantities vary as the stiffness is increased. One expects $\langle R_g \rangle$ (and therefore, the average root mean square end-to-end distance $\langle R_N \rangle$) to increase for a stiffer chain which is the exactly the case. We also observe that $\langle v_{CM} \rangle$ decreases as a function of the chain stiffness. The decrease in $\langle v_{CM} \rangle$ for a stiffer chain can be explained using TP idea which is discussed in detail in section 2.3.4. In short, this happens due to increase in the relative fraction of monomers at an earlier time on the cis side responding to the bias at the pore which increases the viscous drag on the
chain at the cis side [40, 66, 67]. In section 2.3.4, we will resume this discussion and show how the average velocity of the individual monomers inside the pore decreases for a stiffer chain.

![Figure 2.2: Variation of (a) MFPT $\langle \tau \rangle$, (b) $\langle R_g \rangle$, and (c) $\langle v_{CM} \rangle$ as a function of chain stiffness parameter $\kappa_b$ for $N = 128$ (black circles) and for $N = 256$ (red squares).](image)

We further observe by monitoring the time dependence of the $s$-coordinate that for a stiffer chain a given monomer oscillates back and forth between the cis and trans side more often before making a final exit to the trans side. This is reflected in histogram of the MFPT shown in Fig. 2.3 which becomes broader with the peak position being shifted at a higher value. This can be understood by noting that compared to a fully flexible chain the
entropic barrier term is reduced by the corresponding chain persistence length $l_p$ for a stiffer chain.

\[ S(N,n)/k_B = n \ln n + (N-n) \ln(N-n). \]  

Figure 2.3: Histogram of the MFPT for various values of the bending rigidity $\kappa_b = 0.0$ (black circles), 4.0 (red squares), 8.0 (green diamonds), 16.0 (blue up-triangles), 32.0 (magenta left-triangles) for chain length $N = 256$. Each histogram is drawn from 5000 independent runs. Solid lines represent the Gaussian fits to the corresponding data.

For a fully flexible chain of length $N$ with $n$ segments at the cis side the entropic barrier is given by

\[ S(N,n)/k_B = n \ln n + (N-n) \ln(N-n). \]  

Which implies that the change in entropy for $n \to n + \Delta n$ is $\Delta S = k_B \Delta n \ln \left( \frac{n}{N-n} \right)$, where $\Delta n$ represents the change in the number of monomer due to translocation from cis to the trans side. For simplicity if we consider this around $n \sim N/2$, then the corresponding change in free energy $\Delta F = k_B T \Delta n$. Therefore, for $\Delta n = \pm 1$ corresponds to $\Delta F = \pm k_B T$. This energy corresponds to roughly 20% of the energy due to the driving force. Now, when the
chain becomes stiffer $\Delta n \to \Delta n/l_p$ and this free energy decreases and the entropic penalty for moving back and forth becomes less which increases the MFPT.

Figure 2.4: (a) $\sqrt{\langle R_N^2 \rangle /((N-1)\langle b \rangle)}$ as a function of $\kappa_b$ for different chain length $N = 16$ (black circles), 32 (red squares), 64 (green diamonds) and 128 (blue up-triangles), respectively. For a given value of $\kappa_b$, the smallest chain are elongated most. (b) Plot of rescaled end-to-end distance $\sqrt{\langle R_N^2 \rangle / l_p^{0.25}}$ versus $N^{0.75}$ where the rescaled end-to-end distances for different chain stiffness collapse on to the same master plot. The solid line is a fit to a straight line.

We have found that the persistence length $l_p$ for the range of $\kappa_b$ used here satisfies the relation $l_p = 2 \frac{\kappa_b}{\kappa_p T} = -\frac{1}{\ln \langle \cos \theta \rangle}$, where $\langle \cos \theta \rangle$ is the equilibrium average of cosine of bond angle (see Fig. 1.3) which holds strictly for a worm like chain (WLC) [114]. The extension of Flory theory for a semi-flexible chain has been done by Schaefer, Joanny, and Pincus [20] and
by Nakanishi [21] which states that the end-to-end distance exhibits the following scaling relation

$$\langle R_N \rangle \sim N^{\frac{d}{d+2}} l_p^{\frac{1}{d+2}},$$

(2.3)

where $d$ is the physical dimension. For $d = 2$ this reduces to $\langle R_N \rangle \sim N^{0.75} l_p^{0.25}$. We observe excellent data collapse for the renormalized end-to-end distances $\langle R_N \rangle / l_p^{0.25}$ (using $l_p = 2\frac{\kappa_b}{k_BT}$) for different values of $\kappa_b$ shown in Fig. 2.4(b) as expected from Eq. 2.3. Since the variation of the velocity of the center of mass is small compared to the variation of chain extension (Fig. 2.2(c)) as a function of $\kappa_b$ this is reflected in the log-log plot of $\langle \tau \rangle$ as a function of $\kappa_b$ which satisfies a simple power law (Fig. 2.5).

![Figure 2.5: Variation of MFPT $\langle \tau \rangle$ as a function of chain stiffness $\kappa_b$ for different chain of length $N = 64$ (green diamonds), 128 (blue up-triangles), 256 (magenta left-triangles), respectively on a log-log scale. The straight line through the points satisfies a simple power law fit (color online).](image-url)
This can be explained as follows. Using Eq. 2.1 and 2.3 in 2D we can write

\[
\langle \tau(\kappa_b) \rangle = \langle R_g(\kappa_b = 0) \rangle_{p}^{0.25} \frac{\langle v_{CM}(\kappa_b) \rangle}{\langle v_{CM}(\kappa_b = 0) \rangle p^{0.25+\delta}} \\
= \langle R_g(\kappa_b = 0) \rangle_{p}^{0.25+\delta} \\
\text{or, } \langle \tau(\kappa_b) \rangle = \langle \tau(\kappa_b = 0) \rangle_{p}^{0.25+\delta}, \tag{2.4}
\]

where the weak dependence of \( \langle v_{CM}(\kappa_b) \rangle \) on chain persistence length (and possible weak chain length dependence) is accommodated in \( \delta \). Since \( \kappa_b = 2l_p/k_BT \), therefore a log-log plot of Eq. 2.4 exhibits a slope \( 0.25 + \delta \) as in Fig. 2.4(c).

![Figure 2.6](image)

Figure 2.6: (a) Plot of \( \langle x_N(t) \rangle \) as a function of time scaled by the average translocation time for the chain-length \( N = 128 \) and bending constants \( \kappa_b = 0.0, 4.0 \) and \( 8.0 \), respectively; (b) The corresponding second derivatives \( d^2(\langle x_N(t) \rangle)/dt^2 = \langle x_N(t) \rangle'' \) (where the peaks correspond to the tension propagation time \( t_{tp} \). The symbols have the same meaning as in Fig 2.3.
2.3.2 Dynamics of the last monomer

In order to study the effect of the chain stiffness on translocation and to relate our results with the recent non-equilibrium tension propagation (TP) theories [39,40,66], we have monitored the dynamics of the last monomer. Recall that in case of a driven translocation, the first monomer of the chain is initially inside the pore at time $t = 0$. As it is allowed to move driven by the bias inside the pore, a disturbance (TP) starts propagating at the cis side. One can associate a characteristic time when this disturbance reaches the last monomer. This is called the TP time $t_{tp}$. We will see that along with the MFPT $\langle \tau \rangle$ and its histogram several aspects of polymer translocation can be explained using $t_{tp}$. A direct way to calculate $t_{tp}$ is to monitor the motion of the last monomer. In Fig. 2.6(a) we have shown $\langle x_N(t) \rangle$ as a function of $t/\langle \tau \rangle$ where $x_N$ is the perpendicular distance of the $N$th monomer from the wall (see Fig. 2.1). As expected, the average location of $\langle x_N(t) \rangle$ stays more or less constant until $t \approx t_{tp}$ and then starts decreasing when the last monomer starts moving towards the pore. This time delay to respond to the driving force can be used to define the tension propagation time $t_{tp}$. We have determined $t_{tp}$ from the peak position of the second derivative of $\langle x_N(t) \rangle$ as shown in Fig. 2.6(b) for several values of the bending constant $\kappa_b$. By repeating this exercise we have determined the $t_{tp}$ directly from the time dependence of the last monomer. However, to calculate $t_{tp}$ from $\langle x_N(t) \rangle$ requires much more statistics than what is needed to determine $\langle \tau \rangle$. We can also determine $t_{tp}$ from the residence time of the individual monomers using the ideas of the tension propagation theory, as discussed in the next two sections (Sec. 2.3.3 and Sec. 2.3.4) at albeit less computational cost. We have checked that the $t_{tp}$ calculated by
these two methods agrees very well providing direct validation of the tension propagation picture of polymer translocation through nanopore [40,66].

2.3.3 Waiting time distribution

The waiting time distribution $W(s)$ is defined as the amount of time a monomer $s$ spends inside the pore so that

$$
\sum_{s=1}^{N} \langle W(s) \rangle = \langle \tau \rangle.
$$

(2.5)

Evidently a plot of $W(s)$ as a function of $s$ reveals detailed information about the translocation process of the individual monomers. This quantity has been studied in detail in the past for fully flexible chains and more recently for semi-flexible chains. Typical plots of $W(s)$ as a function of $s$ are shown in Figs. 2.7 and 2.8 where each plot is characterized by a peak $W_{\text{max}}$. The position of the peak is in general a function of the chain length $N$ and the chain stiffness $\kappa_b$.

Two special cases are worth considering separately as shown in Fig. 2.7. For a fully flexible chain the position of the peak shifts at a higher $s$-value for longer chain; for a given chain length $N$ this peak shifts towards a lower $s$-value for a stiffer chain as shown in Fig. 2.7. For $\kappa_b \neq 0$ the position of the peak in general will depend on the ratio $t_{tp}/\langle \tau \rangle$, as will be discussed in Sec. 2.3.4.
Figure 2.7: (a) Residence time of the individual monomers as a function of the reduced coordinate $s/N$ for three chain lengths $N=64$, 128 and 256 for $\kappa_b = 0.0$. (b) Residence time of the individual monomers as a function of $\kappa_b$ for chain length $N = 256$. Please note that the peak position shifts at a lower $s$-value for a higher value of $\kappa_b$.

The noteworthy point from all these figures for the waiting time distribution is the fact that $W(s)$ is non-monotonic in $s$ reaching maximum for some $\bar{s}(N, \kappa_b)$. This phenomenon implies a time dependent friction on the monomer for a finite chain length $N$ as discussed below using TP picture.
We now relate this $t_{tp}$ obtained directly from the $\langle x_N(t) \rangle$ with the peak position of the waiting time distribution of the individual monomers. According to the recent Brownian dynamics tension propagation (BDTP) theory proposed by Ikonen et al. [40, 66], this peak corresponds to the tension propagation time $t_{tp}$. We will provide a brief physically appealing argument here. The details can be found in references [40, 66]. Let’s denote $\tilde{s}$ so that $W_{max}(s) = W(\tilde{s})$. Physically a peak in $W(s)$ implies that the monomer $\tilde{s}$ spends maximum amount of time inside the pore compared to the rest of the monomers.
Figure 2.9: The total (a) force $f_x(s)$ and (b) velocity $v_x(s)$ along the direction of translocation, and (c) the total friction $\Gamma(s)$ on the $s$ coordinate for a chain length $N = 128$. A comparison of $W(s)$ and $\Gamma(s)$ shows that the waiting time distribution is the fingerprint of the friction experienced by the monomer inside the pore.

We will provide arguments below and show explicitly (Fig. 2.9) that this corresponds to maximum drag force experienced by the monomer $\tilde{s}$ using tension propagation picture.
Figure 2.10: MFPT $\langle \tau(s) \rangle$ for the $s$ coordinate for a $N=256$ chain for different values of the stiffness parameter $\kappa_b$. The symbols have the same meaning as in Fig. 2.3.

In Table-2.1, we show the $t_{tp}$ calculated both by the direct method from $\langle x_N(t) \rangle$ vs. $t$ and from the waiting time distribution using Eq. 2.6. The excellent agreement of the $t_{tp}$ obtained by two different methods clearly establishes the validity of the nonequilibrium TP theory on a firmer ground in the context of polymer translocation problem. The key idea of the TP theory is to divide the cis side subchain into two distinct (near and far) domains where the distances are measured from the pore. The monomers in the (near) domain closer to the pore move towards the pore being dragged by the external force. The far domain consists of immobile (on an average) monomers yet to respond to the driving force. For a finite chain of length $N$ the total time dependent viscous drag experienced by the monomer $\tilde{s}$ inside the pore $\Gamma(t) = \gamma_{cis}(t) + \gamma_{pore}$. Since the external bias is constant, assuming a force balance [3] this implies a time dependent $\tilde{v}(t) = F/\Gamma(t)$. 

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Table 2.1: Comparison of the ratio $\frac{t_{tp}}{\langle \tau \rangle}$ for different values of $\kappa_b$ for chain length $N = 128$ monitoring $\langle x_N(t) \rangle$ and using Eq. 2.6, respectively.

<table>
<thead>
<tr>
<th>$\kappa_b$</th>
<th>$\left(\frac{t_{tp}}{\langle \tau \rangle}\right)_{x_N(t)}$</th>
<th>$\left(\frac{t_{tp}}{\langle \tau \rangle}\right)<em>{W</em>{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.5810</td>
<td>0.5973</td>
</tr>
<tr>
<td>4.0</td>
<td>0.5301</td>
<td>0.5303</td>
</tr>
<tr>
<td>8.0</td>
<td>0.4900</td>
<td>0.4815</td>
</tr>
<tr>
<td>16.0</td>
<td>0.4012</td>
<td>0.3980</td>
</tr>
</tbody>
</table>

The time dependent viscous drag $\Gamma(t)$ inside the pore becomes maximum when maximum number of monomers at the cis side participate in the translocation process. This happens precisely at $t = t_{tp}$ when the tension front reaches the last monomer. For $t > t_{tp}$ the number of monomers start decreasing at the cis side as they translocate to the trans side and the viscous drag decreases. This explains the shape of the waiting time distribution of Figs. 2.7 and 2.8. We have further looked into this aspect of time dependent friction by monitoring the components of velocity and force along the direction of translocation as shown in Fig. 2.9. The ratio $\Gamma(s) = f_x(s)/v_x(s)$ is the friction experienced by the monomer inside the pore $s$ exhibits a maximum and has the same qualitative feature (Fig. 2.9(c)) as that of $W(s)$ confirming the friction becomes maximum at the tension propagation time $t_{tp}$.

Therefore, in order to test the TP theory we have also measured $t_{tp}$ from position of $W_{max}$ using Eq. 2.6

$$\sum_{s=1}^{\hat{s}} \langle W(s) \rangle = t_{tp},$$

(2.6)
(which is a direct consequence of the TP theory) as follows: (i) First, we have used the plots of \( W(s) \) as a function of \( s \) to identify \( \tilde{s} \) which corresponds to the maximum of \( W(s) \) \( (W_{\text{max}} = W(\tilde{s})) \); (ii) then we have used the simulation data for \( \langle \tau(s) \rangle \) (Fig. 2.10) to obtain \( \langle \tau(\tilde{s}) \rangle \). During the simulation \( \langle \tau(s) \rangle \) was recorded as each monomer arrived at the pore. In Table 2.1, we show the \( t_{tp} \) calculated both by the direct method from \( \langle x_N(t) \rangle \) vs. \( t \) and the waiting time distribution using Eq. 2.6. The excellent agreement of the \( t_{tp} \) obtained by two different methods clearly establishes the validity of the nonequilibrium TP theory on a firmer ground in the context of polymer translocation problem.

Figure 2.11: \( t_{tp}/\langle \tau \rangle \) for different values of \( \kappa_b \) for chain length \( N = 64 \) (green diamonds), 128 (blue up-triangles) and 256 (magenta left-triangles), respectively.

Since it is relatively easier to calculate \( t_{tp} \) from the \( W(s) \) and we have shown that both methods provide the same value \( t_{tp} \), we have used Eq. 2.6 to determine the tension propagation time \( t_{tp} \) for various chain lengths and chain stiffness (Table-2.2). For larger chain
length $N$ the ratio $t_{tp}/\langle \tau \rangle$ becomes almost independent of the chain length and decreases with chain stiffness as expected (Fig. 2.11).

Table 2.2: $\tilde{s}$, $t_{tp}$, $\langle \tau \rangle$, and the ratio $t_{tp}/\langle \tau \rangle$ for different values of $\kappa_b$ for chain length $N = 64, 128$ and $256$.

<table>
<thead>
<tr>
<th>$N$</th>
<th>$\kappa_b$</th>
<th>$\tilde{s}$</th>
<th>$t_{tp}$</th>
<th>$\langle \tau \rangle$</th>
<th>$t_{tp}/\langle \tau \rangle$</th>
</tr>
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<td>840.13</td>
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Finally we would like to discuss how the tension propagation time varies as a function of the external bias. It is expected that the $t_{tp}$ will decrease for larger bias. In the previous section, we have shown the connection of $t_{tp}$ with the waiting time distribution. Previously, for fully flexible chains it has been found $\langle \tau \rangle \sim F^{-1}$. From Eq. 2.5 one expects that plot of $W(s) \cdot F$ versus $s/N$ for different bias will fall onto the same master curve. Plots of $W(s)$ as a function of $s$ for different biases are shown Fig 2.12.

Figure 2.12: Residence time for a chain $N = 128$ with $\kappa_b = 8.0$ for different biases $F = 5.0$ (chocolate plus), 7.5 (violet X), and 10.0 (orange stars), respectively. The inset shows the corresponding data collapse for $W(s) \cdot F$.

Since, $\langle \tau \rangle$ decreases as the bias increases the $W_{max}$ also decreases as the area under each curve is exactly equal to $\langle \tau \rangle$ (Eq. 2.5). The inset of Fig. 2.12 shows the scaled plot $F \cdot W(s)$ as a function of $s$ which exhibits reasonably good scaling as expected. In the limit of very long chain this scaling will become exact. Likewise, Fig. 2.13 shows the plot of $\langle x_N(t) \rangle$ for different values of the external force inside the pore. The inset (a) shows the
peak position of second derivative $d^2\langle x_N(t) \rangle / dt^2$ which clearly shows that the $t_{tp}$ decreases for larger bias. The 2nd inset shows the collapse of $[d^2\langle x_N(t) \rangle / dt^2] \cdot \langle \tau \rangle^2$ when plotted as a function of $t/\langle \tau \rangle$. Since $\langle \tau \rangle \propto F^{-1}$, this collapse shows that $t_{tp} \propto F^{-1}$.

Figure 2.13: $\langle x_N(t) \rangle$ as a function of $t$ for different values of external bias. The inset (a) and (b) show the corresponding 2nd derivatives as a function of $t$ and $t/\langle \tau \rangle$, respectively. The later shows that the ratio $t_{tp}/\langle \tau \rangle$ is almost independent of the external bias.

2.4 Conclusion

We have extended the study of polymer translocation through a nanopore for a semiflexible chain and studied how chain flexibility affects various properties of a translocating chain. First we showed that the MFPT increases for a stiffer chain and argued that this is primarily due to chain elongation. We have also observed that MFPT for different chain stiffness satisfies the relation $\langle \tau(\kappa_b) \rangle = \langle \tau(\kappa_b = 0) \rangle \tau_p^{0.25+\delta}$ and therefore, is a function of the
chain persistence length $l_p$. The other significant outcome of these studies is to validate the physical picture of TP using computer simulation data. The TP theory for driven polymer translocation captured the nonequilibrium aspects of driven translocation; however it was soon found that modification and extension of the TP theory for a finite chain is essential to rationalize a large set of not only simulation data but for correct interpretation of experimental data. An immediate consequence of finite chain effect is the TP time $t_{tp}$ which we have seen introduces a nonmonotonic time dependent drag force as have been demonstrated in BDTP simulation studies. However, the BDTP formalism does not involve a coarse-grained bead-spring chain as used in here. By directly monitoring the time dependence of the last monomer we calculated this TP time $t_{tp}$ and validated the consequence of TP by showing that at $t_{tp}$ the waiting time distribution of the corresponding monomer is indeed maximum. We have also shown that scaling of $\langle \tau \rangle \sim F^{-1}$ implies that the ratio $t_{tp}/\langle \tau \rangle$ is independent of $F$ for a given chain length $N$ and bending constant $\kappa_b$.

Finally we would like to make some remarks about recent results for two dimensional semi-flexible chains [18] and show its relevance in the context of polymer translocation problem. Unlike 3D [19], a semi-flexible chains in 2D do not have a Gaussian regime because of severe dominance of excluded volume (EV) effect in 2D [18]. In 2D a chain behaves like a rod for $n = L/l_p < 1$ ($L = (N - 1) b_l$, the contour length), however for larger $L/l_p > 1$ it crosses over to an EV chain invalidating the well known Kratky-Porod relation $R_N^2 = 2l_p L\{1 - \frac{1}{n}[1 - \exp(-n)]\}$ [9], which predicts Gaussian behavior $R_N^2 = 2l_p L$ for large $n$. However, a 3D EV semi-flexible chain while crossing over from the rod to the EV
chain for a limited range of $n$ behaves like a Gaussian chain [19]. Therefore, in order to extract the translocation exponent for semi-flexible chains in 2D one has to first identify if the combinations $(N, l_p)$ reside in the rod limit or EV limit. Only in either of these two limits correction scaling analysis for the translocation exponents for a semi-flexible chain will be useful to study effects of pore friction leading to an anomalous scaling exponent [67]. We have checked that the chain lengths and stiffness parameters considered in this chapter lie in the crossover region [8]. Much longer chains are needed to extract the translocation exponent properly [67]. These calculations are order of magnitude more extensive in computations; but when done the results can be used to interpret experimental data for polymer translocation through nanopores [8]. We hope our work will lead to future work in this direction.
CHAPTER 3
DECONVOLUTING OF CHAIN HETEROGENEITY FROM
DRIVEN TRANSLOCATION THROUGH A NANOPORE

3.1 Introduction

Unlike traditional Sanger’s method [26, 27], the polymer translocation through a nanopore does not require amplification; thus one can in principle analyze a single genome [115]. Progress towards this target offers challenges to overcome which have attracted a lot of attention from various disciplines of sciences and engineering [116, 117]. A large fraction of theoretical and numerical studies have been devoted to translocation studies of flexible homopolymers [6]. However, to extract sequence specific information for a DNA or a protein, as they translocate and/or unfold through a nanopore, one needs generalization of the model to account for how different segments of the translocating polymer interact with the pore or the solvent. Translocation of the heterogeneous polymer has been studied in the past for a fully flexible polymer where different segments encounter different forces [71, 72, 118, 119]. For periodic blocks one observes novel periodic fringes from which information about the block length can in principle be readily extracted [72, 118]. Recently, de Haan and Slater [74] have studied translocation of rod-coil polymer through a nanopore in the quasi-static limit (weakly driven through narrow pore and negligible fluid viscosity). They have used incre-
mental mean first passage time (IMFPT) [120] approach and verified that in the quasi-static limit the stiff and flexible segments can be discriminated due to local entropic mismatch between the stiff and flexible segments reflected in the steps and plateaus of the IMFPT of different segments.

In this chapter, we provide new insights for the driven heterogeneous polymer translocation through a NP where heterogeneity is introduced by varying both the bond bending as well as the bond stretching potentials. We study the translocation dynamics in the presence of large fluid viscosity and strong driving force so that the system is not in the quasi-static limit as in Ref. [74]. Our studies are motivated by the observation that many bio-polymers, such as DNA and proteins exhibit helical and random coil segments whose elastic and bending properties are very different, so is the entropic contribution due to very different number and nature of polymeric conformations. It is also likely that a double stranded (ds) DNA can be in a partially melted state whose coarse-grained description will require nonuniform bond bending and bond-stretching potentials for different regions. As a result, if one wants to develop a NP based device to detect and identify the translocating segments, a prior knowledge of their residence inside the pore will be extremely useful. Naturally, the length scale of the heterogeneity $\xi(n,m)$, where $m$ and $n$ are the lengths of the stiff and flexible segments, respectively in each block, will obviously be an important parameter for the analysis of the translocation problem. Thus, we first show that a proper coarse graining of the model in units of $\xi$ will lead to the known results for the homopolymer translocation. Then we further analyze the results at the length scale of the blob size $\xi$ and show how the chain elasticity and
the chain stiffness introduce fine prints in the translocation process. We explain our findings using Sakaue’s non-equilibrium tension propagation (TP) theory [39] recently verified for a CG models of semiflexible chain by us [68, 111, 121].

3.2 Simulation details

We have used Lennard-Jones, FENE spring potential and a three body bond bending potential to mimic excluded volume (EV), bond stretching between two successive monomers, and stiffness of the chain, respectively, and applied a constant external force \( F_{ext} = 5.0 \) at the pore in the translocation direction. We have used the BD scheme to study the heterogeneous polymer translocation problem. The details of the BD methods are the same as in chapter 1 (Sec. 1.3). Initially we keep the elastic spring constant \( k_F \) to be the same throughout the chain and choose the bending stiffness \( \kappa_b = 0 \) and 16.0 for the fully flexible and the stiff segments, respectively. Later we show that by making the elastic potential for the relatively more flexible part weaker one can reverse the relative friction on the chain segments which results in novel waiting time distributions serving as the fingerprint of the structural motifs translocating through the pore. All the physical quantities presented here are measured in terms of LJ reduced units.
Figure 3.1: Blob model of a polymer chain of chain length \(N = 24\) and segmental length \(m = 4\). Each repeated unit can be considered as a single blob of length \(\xi \sim m^\beta\). Please see the text below.

### 3.3 Results and discussions

#### 3.3.1 Blobsize and scaling

We consider heterogeneous chains consisting of alternate symmetric \((m = n)\) periodic blocks of stiff and flexible segments of \(m\) monomers so that the block-length is \(2m\) \((m = 1,2,3,4)\) as shown in Fig. 3.1. First we investigate how the alternate stiff and flexible segments of equal length affect the end-to-end distance \(\langle R_N(m) \rangle\) and the MFPT as a function of the periodic block-length (Fig. 3.1), compared to a homopolymer of equal contour length \(N\). To a first approximation one can think of this chain as a flexible chain of \(N/2m\) segments, of certain blob size \(\xi\). The blob size \(\xi\) in general will be a function of the block-length and bending rigidity of the flexible and stiff segments. For our particular choice of bending...
rigidity for the flexible ($\kappa_b = 0$) and stiff ($\kappa_b = 16$) segments from simulation results for $N = 64 - 256$ we find an expected power law scaling $\xi \sim m^\beta$ where $\beta = 0.87$ (Fig. 3.2).

Figure 3.2: (a) Log-log plot of blob-size $\langle \xi \rangle$ as a function of $m$ for $N = 64$ (black plus), $N = 128$ (violet cross) and $N = 256$ (orange right-triangle). The solid line represents $\langle \xi \rangle \sim m^{0.87}$. Insets: (i) log-log plot of $\langle R_N \rangle$ as a function of $N$ for different $m$, (ii) collapse of $\langle R_N \rangle/m^{0.12} \sim N^\nu$ on the same master plot. (b) Log-log plot of $\langle \tau \rangle$ as a function of $N$ for different $m$. Inset: scaling and collapse of $\langle \tau \rangle/m^{0.09} \sim N^{2\nu}$.

Obviously the exponent $\beta$ is non-universal as it depends on $\kappa_b$ and $k_F$, but the universal aspects of the entire chain can be regained through scaling with $\xi$ as shown in Fig. 3.2. The conformation statistics of this basic unit $\xi$ controls both the conformation and transloca-
tion properties of the entire chain as follows. We can write \( \langle R_N \rangle \equiv \langle \sqrt{R_N^2} \rangle \sim \langle \xi \rangle (N/2m)\nu \sim m^\beta N^\nu /m^\nu \), where \( \nu \) is the Flory exponent. This implies \( \langle R_N \rangle /N^\nu \sim m^{\beta-\nu} = m^{0.12} \) (where \( \nu = 0.75 \) is the Flory exponent in 2D). Simulation data in the insets of Fig. 3.2(a) confirms our scaling prediction. Likewise, we show that the MFPT \( \langle \tau \rangle /N^{2\nu} \sim m^{0.09} \) (Fig. 3.2(b)). For small \( N \) it has been found earlier that \( \langle \tau \rangle \sim \langle R_N \rangle /N^{-\nu} \sim N^{2\nu} \) [58]. Therefore, as expected by proper coarse graining by the elemental block we get back the results for the fully flexible chain. We now show how characteristics of translocation are affected by the chain heterogeneity.

### 3.3.2 Effect of chain heterogeneity on translocation

In presenting the results we use the notation \((F_mS_n)_p/(S_mF_n)_p \) to denote \( p \) blocks of an ordered flexible/stiff and stiff/flexible segments of length \( m \) and \( n \), respectively \((N = (m + n)p) \) and that the flexible/stiff segment enters the pore first. Fig. 3.3 and Fig. 3.4 reveal quite a few novel results that we explain using TP theory. For small block-length the order in which the chain enters the pore (either stiff or flexible segment) neither make a big difference in the shape of the histogram (Fig. 3.3(a)) nor in the MFPT (Fig. 3.4). For larger block lengths the difference between the histograms for \( S_mF_m \) and \( F_mS_m \) are quite clear and the dependence of \( \tau \) on \( m \) are also different as seen in Fig. 3.4. For the case when the stiff portion enters the pore first, the MFPT monotonically increases but in the other case it shows a maximum (Fig. 3.4).
Figure 3.3: Histograms of first passage time for chain length $N = 128$ and segmental length (a) $m = 4$, (b) $m = 16$, (c) $m = 32$, and (d) $m = 64$. The dotted/solid lines represent the flexible ($F_mS_m$)/stiff ($S_mF_m$) segment entering the pore first. For larger block size the effect of order of entry is clearly visible.

We now explain this in terms of our recent analysis of the translocation of semiflexible chain using TP theory where we showed that a stiffer chain takes a longer time to translocate [68, 111, 121]. When the block lengths are small, TP gets intermittently hindered as the tension propagates through alternate stiff and flexible regions. For longer blocks tension can propagate more effectively unhindered for a longer time. Therefore, when a long stiff segment enters the pore first it increases the MFPT. But, when a long flexible segment enters the pore first it decreases the MFPT. This results a maximum in the $\langle \tau \rangle / \langle \tau \rangle_0$ vs. $m$ curve.
for the FS orientation. The difference of MFPT for $S_m F_m$ and $F_m S_m$ becomes maximum when $m = N/2$. For relatively longer block lengths it makes a big difference in MFPT.

![Figure 3.4](image)

Figure 3.4: MFPT (scaled by the MFPT of respective flexible homopolymer) for chains $F_m S_m$ and $S_m F_m$ as a function of $m/N$ for chains $N = 64$ (green diamonds) and $N = 128$ (blue up-triangles). The open/closed symbols correspond to flexible/stiff segment entering the pore first. The inset shows the ratio of the MFPT for $SF$ to $FS$ orientation. The nanopore is capable of differentiating if a flexible (F) block or a stiff (S) block entered the pore first.

### 3.3.3 Waiting time distribution

As we defined in chapter 2 (Eq. 2.5), a sum of the waiting time for all monomers is equal to the MFPT. The effect of TP in stiff and flexible parts becomes most visible in the waiting time distribution of the individual monomers of the chain as shown in Fig. 3.5. We notice that the envelopes for the corresponding homopolymers for a fully flexible chain

58
(κ_b = 0, solid orange line) and for the stiffer chain (κ_b = 16, solid green line), respectively serve as bounds for the heterogeneous chains [122]. As explained in chapter 2, the TP time corresponds to the maximum of these curves and shifts toward a lower s value for a stiffer chain. Bearing this in mind we can reconcile the fringe pattern in the light of the TP theory.

Figure 3.5: Waiting time distribution for a N = 128 chain with the block-length (a) 16 and (b) 32. Azure (open circles) and Blue (filled squares) correspond to the flexible and stiff segments when the flexible segment enters the pore first (F_mS_m). Magenta (open circles) and Red (filled squares) correspond to the flexible and stiff segments when the stiff segment enters the pore first (S_mF_m). The solid green and orange lines correspond to the waiting time distributions for the corresponding stiff (κ_b = 16.0) and fully flexible (κ_b = 0.0) homopolymers, respectively.

The pattern has the following features: (i) The number of fringes is equal to the number of blocks. This is because on an average stiffer portions take longer time to translocate.
(ii) The fringes for $S_m F_m$ and $F_m S_m$ are out of phase for the same reason. (iii) The chain heterogeneity affects the waiting distribution most at an early time; beyond the largest TP time (i.e., the peak position of the envelope for $\kappa_b = 0$) the waiting time of the individual monomers (excepting which are at the border separating the stiff and flexible segments) becomes identical to that of the corresponding homogeneous chain. This again exemplifies to analyze the driven translocation as a pre and post TP events. Please note that the maxima of the $W(s)$ for the heterogeneous chain lie in between the maxima for the corresponding homogeneous cases.

3.3.4 Effect of friction and driving force

In Fig. 3.5 we chose a value of the solvent friction associated to each monomer $\gamma = 0.7$ for which we find that a stiffer segment translocates slower through the pore. We now discuss how a variation of the solvent friction will affect this conclusion. We first show that the MFPT of a homopolymer of certain length exhibits a crossover as one varies the solvent viscosity (Fig. 3.6(a)). It is only for extremely small $\gamma$ (quasi-static limit) the stiffer segment translocates faster as studied in [74]. We also have reproduced the result for a particular set of parameters (black line in Fig. 3.6(b)). We have shown 3D (instead of 2D) data in Fig. 6(b) and (c) only for better resolution. This crossover effect can be explained using Sakaue’s tension propagation (TP) theory [39]. When we use a larger value of $\gamma$ (implying stiffer segment translocates slower) and/or a bias $F$ the IMFPT changes qualitatively (Fig. 3.6(b)),
which is more prominently seen in the waiting time distribution of the individual monomers (Fig 3.6(c)).

Figure 3.6: (a) The MFPT for flexible and semiflexible homopolymers of length $N = 64$ as a function of solvent-monomer friction $\gamma$. (b) The IMFPT and (c) the waiting time distribution as a function of $s$-coordinate for a chain ($N = 70$) in 3D with four stiff segments ($\kappa_b = 100$) each of length ($m = 10$) and five flexible segments ($\kappa_b = 0$) each of length ($n = 6$) provided that (for (b) and (c)) the first flexible segment is already in the trans side at $t = 0$.

Using formulae for solvent friction from the bulk $\Gamma_{\text{solv}} = \gamma N^\nu$ and pore friction $\Gamma_{\text{pore}} \sim \frac{A_{\text{pore}}}{d^{1-\nu}} + p\gamma$ which have been discussed in Ref. [66, 67] we have checked that $\gamma = 0.7$ and $\gamma = 0.1$ (for the chain lengths used in our simulation) correspond to solvent dominated and pore friction dominated regimes, respectively. At high $\Gamma_{\text{solv}}$, de-Haan and Slater showed that
the MFPT increases linearly with $\gamma$ [51] for a fully flexible chain. We see the same trend to be valid also for semiflexible chains, albeit beyond a critical value (Fig. 3.6(a)). But at low $\Gamma_{solv}$, the dependence of MFPT on $\gamma$ becomes non-monotonic and it exhibits a minimum for $\gamma = \gamma_m$ [123]. This $\gamma_m$ marks the onset of change in the qualitative behavior of IMFPT or the waiting time distribution of the individual monomers.

In quasi-static limit, significantly larger local entropic barrier of a “coil” segment causes longer residence time. This effect is reflected as steps in the IMFPT (Fig. 3.6(b)) and peaks in the waiting time distribution (Fig. 3.6(c)). But for the non-equilibrium situation, when the stiffer segment enters the pore, tension propagates faster along the chain backbone [39,68] and more monomers in the cis side set in motion. For large solvent friction this may produce larger viscous drag dominating over local entropic barrier resulting in the stiffer segments translocating slower than the flexible segment. In this case the peaks in the waiting time distribution disappear (red color in Fig. 3.6(c)). Accordingly, one sees qualitative changes in the corresponding IMFPT (red color in Fig. 3.6(b)). Therefore, the relative fast/slow translocation of rod /coil segments through the nanopore depends on the relative values of pore friction, solvent friction, and applied bias.

### 3.3.5 Heterogeneous chain with a variable spring constant

Finally we have extended these studies to see the consequences of allowing the elastic potential between the successive beads to be different in each block. This situation may occur
Fig. 3.7 shows the various combination of the spring constants $k_F$ for the heterogeneous chain. The first four graphs Fig. 3.7(a)-(d) correspond to the waiting time distribution for the chain with equal number of monomers in each of the flexible and stiff segments. Fig. 3.7a is the graph where all the $F$ and $S$ segments have the same $k_F = 100$ qualitatively similar to Fig. 3.5. In Figs. 3.7(a)-(d) one can see the effect of reduced value of $k_F$ for the flexible portion only. Figs. 3.7(e)-(f) represent the waiting time distributions for the unequal length of the flexible and stiff segments. The flexible segment, being shorter, loses the conformational entropic height but the contribution of the FENE force in the direction of translocation is enhanced. We can see the effect of this enhancement in the increased back and forth motion (low frequency phonons of larger amplitude to softer bonds) of the chain towards the translocation direction. The smaller is the value of $k_F$ the larger will be the amplitude of the phonons mode which results in a longer translocation time. Therefore, when we reduce the strength of the FENE interaction for the coil, the coil translocates slower and we get the waiting time distribution picture inverted for the stiff and flexible segments as seen from a comparison of Fig. 3.7(a) to Fig. 3.7(d). This will be most prominent if the stiff segments were chosen as rigid rods.

Fig. 3.7(c)-(f) show the end monomer of each semiflexible segment has a larger waiting time. This indicates a larger barrier height for the flexible segments. Once the barrier is overcome by the first monomer of the flexible segment, all the following monomers of the flexible segments pass through the pore faster. The end monomer of the flexible segment
and the first monomer of the stiff segment have the lowest waiting time which means that they have negligible barrier to overcome. Furthermore, a visual comparison of Fig. 3.5 and Fig. 3.7 shows that the origin of the details of the waiting time distributions possibly be differentiated by a spectral decomposition analysis of the waiting time distribution.

Figure 3.7: The waiting time distribution as a function of \( s \)-coordinate for a chain \((N = 128)\) with variable \( k_F \) and stiff-flexible segmental length ratio \((m/n)\). The bending stiffness \( \kappa_b \) for flexible (red circles) and stiff (blue squares) segments are 0 and 16, respectively. The elastic stiffness \((k_F)\) is 100 for stiff segments [(a)-(f)]. For flexible segments (a) \( k_F = 100 \) (b) \( k_F = 40 \) (c) \( k_F = 10 \) (d) \( k_F = 5 \) (e) \( k_F = 5 \) and (f) \( k_F = 5 \). The stiff and flexible segments are of equal length except in (e) \( m: n = 5: 3 \) and (f) \( m: n = 3: 1 \).
3.4 Conclusion

In this chapter, we have demonstrated how a nanopore can sense structural heterogeneity of a bio-polymer driven through a nanopore. Not only do monomers belonging to the flexible and stiff part exhibit different waiting time distributions, we have also demonstrated how a nanopore can sense which end of the polymer enters the pore first. Translating this information for a dsDNA will imply that the nanopore can differentiate the 3-5 or 5-3 ends of a translocating DNA. We have explained these results using the concepts of TP theory. We have clearly demonstrated how the fluid viscosity and an external bias can affect the relative speed of the stiff and flexible segments. Furthermore, unlike previously reported studies [74] we, for the first time, analyzed the interplay of the effects of polymer heterogeneity caused by the variation of elastic and bending stiffness. We have demonstrated that softer elastic bonds raise the MFPT [124]. Therefore, an increase in waiting time for a stiff segment can be compensated by the waiting time for a flexible segment but having softer elastic bonds. This observation can be exploited to tune to control the passage of polymers through NP. It is interesting to note from Fig. 3.7 that the variation in waiting time distribution arising out of the bending stiffness variation and bond length variation can be differentiated. Therefore, these patterns can serve as references to characterize structural heterogeneity of an unknown polymer translocating through a nanopore. We hope the results reported in this chapter will be helpful in deciphering translocating characteristic of bio-polymers observed experimentally.
CHAPTER 4
EFFECT OF SOLVENT VISCOSITY ON TRANSLOCATION
OF SEMIFLEXIBLE POLYMER

4.1 Introduction

Polymer translocation in equilibrium and non-equilibrium limit have been studied intensively [1, 5–7]. Undriven (or weakly driven) translocation in the given condition of narrow pore and low solvent viscosity is considered as a quasi-static system [74]. For a given pore, onset of solvent viscosity from low to high value changes the state of system from quasi-static to non-equilibrium. It is known that the translocation dynamics of a polymer through a nanopore varies significantly in these two limits. This chapter deals with a comprehensive study about the influence of solvent viscosity on translocation dynamics.

In the equilibrium system, monomers on each side of the wall can be treated as Brownian particles [57] and the relaxation time of monomers are decoupled to the translocation time. Such process can be solved analytically by one dimensional (so called, translocation coordinate $s$) entropic barrier crossing method [38]. The driven translocation of polymer through a NP is a non-equilibrium process [62,63] which is characterized by viscous drag on the chain backbone. Such process can be explained by Sakaue’s tension propagation (TP) theory [39]. Ikonen et al. [66] introduced BDTP theory by implementing the TP concept in
Brownian dynamics equation to study the driven translocation of finite chains. In chapter 2, we verified this theory numerically for semiflexible chain by observing ‘last-monomer dynamics’ [68]. Applying parameters which are relevant to non-equilibrium system, we found that the translocation of a semiflexible chain is slower than a flexible chain. Later, Luo’s group [84, 125] also found that a semiflexible chain translocates slower than flexible chain. de Haan and Slater, on their work [74], showed that a flexible segment of ‘rod-coil’ polymer takes longer than a stiffer segment to translocate through a nanopore in quasi-static limit. However, we, recently, carried out simulation of heterogeneous chain (flexible/semiflexible) in a non-equilibrium system and observed faster translocation of flexible segments [85]. Using simulation data, we also showed that the order of translocation speed of flexible and semiflexible chain at low and high viscosity is opposite which simply explains the crossover when going from very low to high solvent viscosity.

The solvent viscosity is an important factor controlling a translocation dynamics. However, only few studies (experiment [126, 127] and theory [51, 128, 129]) have been carried out in this direction. Most of the works that studied the effect of solvent viscosity on translocation dynamics showed that the MFPT of homogeneous flexible chain varies linearly with solvent viscosity in the high viscosity regime. de Haan and Slater [51] showed that the MFPT is independent of solvent viscosity at low viscosity below a threshold. Luo et al. [61] used the high and low solvent viscosity for a driven translocation of a homogeneous flexible chain to explain slow and first translocation. But, their selection of high and low viscosities does not represent the low viscosity regime. Some other works [128, 129] also present a
brief discussion on the influence of solvent viscosity on PT. However, none of the works has been focused on this topic. Therefore, it demands a detailed study of driven translocation of a semiflexible chain through a nanopore in the wide range of very low to high viscosity regime. In this chapter, we will present the effect of solvent viscosity on driven translocation of flexible and semiflexible chain. Unlike unbiased translocation, the MFPT for a driven translocation at very low solvent viscosity shows non-monotonic dependence on viscosity exhibiting a minimum at a certain value of $\gamma (\sim \gamma_m)$. We will discuss how a more flexible chain translocates faster at high viscosity and a stiffer in the low viscosity regime. We show that the translocation, at high viscosity, is mainly controlled by a viscous drag on the chain backbone. But, at the low viscosity, the translocation is determined by the combined effect of conformational entropy, pore friction, osmotic pressure from the trans side and an applied external bias. In Sec 4.2, we will discuss the simulation model and input parameters. We will present the results of simulation in different sub-sections of Sec 4.3. Finally, we will present the conclusion in Sec 4.4.

4.2 Simulation details

We have used a bead spring model (Fig. 1.3) of a polymer as described in chapter 1. In this chapter, we have simulated the translocation of a homopolymer of length $N = 64$ for different chain rigidity. The effect of chain rigidity has been observed by changing the bending rigidity parameter $\kappa_b$ in Eq. 1.13. We also observe the effect of pore friction on the
chain by changing the pore diameter. One dimensional arrangement of particles of size same
as that of monomer represents a wall. Two middle particles of the sequence has been removed
from the wall to create a pore. We vary the pore diameter by changing the size of the wall
particles. We model the polymer solution with the effective solvent viscosity as a variable
parameter. The effective viscosity of the solvent is represented by the friction coefficient
($\gamma$ in Eq. 1.16) between the polymer and solvent, i.e., $\eta_{\text{effective}} = \gamma$. The actual viscosity
of the solvent for biopolymers (e.g. DNA, proteins) is related to the effective viscosity as,
$\eta = \eta_{\text{effective}}^* \sqrt{m\epsilon/(6\pi\sigma^2)}$. Using $m \sim 321$ amu, $\epsilon \sim k_B T$ at $T = 300$K, and $\sigma \sim 0.34$nm,
we can relate the actual viscosity with the effective viscosity as $\eta \sim 1.5\eta_{\text{effective}}^*$ kg.m$^{-1}$s$^{-1}$
(actual viscosity for water at room temperature is $\eta_{\text{water}} \sim 10^{-3}$ kg.m$^{-1}$s$^{-1}$ [130]). We have
studied the translocation dynamics at different solvent frictions from $\gamma = 0.005\sqrt{m\epsilon/\sigma}$ up
to $\gamma = 4\sqrt{m\epsilon/\sigma}$. To study the translocation in the quasi-static state to non-equilibrium
state, we have applied weak to intermediate ($F = 1\epsilon/\sigma$ to $10\epsilon/\sigma$) external driving force at
the pore. The simulation has been carried out in a constant temperature ($T = 1.2\epsilon/k_B$)
heat bath. The cut-off distances for LJ and FENE interactions are chosen as $r_c = 2^{1/6}\sigma$
and $R_0 = 1.5\sigma$, respectively. The strengths of LJ and FENE interaction are fixed at $\epsilon$ and
$k = 30\epsilon/\sigma^2$, respectively. We have used the various chain with strength of the bending
potential $\kappa_b$ ranging from $0\epsilon$ to $100\epsilon$. 

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4.3 Results and discussions

We have presented dependence of MFPT on various factors in the low and high viscosity regimes. All the data shown in this article represent the results obtained from Langevin dynamics simulation in 2D. All averages are taken by simulation of at least 2000 independent runs. We have presented results of simulation in terms of reduced LJ-units.

4.3.1 Viscosity dependence of MFPT

The effect of solvent viscosity on a flexible chain translocating through a nanopore depends on the bias condition. In unbiased case, the translocation time remains independent of solvent viscosity up to a ‘threshold viscosity’ but increases linearly [51] beyond the threshold. Under the applied external bias, it follows the same trend at high viscosity [128,129]. But, we find the MFPT changes non-monotonically at low viscosity exhibiting a minimum between two regimes (high and low viscosity). We observe this effect for a flexible chain under various external bias at the pore within the intermediate force regime (i.e. $k_B T/a \leq F \ll (k_B T/a) N^\nu$). Fig. 4.1(a) shows the effect of external bias on translocation dynamics of a flexible chain over a range (from low to high) of solvent friction $\gamma$. At high solvent viscosity, as previously adopted results [1, 5–7], MFPT varies according to $< \tau > \sim \gamma/F^{\delta}$, where $\delta$ is an exponent of the order of unity.
Figure 4.1: (Color online)(a) The log-log plot of MFPT scaled by external bias as a function of solvent viscosity for various applied external bias ($F$ ranges from 2 to 6) for a fully flexible chain ($\kappa_b = 0$) of length $N = 64$. (b) MFPT scaled by $N^{2\nu}$ (where, Flory exponent $\nu_{2D} = 0.75$) as a function of solvent viscosity for three different flexible ($\kappa_b = 0$) chains of lengths ($N = 32, 64, \& 128$) driven by external bias $F = 5$.

But, in the low viscosity regime, the applied bias does not follow the same scaling criteria rather shows a non-monotonic dependence. Our simulation data show that the MFPT increases as $\gamma$ decreases in the low viscosity regime exhibiting a minimum at $\gamma = \gamma_m$. The value of $\gamma_m$ weakly depends on the applied bias. This weak variation of MFPT with $\gamma$ in this regime is reflected as a peak (which is larger for stronger bias) in the waiting
time distribution near the rear end of the chain. Detailed explanation will be presented in Sec. 4.3.2. Fig. 4.1(b) shows the variation of MFPT for flexible chain of various lengths as a function of solvent friction. We find the $\gamma_m$ shifted towards its smaller value for longer chain. Which is similar to the threshold shifts towards its minimum value for longer chain in Ref. [51], for an unbiased translocation of fully flexible chain. This effect, for a longer chain, can be explained as the solvent friction from the bulk in the cis side dominates over the pore friction earlier when the solvent viscosity increases from its smallest value. As mentioned in section 4.1, at high viscosity, the dynamics of a translocating chain can be described by Sakaue’s [39] tension propagation (TP) theory. But, at low viscosity, the dynamics is dominated by the pore friction and can be described by ‘entropic barrier crossing’. For unbiased translocation, the system goes to its equilibrium state at $\gamma_m$ (a threshold) below which the MFPT remains almost independent of $\gamma$. Entropy, frictional force due to pore-friction and crowding effect of translocated chain-segments in the trans side control the translocation dynamics.

We also observe that the chain stiffness affect the dependence of $\langle \tau \rangle$ on the solvent viscosity. At high viscosity, we find larger slope of the MFPT vs. $\gamma$ graph for a stiffer chain. At low viscosity, we find the non-monotonic variation of MFPT against $\gamma$ which exhibits the minimum at lower value of $\gamma$ (i.e. $\gamma_m^{\text{flexible}} > \gamma_m^{\text{stiff}}$). Since the slopes of $\tau - \gamma$ curve for a flexible and a semiflexible chains are different, they cross each other at a certain point which implies that at viscosities lower than the cross-point [74], stiffer chain translocates faster while above the cross-point the flexible chain translocates faster [85]. In weakly biased
condition, smaller the value of solvent friction, the closer is the system towards its equilibrium state.

Figure 4.2: (Color online) The effect of solvent friction for translocating polymers of length (a) $N = 32$, (b) $N = 64$ and (c) $N = 128$ of different flexibilities ($\kappa_b = 0, 16 & 100$) driven by force $F = 2$.

Translocation dynamics of a polymer in the equilibrium state can be described as an entropic barrier crossing problem. This regime is narrower for stiffer chain because of the smaller entropic barrier height. The entropic barrier for a rodlike polymer is negligible, therefore we do not expect the non-monotonic dependence of MFPT on $\gamma$. From the simulation data (Fig. 4.2), we find the regime where a stiffer chain translocates faster than a flexible chain is very narrow. We also noticed that the pore friction dominated regime
where the entropic effect dominates is wider for shorter chains. This regime disappears for longer chains (Fig. 4.2(c)) and the viscous drag dominates over the pore friction. In most of the biological phenomena, the polymers being very long comparing to the pore size, the viscous drag determines the translocation rate and therefore stiffer polymer always translocates slower.

Figure 4.3: Histograms of the first passage time as a function of chain rigidity at (a) $\gamma = 0.01$ and (b) $\gamma = 0.1$ when driven by a small force $F = 2$.

Histograms of first passage time clearly show a crossover when the solvent friction increases from very low value. In Fig. 4.3, we have plotted the histogram of the first passage time as a function of $\gamma$ for a driving force $F = 2$ keeping the pore diameter $P_d = 2.0$. The
order of the peak value for flexible and stiff chain becomes opposite when \( \gamma \) increases from 0.001 to 0.1.

### 4.3.2 Waiting time distribution

Waiting time distribution shows the clear picture of the translocation process. We have shown the data for waiting time distribution obtained from the simulation of a chain of length \( N = 64 \) as a function of stiffness at three different values of \( \gamma \) which provides a better understanding of the crossover effect (Fig. 4.4(a), (b) and (c)). In high viscosity regime, the non-monotonic curve of waiting time distribution has two stages representing the pre- and post- TP processes separated by a peak which corresponds to the tension propagation time [40, 66]. For a stiffer chain, we observe a flat structure on the waiting time distribution near the position of tension propagation. The flat peak lasts for length of the order of persistence length of the chain as expected. At low viscosity, tension propagates on the chain backbone very fast therefore we can not see the peak as in the high viscosity regime. However, we see a peak at the rear end of waiting time distribution. This peak is due to the combined effect of two resisting forces: pore friction and osmotic pressure from trans side [131], both of which are effective in the low viscosity regime.

The pore friction is determined by its geometry and the velocity of monomers inside the pore. The end-monomers of the chain have significantly larger velocity at the pore and hence experience larger pore friction. On increasing the applied bias, the monomer-velocity
at the pore increases which enhances the resisting force due to pore friction. The frictional force due to the pore-friction is [131]:

\[
 f_p \sim \frac{\gamma_p f(t)}{\gamma R(t)} \tag{4.1}
\]

where \( f(t) \) is the total effective force at the pore, \( R(t) \) is the length of tensed segment of the chain in the cis side at time \( t \) and \( \gamma_p \) is effective pore friction.

Figure 4.4: The waiting time distribution as a function of bending rigidity \( \kappa_b \) for the various solvent viscosities (a) \( \gamma = 0.01 \), (b) \( \gamma = 0.1 \) and (c) \( \gamma = 0.2 \) when a chain of length \( N = 64 \) is driven by weak force \( F = 2 \)

The pore friction can be expressed as \( \gamma_p = \frac{A_{pore}}{(P_d - 1)} + p\gamma \) which has been discussed in Ref. [66]. From the above Eq. 4.1, we know \( f_p \propto f(t) \) which is mainly proportional to the external bias \( F \). This implies that the peak on the waiting time distribution becomes larger.
when applied bias is stronger as shown in Fig. 4.5(a). For a stiffer chain the value of $R(t)$ decrease very slowly and since $f_p \propto \frac{1}{R(t)}$, the peak decreases slowly as stiffness of the chain increases.

Figure 4.5: The waiting time distribution for a flexible chain $\kappa_b = 0$ of length $N = 64$ (a) at low solvent friction $\gamma = 0.01$ as a function of external bias in the intermediate force range, (b) as a function of solvent friction $\gamma$ when the chain is driven by a constant force $F = 5$.

The osmotic pressure also resists the translocation process as the number of monomers in the trans side creates crowding in the vicinity of the pore. The force due to this crowding depends on the concentration of monomers in the trans side. We assume this concentration increases when the size of the globule becomes greater or equal to the radius of gyration of the chain. Fig. 4.6 supports our assumption for a flexible chain. For a stiffer chain the concentration of monomers in the trans side becomes smaller. Therefore, the peak in the waiting time distribution becomes smaller and completely disappears for stiff chain ($l_p \geq L$). For the unbiased translocation, we do not expect such a peak in the waiting time distribution because effect of both of the factors are minimized. The height of this peak also decreases
(Fig. 4.5(b)) when the solvent viscosity increases. From Eq. 4.1, \( f_p \) is significant for very short \( R(t) \) (i.e. at the end of the chain), for larger \( f(t) \) (i.e. strong applied bias) and at low \( \gamma \). Since \( f_p \propto \frac{\gamma_r}{\gamma} \), we find the peak decreases on increasing the value of \( \gamma \) and becomes independent of \( \gamma \) when \( \gamma \sim \gamma_r \). For larger value of \( \gamma \) the viscous drag on the chain backbone in the cis compartment increases significantly which dominates over the combined effect of pore friction and crowding.

![](image)

Figure 4.6: The force \( f_x^{\text{trans}} \) as a function of monomer index. \( f_x^{\text{trans}} \) is the total force experienced by a monomer at the pore in the direction of translocation which is exerted by the monomers that are already translocated in the trans side.

4.3.3 Effect of pore size

We study the effect of solvent friction on the translocation of polymer through nanopore of different diameter. The minima of the curve shifts towards its larger value when the pore diameter \( (P_d) \) decreases as shown in Fig. 4.7(a) and (b). Therefore, the crossover
effect of MFPT (discussed in Sec. 4.3.1) for flexible and semiflexible chain is distinct when
the pore becomes narrower.

Figure 4.7: The MFPT $\langle \tau \rangle$ vs solvent friction as function of chain rigidity $\kappa_b = 0, 16 \& 100$ of chain
of length $N = 64$ translocating through a nanopore of diameter (a) $P_d = 1.6$ and (b) $P_d = 2.0$.

When the pore becomes narrower, the pore friction dominates the system up to a
larger value of $\gamma$. In Fig. 4.8(a) and (b), we observe the MFPT of flexible and semiflexible
chain translocating through three different pore diameters ($P_d = 2.0, 1.6$ and $1.4$). We find
the translocation dynamics is affected by size of the pore only in the low $\gamma$ regime, where the
pore friction dominates the system. The effect of pore-diameter on translocation decreases
gradually when the chain stiffness increases. This is mainly due to the reduced barrier height
for stiffer chain. The pore diameter also responds to the bending stiffness of the chain.
Figure 4.8: The MFPT $\langle \tau \rangle$ vs solvent friction as function of pore diameter $P_d = 1.4, 1.6$ and 2.0 for chain stiffness (a) $\kappa_b = 0$ and (b) $\kappa_b = 16$ of chain of length $N = 64$.

4.4 Conclusion

We explore the viscosity dependence of MFPT for a driven translocation of a polymer by using LD simulation in 2D. We compare the translocation speed for a flexible and semiflexible chain in the low to high solvent viscosity regimes. In the high viscosity regime, the MFPT varies linearly with solvent viscosity for all flexibilities of the chain, but the slope of the linearity depends on $\kappa_b$. We find a stiffer chain translocates faster in the low viscosity regime while the order of speed of translocation is reversed in the high viscosity regimes. In particular, we demonstrate how the probing of chain-stiffness using nanopore sensing depends on solvent viscosity. At very low viscosity, the MFPT varies non-monotonically with
the solvent viscosity exhibiting a minimum at a particular value of solvent viscosity. The value of this viscosity depends on different factors such as: chain length, chain stiffness, pore diameter and applied bias. In this regime of viscosity, the driven translocation of more flexible chain is found to be affected more by frictional force at the pore and osmotic pressure caused by the translocated monomers.
CHAPTER 5
TRANSLOCATION OF A SEMIFLEXIBLE POLYMER THROUGH A NANOPORE IN PRESENCE OF ATTRACTIVE BINDING PARTICLES

5.1 Introduction

Translocation of biomolecules from the cis to the trans compartment often requires a driving force. This driven translocation of bio-molecules under the influence of external forces has been studied extensively experimentally and using various theoretical and computational methods [1, 5–7]. However, it is well known in molecular biology that certain transportation of biomolecules occurs without involvement of molecular motors [132, 133]. Examples include translocation of polymers in presence of binding particles (BPs) (e.g., Chaperones) [37, 75–84, 109, 133, 134] and the translocation of chains due to asymmetric solvent condition, some of which has been studied recently using CG models [102, 135, 136].

Simon, Peskin, and Oster (SPO) [75], while searching for a generic but a faster mechanism than simple diffusion, used the Brownian ratchet (BR) mechanism [137] to interpret the translocation of proteins, where the BPs present in the trans compartment rectify the pure diffusive motion along the translocation direction. The difference between simple diffusion and directed diffusion can be understood quite easily in the context of one dimensional (1D) diffusion along a line. In a medium characterized by the monomer friction $\Gamma$, the diffusion
time of the chain of the order of its own contour length \( L = (N - 1)\sigma \simeq N\sigma \) \((N\) and \(\sigma\) are the number and size of the monomeric building blocks of the chain, respectively) is given by

\[ \tau_{\text{chain}} = \frac{L^2}{2D_{\text{chain}}}, \]

where \( D_{\text{chain}} = \frac{k_B T}{(N \Gamma)} \) is the diffusion coefficient of the chain, and \( k_B \) and \( T \) are the Boltzmann constant and temperature, respectively. In the simplified 1D model, SPO introduced equally spaced \( M \) binding sites along the chain (so that the separation between successive binding sites is \( \delta = \frac{L\sigma}{M} \)) with the stipulation that the binding particles attach irreversibly once and for all at these sites as soon as these binding sites are available at the \textit{trans} side immediately after translocation [75]. SPO further assumed that once the particles are bound to the specific sites of the chain, the \textit{trans} segment of the chain cannot go back to the \textit{cis} side. For this directed translocation, it is then easy to see that the efficiency for this directed diffusion rectified by ratchet increases \( M \)-fold and

\[ \tau_{\text{ratchet}} = \frac{M\delta^2}{2D_{\text{chain}}} = \frac{\tau_{\text{chain}}}{M}. \]  

However, there are several assumptions in this derivation by SPO, namely the 1D motion of a rod, ideal ratchet condition, etc. which in reality are not met. For example, biopolymers are semiflexible and not strictly rods, translocation of a rod thorough a nanopore in most cases is not a 1D diffusion, the binding and unbinding of particles depend on the interaction strength between the particles and the binding sites, which in turn can depend on the surrounding solvent conditions, and the ready availability of the binding particles, which may be kinetically hindered. However, the simplicity of this idea has resulted in exploring how these factors affect a realistic translocation process [76]-[102] through a nanopore. Zandi \textit{et al.} [76], using BD simulations for short 1D rigid rods, found the role of BPs is not
only limited to the ratchet mechanism but also provides a pulling force in the direction of translocation which makes the actual translocation process faster than the ideal BR process. Yu et al. [83] have repeated the same argument for longer 1D compressible rods. The effects of size mismatch between BPs and binding sites [77–81, 109], sequence-dependent binding affinity [79–81], and some aspects of chain flexibility have also been studied [84].

The asymmetry introduced by the presence of BPs at the trans compartment introduces several new features of single file translocation across the pore. In this study we consider translocation of a semiflexible chain facilitated by attractive BPs present at the trans compartment. We demonstrate the similarity as well as the differences of this process with that of the well studied problem of driven translocation through a nanopore where the force is present only inside the pore [1,5–7]. However, unlike the case of driven translocation of a semiflexible chain [68, 111], in addition to the chain flexibility, there are other factors, e.g., concentration and strength of the attractive binding particles affect the translocation process in a non-trivial way, and much more, the inter-dependency of the various factors is subtle. Despite these additional complications, we have been able to make a thorough analysis of our simulation results, and we came up with algebraic equations that we believe will promote further theoretical work. Before we go to the subsequent sections, we first show some snapshots produced from the coordinates of the chain and the particles provide a picture (Fig. 5.1) of how the ratcheting mechanism is affected by chain flexibility and concentration of BPs. In Sec. 5.2 we briefly discuss the model and the simulation techniques.
Figure 5.1: Snapshots of translocation from BD simulations for a fully flexible (left column) and very stiff chain (right column) for three different values of binding particle (BP) densities; (a), (c), and (e) correspond to flexible chains ($\kappa = 0$) and for $\rho = 1\%$, 5\% and 10\%, respectively, and (b), (d), and (f) correspond to a stiff chain ($\kappa = 256$) for the same densities. In each case the length of the translocated segments are the same. The cyan, red, and blue circles represent BPs, chain monomers, and wall particles, respectively.
The results and their interpretation are presented in Sec. 5.3. In Sec. 5.4 we provide a broader perspective of the problem and suggest generalization of the recently proposed scaling ansatz [67] to include other factors that affect the translocation as studied in this chapter.

5.2 Simulation details

We have used the bead spring model [42] of a polymer chain with excluded volume, spring, and bending potentials as follows. The excluded volume interaction $U_{\text{LJ}}$ between any two monomers is given by Eq. 1.14 with cut-off distance $r_c = 2^{1/6}\sigma$. The connectivity between neighboring monomers is modeled as a Finite Extension Nonlinear Elastic (FENE) spring with $U_{\text{FENE}}$ (Eq. 1.12). The chain stiffness is introduced by adding an angle dependent three body interaction $U_{\text{bend}}$ (Eq. 1.13) term between successive bonds as shown in Fig. 1.3. The strength of the interaction is characterized by the bending rigidity $\kappa_b$ associated with the $i^{th}$ angle $\theta_i$.

The BPs are chosen to be of the same size and mass as that of the polymer beads and they interact with each other with the same repulsive LJ interaction given by Eq. 1.14 with cut-off distance $r_c = 2^{1/6}\sigma$. The attractive interaction of the BPs with those of the chain monomers is denoted as $U_{\text{binding}}$ and is modeled by an attractive LJ interaction with a cut-off distance of $r_c = 2.5\sigma$. The strength of the interaction $\epsilon_c$ is kept as a variable parameter.
which controls the rate of reversible binding and unbinding of the BPs to and from the chain during the translocation process.

The purely repulsive wall consists of one mono-layer (line) of immobile LJ particles of diameter $\sigma_w = \sigma$ at $x = 0$. The LJ interaction $U_W$ between the mobile particles (monomers or the BPs) and immobile wall particles is given by Eq. 1.15. The pore is created by removing two particles at the center of the wall. The wall divides a square box into two rectangular compartments on each side (cis and trans) as shown in Fig. 5.1. We integrate the Eq. 1.16 with $U = (U_{LJ} + U_{FENE} + U_{\text{bend}} + U_{W} + U_{\text{binding}})$ for the $i^{th}$ monomer and $U = (U_{LJ} + U_{W} + U_{\text{binding}})$ for the $i^{th}$ binding particle. We express length and energy in units of $\sigma$ and $\epsilon$, respectively. The parameters for the FENE potential in Eq. 1.12, $k_F$ and $R_0$, are set to $k_F = 500\epsilon/\sigma$ and $R_0 = 1.5\sigma$, respectively. The friction coefficient and the temperature are set to $\gamma = 0.7\sqrt{m\epsilon/\sigma^2}$, $k_B T/\epsilon = 1.2$, respectively. The equation of motion is integrated with the reduced unit time step $\Delta t = 0.005$ following the algorithm proposed by van Gunsteren and Berendsen [43].

5.3 Results and discussions

We carried out simulations for chain lengths $N$ from 16 - 256 for different chain rigidity $\kappa_b$ (in 2D the chain persistence length $\ell_p = 2\kappa_b/k_B T$) and for several choices of concentration $\rho$ and the strength of the attractive interaction $\epsilon_c$ for the BPs. Due to a large number of runs for a variety of combinations of parameters most of our runs are carried out
for chain lengths $N = 64$ and 128, respectively, although in certain cases we have extended our calculations for chain length $N = 256$.

The polymer chain is equilibrated for times proportional to $N^{1+2\nu_{2D}}$ (Rouse relaxation time) [138] fixing the first monomer at the pore with the rest of the chain at the cis compartment. Here, $\nu_{2D} = 0.75$ is the Flory exponent in 2D [9, 138]. The chain is then allowed to thread through the pore. When the last monomer exits the pore towards the trans compartment then we stop the simulation and note the translocation time. To get good statistics for all the quantities presented here, we have taken average over at least 1000 independent runs. We do not apply any external force at the pore to drive the polymer but the BPs present in the trans compartment provide an effective force to make the translocation possible.

In a previous theoretical treatment based on simplified models, polymer translocation has been analyzed in terms of relative time scales of the BPs and the translocating chain [77], i.e., the diffusion time of the BPs ($\tau_{BP}$), the diffusion time for the chain ($\tau_{\text{chain}}$), and the MFPT $\langle \tau \rangle$ of the chain, respectively. We define $\tau_{\text{chain}}^1 \sim \sigma^2/4D_{\text{chain}}$ as the diffusion time for the chain to travel a distance of the size of the monomer $\sigma$. Likewise, $\tau_{BP} \sim \sigma^2/(4D_{BP})$, where $D_{BP}$ is the diffusion coefficient of the Brownian particles. We have also looked at two other quantities $\tau_{\text{unocc}}$ and $\tau_{\text{occ}}$ defined as the the average time the binding sites (chain monomers) remain unoccupied and the average time that a BP needs to bind to the chain [77], respectively. For the simpler case of one dimensional diffusion of a rod one can show [77] that $\tau_{\text{unocc}} \sim \sigma^2/(4\pi \rho D_{BP})$ and $\tau_{\text{occ}} \sim \rho \exp (|\beta \epsilon_c|) \tau_{\text{unocc}} = \exp (|\beta \epsilon_c|) \sigma^2/D_{BP}$. We have used these estimates to quantify the regimes of our simulation studies in two dimensions.
We have calculated these quantities from the coordinates of the chain and the BPs. In all cases studied here we find $\tau_{BP} \ll \langle \tau \rangle$ so that the BPs attach almost instantly to the segment of the chain on the trans side. Thus the *diffusive regime* characterized by $\tau_{\text{unocc}}, \tau_{\text{occ}} \gg \tau_{\text{chain}}^l$ is absent in our studies. Furthermore we find that for interaction strength $\epsilon_c/k_B T = 5.0$, $\tau_{\text{occ}} \gg \tau_{\text{unocc}}, \tau_{\text{chain}}^l$; so that for all practical purposes the BPs bind irreversibly during the translocation process and relatively insensitive to the density of the BPs. However, reversible binding and unbinding take place for $\epsilon_c/k_B T = 2.0$ and in this case we find $\tau_{\text{chain}}^l \gtrsim \tau_{\text{occ}}, \tau_{\text{unocc}}$. We further find that in this case $\tau_{\text{unocc}} \geq \tau_{\text{occ}}$ for low density of the BPs and gets reversed for larger density of the BP. This subtle interplay of BP density and interaction strength, as well as the chain flexibility is a coupled nonlinear problem manifested in several quantities as presented in the next section.

### 5.3.1 Perfect ratchet and translocation

We begin presenting our results by making a comparison of the MFPT $\langle \tau(s) \rangle$ as a function of the translocation coordinate $(s)$ of the polymer chain in 2D for different chain rigidity $(\kappa_b)$ with the corresponding perfect ratcheting time $\tau_{\text{ratchet}}$ shown in Fig. 5.2 for a chain of length $N = 128$ and binding strength $\epsilon_c = 5\epsilon$ with different concentrations of the BPs ($\rho \approx 1\% - 10\%$) and chain rigidity $\kappa_b$ ranging from 0 to 256. In each figure the black dashed line calculated as

$$
\tau_{\text{ratchet}}(s) = \frac{0.5^2}{2dD_{\text{chain}}} + \sum_{i=2}^{i=s} \frac{\delta^2}{2dD_{\text{chain}}}.
$$
represents the perfect ratcheting [83]. Here $d$ is the physical dimension. It is noteworthy in this point that for Brownian dynamics $D_{\text{chain}}$ does not depend on the chain flexibility [139] so that $\tau_{\text{ratchet}}$ is the same in Figs. 5.2(a)-(c).

![Figure 5.2: MFPT as a function of the s-coordinate for several concentrations of BPs for (a) flexible ($\kappa_b = 0$), (b) semiflexible ($\kappa_b = 32\epsilon$), and (c) stiff ($\kappa_b = 256\epsilon$) polymers. The binding strength is fixed at $5\epsilon$. The circles (black), squares (red), diamonds (green) and up triangles (blue) represent the 1%, 2.5%, 5% and 10% concentration of BPs, respectively and the black dashed line represents the time for perfect ratcheted motion.](image)

Several important conclusions can be drawn from Fig. 5.2. (i) Translocation is most effective for a fully flexible chain and beyond a certain density the translocation is faster than
the one dimensional Brownian ratchet (1DBR). (ii) For a given density, the translocation becomes slower for a stiffer chain and (iii) in the limit of a very stiff chain the translocation time is longer than the 1DBR time except for a high density of the BPs. We believe the results are quite general and will be valid for a more realistic situation in three dimensions [140]. Therefore, efficient design of translocation based devices may benefit from these conclusions. From our previous studies of driven polymer translocation of semiflexible chains, we know that a stiffer chain translocates slower which can be explained using the tension propagation (TP) theory of Sakaue [39,95]. It is tempting to think that the binding particles produces a pulling force and therefore the BP assisted translocation would share similarities with driven translocation [76]. We will come back to this issue. This result shows that the 1DBR (where the chain cannot slide back) time is not the lower limit for translocation of semiflexible chain driven by BPs through a nanopore. For a 1D rod Zandi et al. [76] and Yu et al. [83] have seen this trend. Our studies establishes a far more general result in this context.

5.3.2 How efficient is the actual ratcheting mechanism?

The ratcheting of the chain through the pore due to the presence of BPs depends on the density $\rho$ and interaction strength $\epsilon_c$ of the binding particles. The chain flexibility parameter $\kappa_b$ also plays a crucial role in attractive sites to be available to the binding particles (see Fig. 5.1).
Figure 5.3: The average number of back-sliding of (a) a flexible and (b) a stiff chain as a function of monomer index $m$ for different binding strengths when the density of BPs is 1%. In sub-figures (a) and (b), black down-triangles, red stars and green crosses represent the binding strengths $2\epsilon$, $3.5\epsilon$ and $5\epsilon$, respectively. The same as (a) and (b) but for different chain-flexibility (black circles, red squares, green diamonds and blue up-triangles represent for $\kappa_b = 0\epsilon, 4\epsilon, 16\epsilon$ and $256\epsilon$, respectively) and fixed binding strength $\epsilon_c = 5\epsilon$ of BPs with density (c) $\rho = 1\%$ and (d) $\rho = 10\%$.

Unlike 1DBR (where once a monomer translocates to the trans side it cannot go back to the cis side) we expect that there will be some backward translocation for the monomers. Thus in order to study the efficiency of the ratcheting process we calculate the average of the quantity $n_b(m)$ which represents the number of times the $m$-th monomer goes back and forth from the cis to the trans side and vice versa, before finally exiting to the trans side. This captures the back and forth motion of the monomers across the pore. Fig. 5.3(a) shows $\langle n_b(m) \rangle$ as a function of the monomer index $m$ for various combinations of $\rho$, $\epsilon_c$ and $\kappa_b$. 

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A common feature of these plots is that for a low density and a low binding energy the translocation of the chain is most affected by its flexibility. It is worth noting that when the frequency $f_b$ of binding and unbinding is small, *i.e.* the time period $T_b = 1/f_b > \langle \tau \rangle$, for all practical purposes we can think that the particles are bound reversibly and make further analysis based on this assumption. However, one can expect qualitative changes in the limit of $T_b = 1/f_b \simeq \langle \tau \rangle$. If the particles bind and unbind several times during the time the chain translocates, this will be reflected in an oscillatory behavior in $\langle n_b \rangle$. Fig. 5.3(a)-(b) shows $\langle n_b \rangle$ for a fully flexible and very stiff chain for several binding energies. For a fully flexible chain and for weak binding strength $\epsilon_c = 2\epsilon$, $\langle n_b(m) \rangle$ shows a nearly symmetric behavior as a function of the index $m$, while for very stiff chain one can clearly see an oscillatory pattern for back-sliding. Fig. 5.1 can help us in getting a better physical understanding. For a fully flexible chain the *trans* segment forms a near spherical “blob” and beyond a critical size this blob hinders the back translocation of the incoming monomers; as a result for a fully flexible chain this back and forth motion saturates and then eventually decreases. On the contrary, for a stiff chain when $\kappa_b >> \epsilon_c$, the *trans* segment of the chain is relatively straight and binding and unbinding is relatively insensitive to the monomer index $m$. However, binding/unbinding of BPs makes the chain more/less sluggish reducing/increasing the back-sliding, which is reflected in the slightly oscillatory behavior. We think for $\epsilon_c \simeq k_B T$ this will be a generic feature but will be hard to see in a simulation as lowering the strength of the attractive interaction drastically reduces the probability of successful translocation. For $\epsilon_c > k_B T$ increasing the chain stiffness will enhance the probability of particles getting
adsorbed on the chain more permanently in the time scale of the translocation process and hence will decrease the back-sliding as is clearly seen in Fig. 5.3(c)-(d). Therefore, the back-sliding of the chain is controlled by the total number of bound BPs and the total force exerted by that bound particles. The number of bound BPs and force exerted on the chain by the bound BPs will be discussed in Sec. 5.3.4

5.3.3 Waiting time distribution and back-sliding

![Figure 5.4: The corresponding waiting time distribution of Fig. 5.3.](image)

Evidently a plot of waiting time as a function of $s$ coordinate reveals detailed information about the translocation process of the individual monomers. This quantity has been studied in detail in the past for fully flexible chains and more recently for driven translocation of semiflexible chains [68, 111], and for translocation driven by binding particles [84].
For the case of driven translocation the shapes of the plots have been rationalized using TP theory [39,95]. Here we briefly mention the salient features of $W(s)$ in presence of binding particles and compare the graphs of Fig. 5.4 with those of Fig. 5.3.

At low concentration of the BPs the qualitative features of $W(s) \sim s$ (Fig. 5.4(a)-(b)) and $n_b(s) \sim s$ (Fig. 5.3(a)-(b)) are very similar. However a point worth noting is that although the back-sliding is reduced drastically for a stiffer chain (Fig. 5.3(c)-(d)), the chain takes longer time to translocate as also seen in the $W(s)$ of the individual monomer. This is partly due to the fact that a stiffer chain takes longer time to translocate as shown by us previously in the context of driven translocation [68,111], and partly due to the fact that a stiffer translocating segment adsorbs more bound particles (see Fig. 5.1). For smaller $\epsilon_c$ we also notice a slight oscillatory behavior for the middle monomers. Contrary to Figs. 5.4(a)-(b) which look similar to Figs. 5.3(a)-(b), for larger binding strength the behavior of $n_b$ and $W$ are opposite. At a larger binding energy $n_b$ decreases with the chain stiffness but $W$ increases in general. For low concentrations (Fig. 5.4(c)), $W(s)$ is distinct for each stiffness. Both Fig. 5.4(c) and (d) share the features of a driven translocation in that the position of the maximum for a stiffer chain shifts toward a smaller value of the monomer index. Also, a noticeable feature is that it is the extreme stiff chain which exhibits very different behavior than the semi–flexible chains whose contour length $L \leq \ell_p$. Increasing the concentration of the BPs markedly reduces the values of $W(s)$ and hence the MFPT $\langle \tau \rangle$. The similarity of the variation of the waiting time distribution as a function of chain stiffness for larger strength of the attractive interaction leads us to think that the TP theory can also be extended to
the case, where no external bias is present, however, the chemical potential difference may produce an effective force on the chain monomer leading to a propagating tension front.

Figure 5.5: The number of bound BPs on the translocated segment as a function of $s$-coordinate for (a) 1% and (b) 10% concentration of BPs. The circles (black), squares (red), and diamonds (green) represent fully flexible and semiflexible chains with $\kappa = 0$, $8\epsilon$ and $256\epsilon$, respectively. The inset shows the same for the number of bound BPs per unit length.

5.3.4 Number of bound BPs and driving force

An important aspect of the polymer translocation facilitated by attractive binding particles is how these particles impart an effective force on the translocating segment and
how the force depends on various factors. Since this force is a function of the number of bound particles \( n_{\text{bound}}(s) \), we first look at this quantity as a function of the translocated segment \( s \) as shown in Fig. 5.5. We also find the quantity \( \tilde{n}_{\text{bound}}(s) = n_{\text{bound}}(s)/s \), is useful in depicting the evolution of the bound pairs shown in the insets of Figs. 5.5(a) and (b).

Several noticeable features of Fig. 5.5 are the following. We consider two concentrations of the binding particles, namely 1\% (Fig. 5.5(a)) and 10\% (Fig. 5.5(b)) of strength \( \epsilon_c = 5\epsilon \). This value of \( \epsilon_c \) is close to the bending stiffness of the moderately flexible chain \( (\kappa_b = 8\epsilon) \). We observe that the dependence of \( n_{\text{bound}}(s) \) on the chain stiffness is markedly different for a stiff chain \( (\ell_p \gg L \text{ or equivalently } \kappa_b \gg \epsilon_c) \) than that of a fully flexible chain, or a moderately flexible chain. While for a stiff chain \( n_{\text{bound}} \propto s \) or \( \tilde{n}_{\text{bound}} \approx 0.8 \text{ or } 1.4 \) (for 1\% and 10\% density of the BPs) \( \tilde{n}_{\text{bound}}(s) \) either saturates at \( \rho = 1\% \), or decreases as a function of \( s \). These qualitative behaviors of \( n_{\text{bound}} \) as a function of chain stiffness are rightly captured in various snapshots of Fig. 5.1. As long as \( \kappa_b \lesssim \epsilon_c \), the binding particles are capable of bending the chain and more than one monomer attach to the same binding particle. For a larger value of \( \rho = 10\% \) preexisting bound particles accommodate the incoming translocated monomers and hence \( \tilde{n}_{\text{bound}} \) decreases. For stiff chains, at least for the concentration considered here, the number of bound particles continues to increase linearly with the translocated segment.

The attractive interaction between the BPs and translocated monomers of the chain causes a net force on the translocated segment of the chain. We calculate \( x \)-component (in the translocation direction) of the force exerted by the total number of BPs \( (N_{BP}) \) as:

\[
F_x(s) = -\sum_{i=1}^{s} \sum_{j=1}^{N_{BP}} \partial U_{\text{binding}}(r_{ij}) \frac{\partial}{\partial x}. \tag{5.3}
\]
Figure 5.6: (a) The total force on the translocated segment as a function of number of bound particles for 1% concentration of BPs. The circles (black), squares (red), and diamonds (green) represent fully flexible and semiflexible chains with $\kappa = 0, 8\epsilon$ and $256\epsilon$, respectively. Inset: the total force on the translocated segment per unit length as a function of $s$-coordinate. (b) The same as (a) for 10% concentration of BPs. Insets: (i) the asymptotic value of total force on the translocated segment per unit length for very stiff chain $\kappa_b = 256\epsilon$ as a function of density of the BPs $\rho$ for chain lengths $N = 64$ (red stars) and $N = 128$ (black triangles). The lines are logarithmic fits to the data. (ii) same as the inset of (a) for a 10% concentration of BPs.

Fig. 5.6 shows the force $F_x$ due to the BPs along the direction of translocation as a function of $n_{\text{bound}}(s)$. For stiff chain it is clear that $F_x(s) \propto n_{\text{bound}}(s)$ and hence $F_x(s)/n(s)$ remains roughly constant for a stiff chain. For a fully flexible or moderately flexible chain
the force reaches a maximum value which is expected from Fig. 5.5. For extreme stiff chains our results qualitatively are the same as the previous work of Zandi et al. [76] who found similar behavior for the translocation of a rod, although they considered the motion of the rod to be restricted along the translocation axis only. In the extreme stiff limit it is expected that the qualitative feature will be the same. We have also calculated the concentration dependence of the \( F_x \) from the asymptotic values of \( F_x(s)/n(s) \) in the limit of extreme stiff chains shown in the inset (i) of Fig. 5.6(b). We find \( F_x \propto \ln \rho \) as expected as the free energy is proportional to \( \ln \rho \).

5.3.5 Universal aspects and scaling of MFPT

We now discuss the MFPT for translocation facilitated by binding particles. The dependence of MFPT on chain length \( N \) has been a matter of considerable interest for the last two decades [1, 5–7] and theoretical studies have achieved a rather mature state in delineating the factors affecting the translocation exponent \( \alpha (\langle \tau \rangle \sim N^\alpha) \). For the case of driven translocation a scaling ansatz has been established [67]

\[
\langle \tau \rangle = A(f, \eta_{solv}) N^{1+\nu} + B(f, \eta_{solv}) (\eta_{pore}/\eta_{solv}) N \tag{5.4}
\]

Here, \( f, \eta_{solv}, \eta_{pore} \) are the external force, the solvent friction, and the pore friction, respectively, and \( A \) and \( B \) are nonuniversal quantities whose numerical values are close to unity. Eq. 5.4 explains the non-universal finite \( N \) effect arising out of the second term due to relative influence of pore friction over solvent friction. Detailed numerical calculations [66] show
that Chuang-Kantor-Kardar limit \[50\] \((\langle \tau \rangle \sim N^{1+\nu})\) is achieved only in the limit of very large \(N \to 10^6\). For moderate chain length of 100-1000 most of the reported translocation by various groups exponent is within \(2\nu \leq \alpha \leq 1+\nu\) \([56,58,141]\). In the case of translocation assisted by the BPs, we also find that the translocation exponent \(\alpha \simeq 1.5\) which is another reason to believe that TP theory can be generalized for chemical potential induced tension propagation. In the following subsections we discuss how the MFPT depends on the density and strength of the binding particles as well as on the persistence length of the chain.

### 5.3.5.1 Density dependence of MFPT

Consistent with Eq. 5.4, we also find that the translocation exponent \(\alpha\) is within the above mentioned bound. This is first verified in Fig. 5.7 where we observe that the scaled MFPT \(\langle \tau \rangle/N^{1.5}\) for two chain lengths \((N= 64 \text{ and } 128)\) collapse on the same master plot as a function of the density of the BPs. We have already shown that the effective driving force \(\langle F_x \rangle\) due to the BPs is a function of chain stiffness \(\kappa_b\), binding strength \(\epsilon_c\) and density \(\rho\) of the BPs. It is expected that the MFPT will also satisfy Eq. 5.4 with an enlarged set of variables, \(\langle \tau \rangle \equiv \langle \tau (\tilde{f}, \eta_{\text{solv}}, \eta_{\text{pore}}, \kappa_b) \rangle\) so that in addition to its dependence on \(\eta_{\text{pore}}, \eta_{\text{solv}}\) and \(\kappa_b\), it will depend on an effective force \(\tilde{f} \equiv \tilde{f} (f, \rho, \kappa_b, \epsilon_c)\). which in addition to \(f\) will now depend on \(\rho, \kappa_b, \text{ and } \epsilon_b\). The problem considered here, is the special case with external bias \(f = 0\) and \(\langle F_x \rangle \equiv \langle \tilde{f} (\rho, \kappa_b, \epsilon_c) \rangle\). For the low densities considered here, we observe that the
MFPT satisfies a power law dependence on the density of the BPs

$$\langle \tau \rangle = A \rho^{-\beta}$$

(5.5)

where $\beta$ is a non-universal exponent that depends on persistence length of the chain and binding strength of the BPs.

Figure 5.7: The normalized MFPT as a function of density of the BPs $\rho$ for several values of the stiffness parameter $\kappa_b$. The open symbols represent the data for shorter chain ($N = 64$) and the closed symbols are for longer chain ($N = 128$). Black circles, green diamonds, red left-triangles and blue down-triangles represent the chain-flexibility $\kappa_b = 0\epsilon, 8\epsilon, 32\epsilon$ and $256\epsilon$, respectively. The lines through the points are power-law fits with persistence length dependent exponents, and the inset shows the corresponding log-log plot.

This aspect can be qualitatively justified by noting that for the low densities the MFPT will initially decreases significantly as more and more BPs are available to the translocating chain. But the effect will tend to saturate as the number of unbound monomers decreases as the density of the binding particles increases. Thus the dependence is not linear.
and the dependence of the exponent $\beta$ on the chain persistence length $\ell_p$ is expected as the effect of the BPs on a stiffer chain is more pronounced. Evidently, the dependence of MFPT will saturate at moderate densities when the number of binding particles is more than needed. It is also worth noting that one can argue that for a fully flexible chain, the attractive interaction of the BPs with the chain segment can lead to a collapse of the chain which will speed up the translocation process [142]. However, this argument will not hold for a stiff chain. As a matter of fact from the figure, we observe that for the stiffer chains the effect of increasing the density of the BPs in reducing the MFPT is more pronounced as compared to a fully flexible chain. Thus an “effective pulling” force is responsible for the reduction of the MFPT.

5.3.5.2 Binding strength dependence of MFPT

Now we discuss the effect of the binding strength of the BPs on the MFPT. For a driven translocation process we know that $\langle \tau \rangle \propto f^{-1}$ [1, 5–7]. Here as we just discussed the dependence of MFPT on the “effective force” $\tilde{f}$ produced by the BPs is expected to be more complex as $\tilde{f} \equiv \tilde{f}(s, \rho, \epsilon_c, \kappa_b)$, in addition to the pore and the solvent friction. We show the dependence of MFPT on $\epsilon_c$ in Fig. 5.8 for a low density of the BPs. We observe that for large binding energies, asymptotes of the rescaled MFPT $\langle \tau \rangle/N^{1.5}$ for different stiffness roughly saturate at a common value. From further analysis of these graphs we note that for
all chain stiffness each curve could be fitted to a polynomial as follows:

\[
\frac{\langle \tau \rangle}{N^{1.5}} = a_0 - a_1 \epsilon_c + a_2 \epsilon_c^2 - a_3 \epsilon_c^3 + a_4 \epsilon_c^4.
\]  

(5.6)

We further notice that to a first approximation \(a_1 \simeq 0.5a_0\), \(a_2 \simeq 0.1a_0\), \(a_3 \simeq 0.01a_0\), and so on.

Figure 5.8: (a) Scaled MFPT \(\langle \tau \rangle/N^{1.5}\) as a function of binding strength \(\epsilon_c\) of BPs for different chain stiffness (\(\kappa_b = 0, 8\epsilon, 32\epsilon, 256\epsilon\)) and for \(N = 64\) (open symbols) and \(N = 32\) (closed symbols), respectively. Black-solid, red-dashed and green-dotted lines are 4-th degree polynomial fits to the data for \(\kappa_b = 256\epsilon, 32\epsilon\) and \(8\epsilon\), respectively. The fitted line for the data corresponding to \(\kappa_b = 8\epsilon\) is almost the same as for \(\kappa_b = 0\epsilon\). (b) Scaled MFPT \(\langle \tau \rangle \rho^{0.8}\) as a function of binding strength \(\epsilon_c\) of BPs for stiff chain (\(\kappa_b = 256\epsilon\)) of length \(N = 64\). Open symbols correspond to \(\rho = 1\%\) and closed symbols correspond to \(\rho = 5\%\). The solid line represent the 4-th degree polynomial fit to the data.
We provide a physical picture as follows, which we have verified for at least two different chain lengths and for several low concentrations of the BPs. The first term $a_0$ represents the density and stiffness dependence of translocation in the limit $\epsilon_c \to 0$ and approximately we find $a_0 \simeq \rho^{-\beta}$. We have seen it before [68] that the MFPT increases with the chain stiffness. Once the attractive BPs are introduced the translocation acquires signature of a driven translocation and MFPT decreases which is reflected in the negative contribution of the linear term $a_1 \epsilon_c$. The quadratic term $a_2 \epsilon_c^2$ and the higher order terms represent many-body effect where two or more binding particles would be attached to the same monomer and introduce “crowding” and increase the MFPT. It is worth noticing each graph in principle can exhibit minima for certain combination of the coefficients are reported previously [84, 143] but have not been analyzed adequately. We re-confirm our analysis in Fig. 5.8 by showing data collapse of $\langle \tau \rangle \rho^{0.8}$ for two different concentrations for a stiff chain.

5.3.5.3 Chain stiffness and MFPT

Finally in Fig. 5.9 we analyze the translocation data as a function of the chain stiffness for a moderate strength of the attractive interaction ($\epsilon_c / k_B T \simeq 4\epsilon$) for several densities. For $\ell_p \leq L$, the MFPT varies approximately linearly as a function of the chain stiffness. However, beyond $\ell_p \geq L$, the strict linearity will no longer be valid as the effect of the chain stiffness will saturate. The inset of Fig. 5.9 shows the saturation effect.
Figure 5.9: The MFPT varies linearly with the chain rigidity $\kappa_b$ for the smaller values of $\kappa_b$. After certain value of rigidity the MFPT saturates. Red-squares, green-diamonds and blue-triangles represent the density $\rho = 2.5\%, 5\%$ and $10\%$, respectively. The inset is the same plotted in log-log scale.

5.4 Conclusion

To summarize, we have studied translocation of a homopolymer through a nanopore in presence of attractive BPs at the trans side responsible for the directed motion of the chain. The motivation of the problem stems from a seminal paper by Simon, Peskin and Oster [75] which raised an important issue of non-specific transport in the biological world which is as generic as diffusion, albeit a faster process, and suggested directed diffusion rectified by binding particles as a possible solution. As an example, this process occurs in the biological world when a DNA enters a nucleopore the chaperonin proteins provides the necessary driving force for the translocation. Thus a study of a coarse-grained model is of
practical value. Theoretical studies based on idealized and simpler models, based on several assumptions predict how the attractive BPs enhances the directed diffusion and exert a force on the translocating chain. However, the assumptions are often not satisfied which resulted some numerical works in the past. One of the important results that we find that ratcheting mechanism as introduced through the reversible binding of the BPS under certain conditions can outperform the ideal ratchet. This was demonstrated earlier by Zandi et al. [76] for the 1D translocation of a rod. Here, we have demonstrated its generic validity.

There is no net external force in this system, however, we have demonstrated that there is an effective pulling force exerted by the attractive BPs on the translocating chain. Indeed we find that we can find consistent explanations to some of our simulation data using the original TP theory [39, 95] and the results from our previous simulation studies of driven translocation of a semiflexible chain through a nanopore [68], where we demonstrated how the chain stiffness affects the tension propagation and hence the translocation process. A plausible physical reason for this connection is that unlike the case of driven translocation, here the asymmetry in chemical potential creates and drives a tension in the cis side. Therefore, for the stronger interaction strength of the BPs, the waiting time distribution is asymmetric and qualitatively is similar to that of driven translocation. Based on these evidences from simulation results, we have suggested that by generalizing the external force variable to an effective force so as to include other factors responsible for a pulling force, it is likely that the TP theory can be extended to such directed diffusion process. In most cases we have provided scaling relations for the dependence of MFPT on various variables and
provided phenomenological equations and data collapse in the limit of extreme stiff chains which will be useful for further theoretical studies.

We now like to comment on the relevance of our work and the choice of the parameters in regard to actual biological processes. The experimental values of diffusion coefficient for short chains translocating through a nanopore is $D_{\text{chain}} \sim 10^{-8} \text{cm}^2/\text{s}$ [144,145]. The diffusion constant for the short macromolecules in cellular solution is $D_{\text{BP}} \sim 10^{-6} \text{cm}^2/\text{s}$ [146], so that the ratio $D_{\text{BP}}/D_{\text{chain}} \sim 100$. For the parameters used in our simulation we find that this ratio $D_{\text{BP}}/D_{\text{chain}} \sim 20 - 50$, which implies that the choice of the parameters can be associated with actual biological processes. We have also checked that the diffusion time of the chain $\tau_{\text{chain}} \ll \langle \tau \rangle$. Thus we expect that our numerical studies augmented by good theoretical estimates will promote further theoretical and experimental work in this field.
CHAPTER 6
CONCLUSIONS

We have developed theoretical understanding of the translocation of a semiflexible polymer through a nanopore, using Langevin dynamics simulation in two dimensions. We have showed that a stiffer chain, under the action of an external bias at the pore, translocates comparatively slower than the more flexible chain of the same length. This result is also true for a single chain consisting of alternate block of different flexibility while translocating through a nanopore driven by an external force at the pore. In this thesis, we have verified the so-called tension propagation theory for a semiflexible polymer by the direct observation of the dynamics of the last monomer of the chain. In the local force balance equation of the tension propagation, the solvent friction plays a crucial role. We have studied the effect of the solvent viscosity on the dynamics of the semiflexible polymer. The translocation time varies non-monotonically with the solvent viscosity in the most practical range of the viscosity of the most commonly used solvents. We have also studied the translocation of a semiflexible polymer assisted by the attractive particles in the \textit{trans} side. We showed that the presence of attractive particles in the \textit{trans} side causes the rapid translocation process. For a particular value of the concentration and strength of the binding particles, the translocation process is faster than the Brownian ratchet process.
We validate the Brownian dynamics tension propagation theory numerically by observing the motion of the last monomer of the chain. The tension propagation time obtained from the direct observation of the last monomer is found the same as that calculated from the waiting time distribution method as discussed in the BDTP theory. The translocation time of a semiflexible polymer depends on the persistence length according to power law with a chain-length-dependent exponent. We also showed that the tension propagation time normalized by the respective translocation time is independent of the applied bias at the pore in the intermediate range of the force. The semiflexible polymer elongates and velocity of center of mass of the chain decreases as its persistence length increases. Both of these changes enhance the translocation time for a stiffer chain in the presence of a substantial bias at the pore. We explained these results on the basis of tension propagation theory. However, a stiffer chain translocates faster than a corresponding flexible chain in the quasi-static limit.

In chapter 3, we explained how the same chain consisting of an alternate flexible and stiff blocks produces a fringe like waiting time distribution with maxima and minima on the curve reflecting the number of flexible and stiff segments. We have showed that by observing the total translocation time of the chain, one can identify which end (flexible or stiffer) enters the pore first. We also explained the effect of the strength of the bond elastic potential of the chain. The stronger elastic potential results with shorter bond length between the successive monomers and the shorter chain translocates faster.

We found that the stiffer chain translocates slower in the non-equilibrium which we have showed in the chapter 2. The results found in chapter 3 of this thesis and Ref. [74]
showed that the semiflexible polymer translocates faster in quasi-static limit. Therefore, by varying the solvent friction from very low value ($\sim 0.0015 \text{ kgm}^{-1}\text{s}^{-1}$) to the moderate value ($\sim 1.5 \text{ kgm}^{-1}\text{s}^{-1}$), we can intrapolate from the quasi-static to the non-equilibrium regime where we observe the non-monotonic behavior of the translocation time as a function of solvent viscosity. We find that most of the solvents (in experiments or biological fluids) have the viscosity in the above mentioned range.

In another project, we chose a system of driven translocation where no explicit external force is applied at the pore. However, attractive binding particles in the trans side through binding and unbinding on the translocated chain segment provide an effective bias on the chain. This effective force on the translocated chain exerted by the binding particles in the direction of translocation which depends on the concentration and the binding strength of the particles controls the translocation dynamics.

Although many theoretical and experimental works have been already done in the field of polymer translocation, the extension of the study of polymer translocation to the biological processes is now becoming a new emerging area of research. Several novel techniques such as the development of hybrid nanopore have been developed to bridge the gap between the artificial to real biological processes. A natural extension of this work would be to introduce an “smart nanopore” with additional capabilities of sensing and altering the dynamics of the translocating chain.
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[121] Sakaue’s TP picture was demonstrated to be valid for a fully flexible chain by translating the original theory to a BD scheme ([40,66]). In refs. ([68,111]) we discussed how the TP picture will be affected by the stiffness of the chain.
This characteristic pattern of waiting time distribution seems to be a generic feature as it was seen earlier for segments under different bias or due to different pore-segment interaction.

R. Adhikari and A. Bhattacharya, In the pore friction dominated regime upon decreasing the solvent viscosity the system is closer to its equilibrium state and the translocation dynamics is determined by entropic barrier crossing. This entropic barrier is smaller for a stiffer chain and becomes negligible for rod-like polymer. At low viscosity, the force due to pore friction increases as the solvent viscosity decreases resulting in an increase in the MFPT which explains the minimum of the MFPT at a particular viscosity $\gamma \sim \gamma_m$. Unpublished.

We have simulated driven translocation of a one dimensional compressible chain and find that the MFPT with the elastic constant $k_F$ increases as $\langle \tau \rangle \sim N^2 k_F^{-1/8}$.


For stiff chains the total force on the chain increases linearly with the number of bound particles $n_b$ which is proportional to the physical dimension $d$ (Fig. 7). We also know that $\langle \tau \rangle \propto 1/F [1,5–7]$ which implies that $\langle \tau \rangle \propto 1/d$. Thus from Eqn. 10, to a first approximation $\tau_{\text{ratchet}}/\langle \tau \rangle$ will be independent of the physical dimension $d$. However how the “perfect ratchet” condition will be over or under satisfied will depend on the parameters of the model.

Simulation of short chains by various groups produced a translocation exponent $\alpha \simeq 1.5$ [56,58]. Realizing that in two dimensions $2\nu = 1.5$, an explanation has been given that for short chains $\langle \tau \rangle \sim N^{2\nu}$ [58]. According to more recent theories [66,67] it is perceived as a finite chain length effect.