Ring polymer translocation through nanopore in a crowded environment

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Ring polymer translocation through nanopore in a crowded environment

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Abstract In this paper, we use a Monte Carlo (MC) simulation method in two dimensions with a bond fluctuation model (BFM) to investigate the translocation of a ring polymer through a nanopore in a crowded environment. We put the two middle monomers in the center of the pore, to conquer the entropic obstruction caused by the presence of an impenetrable membrane wall. In our system, a fixed size and same density of crowding agents ($\phi$) are populated orderly on the left (cis) side and randomly on the right (trans) side of the wall. As the translocation of macromolecules is an important process to study the properties of polymers, we explored the static property of the polymer which is characterized by a radius of gyration and the dynamic properties, characterized by mean square displacement and escape time. We found that the scaling exponents of the average square of radius of gyration as a function of size of the polymer $N$ varies with density of the obstacle beads, $\phi$. Our current investigation appears that the universal power-law relation of escape time $\tau$ as a function of polymer size ($\tau \sim N^{2.50}$) is influenced by the density of the crowding agents. Furthermore, our research shows that the size of the polymer, the size of the pore, and the density of the obstacles all have a significant impact on polymer diffusion.

Keywords Ring polymer · Translocation · Nanopore · MC · BFM · Crowded environment

1 Introduction

Biopolymer transportation through very small hole is an important process in biological, physical and chemical systems. This process, the transportation of macromolecules through very small hole is often called translocation. It involves processes like DNA injection into a host cell, protein transportation through the membrane narrow channel, and mRNA passage through nuclear nanopores [1]. Therefore, these biopolymers, RNA, DNA, and proteins, which are the fundamental features of biological structure and function, control life at the molecular scale [2, 3]. As their physical properties play a vital role in their technological application, it is important to study the properties of polymers. The type of polymer is usually focused on when studying its physical properties (static and dynamic properties). The polymer class, ring, on which we focused in this study is a very interesting type of polymer as it has no ends. Its formation in macromolecules is a crucial aspect of chromatin organization, as it plays an important role in transcriptional gene regularization [4, 5] and compactification of DNA in the nucleus [6, 7]. Cyclic peptides, Cyclic DNA, and polysaccharides are examples of ring biopolymers. The Circular polymers are uniquely defined by their lack of ends and the presence of translational symmetry. They are formed by connecting the ends of two linear polymers and do not have the ability to "reptate" as linear chains or "retract" like branched polymers. In biophysics, the properties of polymer transportation are a censorious issue. Furthermore, the translocation of different architectures of polymers, mostly linear polymers, has been the subject of recent studies [8–10].

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Polymer translocation has been tremendously studied in experiments [11–13], theories [14–16] and computer simulations [17–21] as it is important in science and technology. In our previous study [21], we investigated the structural and dynamical properties of linear polymer \((N < 100)\) in a crowded environment. From our study [21], we observed that the density of the crowding agents is one of the factors that affects the polymer translocation. Although a few researches have been done on the translocation of linear polymers for a long time, the properties of other types of polymer are rarely studied. In particular, ring polymer translocation in a crowded environment is seldom studied.

As a large number of biological intracellular and extracellular environments are densely crowded by other macromolecules [22,23], it is very important to deal with the properties of polymers in such environments. In our present study, we considered a crowded environment of same density and constant size of a crowding agent at both sides of a biomembrane, and we studied a translocation of ring polymer in the environment without external driving force, which is merely caused by thermal fluctuation. In all simulations, we considered excluded volume (EV) obstacles and polymers (no monomer-monomer and monomer-obstacle interaction).

Moreover, in this paper, we investigated ring polymer transportation in a biological environment crowded with other molecules. In a sense, we observed how the density of the obstacles \((\phi)\) affects the structural and dynamical properties of the loop macromolecule translocation in two dimensions (2D). This means that we observed how \(\phi\) affects the power-law relationship of each average square radius of gyration \((\langle R_g^2 \rangle )\) and mean escape time \((\tau)\) with a polymer size \(N\). In addition, we investigated the impacts of pore size on the probability distribution of escape time and the diffusion of the polymer.

So far, to investigate the properties of different structures of polymers, a number of simulation methods have been used. The most often used to simulate polymers are the Molecular Dynamics (MD)[24,25] and Monte Carlo (MC) [26,27] methods. The method by which the process of tolerating or dismissing the attainable polymer states is stochastic has been used in this study[28,29]. This method is referred to as the Monte Carlo method. To examine the properties of the polymer by this method, a well known lattice model, bond fluctuation model (BFM) is used. We presented the details of the model and simulation procedure in the next section.

2 Model and Simulation Procedure

2.1 Bond Fluctuation Model (BFM)

As stochastic process is a process of controlling the possible states of the polymer in our method (MC), it is necessary to focus on the strategy of performing the task. In order to complete the objective, we use the Bond Fluctuation Model (BFM) in our simulations. The model is a proficient lattice MC procedure in which each monomer possess a particular number of lattice destinations solely on a square grid cell [30]. The polymer and the crowding environment are modeled by putting a molecule beads on square grid.

Bond Fluctuation Model (BFM) [30] is lattice model which has been substantially employed to investigate the properties of a various number of polymer systems. It is a popular lattice model. A bead-stick model is used to demonstrate the polymer, which is an atomistic model a coarse-grained version. Therefore, the monomers of the polymer are represented as a bead and its chain is as a string of beads put on a lattice where there is a bond between each monomer including the end monomers. To guarantee self-avoiding walk (SAW) confinements, a single monomer resides in one lattice location. Therefore, one can understand that each bead is located at the four vertex points of a square site on the lattice. The monomers were at that point joined to their closest neighbors by means of a predestined set of bond vectors. The set (Equ.1) consists the allowed bond vectors for 2D SAW polymer.

\[
\{(2,0), (2,1), (2,2), (3,0), (3,1), (3,2)\}
\]

The string length that links the neighboring monomers must be within the bond sizes set (Equ. 1), which are involved in the range of \(2 \leq b \leq \sqrt{3}\), where \(b\) is the magnitude of the bond vector between two consecutive beads. Despite the fact that the magnitudes of the bond vectors are allowed to vary, they must fall within the set. All the magnitudes of the vector are given in lattice size units. This means, the EV effect is ensured by the least distance 2 and the maximum bond length \(\sqrt{3}\), prevents the bonds from crossing. As a result, BFM governs the local movement of the randomly chosen monomer and the attempted displacement in a randomly chosen lattice direction throughout the simulations. The simulation and calculation procedures are presented in the following section.

2.2 Simulation and Calculation Procedures

As the model (BFM) is a lattice model, first we prepared a square lattice of \(L \times L\) with a lattice spacing of \(\Delta\), then we indexed sites \((i, j)\) as \(L_x \leq i \leq L_x\) and \(L_y \leq j \leq L_y\). Hence, each site has a location of \((x,y) = (i\Delta, j\Delta)\). The lattice dimensions are \(L_x \leq i \leq L_x\) and \(L_y \leq j \leq L_y\) in our simulation we considered, \(\Delta = 1\) lattice constant, \(L_x = L_y = 200\), which are long enough to simulate the sizes of the polymer sampled in our study. Then we inserted an impenetrable membrane wall in the middle of the square lattice at \(x = 0\), which is perpendicular to the \(x\)-axis. We added a pore of size \(\sigma = \sigma_x \times \sigma_y\)
where $\sigma_x = 1$ lattice size to x-direction and $\sigma_y$ is the number of lattices between the lattice locations, $(0, -w + 1)$ and $(0, w - 1)$, to start with we considered $w = 3$, so that $\sigma_y = 5$ lattice constants, at the middle of the membrane, which allows at most two monomers to pass through it without interacting with the edges of the pore, the two lattice locations $(0, -w)$ and $(0, w)$ are the lower and upper edges of the pore, respectively. Therefore, the thickness of the pore is 1 and the width is 5 in lattice size unit. This means that the thickness of the wall itself is 1 lattice size unit. On both sides (cis and trans) of the membrane, the impenetrable, immobile and fixed-size obstacle beads are populated on the square lattice with the same area fraction of the obstacles ($\phi$). In estimation, a 20%-30% of the total surface is occupied by the obstacles [31]. This area fraction of the crowding agents is defined as [21]:

$$\phi = 4N_c/A$$  \hspace{1cm} (2)

where $N_c$ is number of obstacles (crowding agents) and A is the entire cross section focuses secured by the impediments, the factor 4 is due to the reality that each impediments involves at 4 vertex points of the square lattice. In our study, $\phi$ is a measure of how much the crowding agents are populated, in a sense, the concentration of the crowding agents in the polymer solution. On the trans side, the obstacles are randomly populated. Whereas, the obstacles on the cis side are systematically arranged. We simulate the polymer at various area fractions of the obstacles, which are $\phi \leq 0.3$, as considered in some studies [21, 32].

The simulations of polymers with higher dimensions ($d > 1$) are necessary, to deal with the effect of self-avoidance on the entry of polymers through a nano pore within the coiled state. We are motivated to focus on 2D polymers, because 2D polymers are pertinent to this goal for two reasons. The first is, it requires shorter computation time, comparing with that of 3D case. The second reason is the EV effects are more credible.

Our simulation continues as takes after. To induce the initial configuration of the polymer, we embed none concatenated ring polymer symmetrically at the center within the simulation box, as shown in Fig. 1 (a). The size of the polymer (number of monomers) $N$ is arbitrarily chosen and the center monomers (the $1^\text{st}$ and $1 + (\frac{N}{2})^{th}$) put within the hole symmetrically to overcome the entropic obstruction. We characterize this setup by guaranteeing that any monomer of the ring polymer is associated with two neighbor monomers and that there are no ends. And the EV property is controlled by setting that each lattice location be analogous to one square doubtlessly. The magnitudes of the distance between the joins of the neighbor monomers are administered by BFM in 2D.

Beginning from the initial arrangement of monomers of the polymer, numerous moves are achieved until its equilibration is come to. To achieve such an equilibrated setup, the polymer is relaxed by making numerous local moves and squeezing the center monomers at the center of the pore. The relaxation time is $\tau_{\text{equiv}} \sim N^{1+2\nu}$, where $\nu = 0.75$ for 2D. This implies, $\tau_{\text{relax}} = cN^{1+2\nu}$, $c$ could be a constant given in MC step time unit, as the unit of time in this study is Monte Carlo step (MCS), characterizing one MC step as $N$ elementary moves. It is tallied when the N monomers are made a neighborhood move without absorbing the Self avoiding and prohibited volume confinements. In our simulations, each monomer has been relaxed for $10^6$ MCS ($c = 10^6$ MCS) [21]. The reason, why we utilized this much MC steps for relaxation was to urge the completely relaxed polymer. At $t = 0$, the center monomers which were anchored in the pore during the relaxation process, are allowed to move openly after the equilibration is completed. The relaxed polymer is portrayed in Fig. 1 (b). Hence, the simulation is completed at a time $t > 0$ when all the monomers are exited to either side (cis or trans) of the biomembrane as appeared in Fig. 1 (c). In this study, it is typically referred to the escape time ($\tau$). The procedure is rehashed an expansive number of times (5000 runs) for each polymer size N, and the escape time, $\tau$ that happened at most is recorded.

In the simulations, the average square distance of the monomers from the center of mass of the polymer, radius of gyration in square lattice constant unit is calculated as follows. Since the polymer has distinctive conformations at each MC step, it is important to calculate the square radius of gyration at each MCS time interval. At long last, we record its average over the overall number of the intervals. Radius of gyration is more helpful quantity that portrays any architecture of polymers. Like end-to-end distance, it depends on the measure of polymers size. Therefore, we calculate this parameter in our simulation as follows. To begin with, we determine the centre of mass of the ring polymer at each step time interval as:

$$x_{cm} = \frac{1}{N} \sum_{i=1}^{N} x_{ki}$$  \hspace{1cm} (3)
where \( k = 1, 2, 3, \ldots, n \) (number of MCS intervals). Therefore, the square of radius of gyration \( (R_g^2) \) at each interval is:

\[
R_g^2 = \frac{1}{N} \sum_{j=1}^{n} (x_{kj} - xcm_k)^2 + (y_{kj} - ycm_k)^2
\]

At last, we obtain the average square radius of gyration \( (R_g^{2ave}) \) by:

\[
(R_g)^{2ave} = \frac{1}{n} \sum_{k=1}^{n} R_g^2
\]

Following this procedure, we simulated a given polymer of \( N \) number of monomers 5000 times (i.e., 5000 runs) and calculated \( R_g^2 \) by averaging the results we got at each run over the number of runs. The discussions of the results are stated in the following section.

3 RESULTS AND DISCUSSION

3.1 RING POLYMER’S STATIC PROPERTY IN A CROWDED ENVIRONMENT

3.1.1 Radius of gyration of ring polymer

A ring polymer can not be described by a parameter called end-to-end distance, as it has no ends. The authentic depiction quantity of all types of polymers is a radius of gyration. It, like end-to-end distance, is affected by polymer size, and \( \langle R_g^2 \rangle \sim N^{1/2} \) is scaling relationship between mean square radius of gyration and polymer size. Which have been observed by ideal polymer model. In any case, ideal polymers, by speculation, contravene the EV effect constraint between the monomers. Therefore, P. Flory [33] showed that the relation exponent is \( \nu = 3/(2 + d) \) using specific and functional estimation on the SAW polymer chains Rouse model. The exponent depends on dimension, \( d \) denotes dimension. In the plots of \( \langle R_g^2 \rangle \) against polymer size \( N \) of the polymer (Fig. 2), the relation has been appeared. We take into account nearly brief measure polymers (\( N < 100 \)) because of the large amount of computational time required to mimic exceptionally long polymers, in our system. One can see from Fig. 2, in free environment \( (\phi = 0) \), the slope is = 1.48 ± 0.01, as a result, it approaches to 2\( \nu \) \( (\nu = 3/4 \) in 2D) which is line with the Florys [33] scaling exponent of the relationship of the parameters, average square radius of gyration and degree of polymerization, \( N \). If there are no obstacles on either side of the membrane, the scaling relation of mean square radius of gyration and \( N \) is \( \langle R_g^2 \rangle \sim N^{2\nu} \). Nevertheless, as illustrated in the figure (Fig. 2), the scaling exponent changes with the surface area of the obstacles in the crowded environment [34].

Prior studies [21,32,35,36] of polymer characteristics in crowded systems have reported such nonmonotonic fluctuation in size of polymers and obstacle concentration in the polymer solution. As illustrated in the figure, as impediments get closer, means as the density of the crowding agents increases, the average radius of gyration rises, and the scaling relation exponent of the quantities changes. This implies that the ubiquitous power law relation \( \langle R_g^2 \rangle \sim N^{2\nu} \) is contravened as a result of the crowding agents contorting the polymer conformations [32]. This result demonstrates that the density of the obstacles determines the scaling relationship. From our previous [21] and present studies, we can also observe that, in spite of the quantity difference, the behavior of the mean radius of gyration of both a linear and ring polymers is the same.

3.2 RING POLYMER TRANSLOCATION (DYNAMIC PROPERTIES) IN A CROWDED ENVIRONMENT

3.2.1 Ring Polymer Escape Time with Effects of Obstacles and Size of the Pore

Effect of the Density of Obstacles (\( \phi \))

To investigate the effect of \( \phi \), the probability distributions \( (P(\tau)) \) of the escape times \( \tau \) for ring polymer translocating through the pore of size, \( w = 3 \), in different crowding agents amount have also been computed. The probability distribution of escape times of a ring polymer of size \( N = 42 \) in an environment where the obstacles are less than 30% is shown in Fig. 3. As appeared within the figure, our simulations show that the most likely escape time increases as the environment gets to be more crowded, i.e., the crest of the graph shifts to the right, as the density of the impediments increases. Furthermore, as shown within the figure, our simulation results uncovered that the time histogram is a long-tailed likelihood distribution, as the distribution function reimburses for the expansive escape times \( \tau \).

The power law relationship between translocation time \( \tau \) and polymer size \( N \) is another important notion in poly-
it increases when the size of the pore becomes larger. Such nonmonotonic relation of translocation time and size of the pore is also found in the study of Q.Gao et al. [41]. This is not universal. Unlike these, Q.Gao et al. [41], discovered that the presence of obstacles has no effect on the translocation time of linear and ring polymers in crowded environments when no electric potential is applied. Nonetheless, as shown in the figure, our simulation results allowed us to discover that the power-law relation changes with the density of crowding particles which is consistent with our recent study of linear polymer [21]. The increase in escape time with φ results from the entropic obstruction increasing as obstacle content increase [21].

Effect of the pore size (w) on escape time

In our present study, we have also considered the influence of the pore size (w) on the translocation of the polymer. We took the ring polymer of size N=42 as the object in the study and set the size of the pores as w = 3, 4, 5, 6, 7, 8 in a crowded environment of φ = 0.2. We calculated the probability distribution of escape times of the polymer for its translocation through each size of the pore as shown in Fig.5. As it can be seen from the figure, the crest of the graph shifts to the left for the size of the aperture w < 5 and then shifts to the right for the size of the pore w > 5. This means, when the size of the pore increases to 5, the translocation time decreases, and it increases when the size of the pore becomes larger. Such nonmonotonic relation of translocation time and size of the pore is also found in the study of Q.Gao et al. [41]. This is due to the presence of access to chaotic direction caused by the widening of the pore.

Furthermore, because there is no driving force acting on the polymer to favor either side, the polymers exit to one of the sides without any external influence. Therefore, from the simulation study, we discovered that, like linear polymer [21], ring polymer translocation favors the disordered side (trans), and that in the non-appearance of crowding agents.
in the environment, the probability of exiting the pore to either side is equally likely, as shown in Fig. 7. Because half of the polymer is initially on the cis-side and the other half on the trans-side, by pinching the middle monomers in the pore, the polymer will exit the pore with an equal probability on either side unless an external driving force is applied upon. Nevertheless, The translocation probability to trans-side rises as the area fraction of the obstacles increases [21, 41].

3.2.2 Effect of Crowding agents on Diffusion of Ring Polymer

The polymer’s dynamic property has also been examined by observing the polymer’s diffusion motion. The proper parameter to define the overall diffusion of the polymer system is the mean square displacement (MSD). The MSD \( \langle \tau^2(t) \rangle \) is time dependent parameter. It can be expressed as:

\[
\langle \tau^2(t) \rangle = \langle (\tau_{cm}(t) - \tau_{cm}(t = 0))^2 \rangle
\]

\( xcm(t) = \frac{1}{N} \sum_{j=1}^{N} x_j(t) \)

\( ycm(t) = \frac{1}{N} \sum_{j=1}^{N} y_j(t) \)

\( \tau_{cm}(t) = (xcm(t), ycm(t)) \)  

The following relationships are predicted by the Rouse model[37]:

\[
\langle \tau^2(t) \rangle \sim t
\]

and

\[
D \sim N^{-1}
\]

The Eqn. 13 is the definition of diffusion coefficient of polymers \((D)\), in an obstacle environment. This suggests that the diffusion coefficient \(D\) is given by the slope of the graph of the respective MSD of the polymer size \(N\) against the time \(t\).

\[
4D = \lim_{t \to \infty} \frac{\langle \tau^2(t) \rangle}{t}
\]

In an obstacle free environment, in our previous study of linear polymer [21], we observed that \(\tau^2(t) \sim t^\beta\), where \(\beta = 1.00 \pm 0.01\), as predicted by Rouse Model. This shows that diffusion is normal, and in the crowded environment we observed that \(\beta < 1\), this means, the diffusion changes to subdiffusion. Consistent with this, W. F. Cao et al. [39] and A.J.Ellery et al. [42] found the same relation. \(\beta\) is the slope of the log-log plot of the MSD versus time and is the quantity used to examine the relation of the two parameters. The result of our present study of ring polymer in the same system is agreed with this for both the obstacle free \((\phi = 0)\) and the crowded environments \((\phi > 0)\), which can be seen from the Fig. 8.

We have also calculated the diffusion coefficient using the definition (Eqn. 13) for normal diffusion after calculating the MSD of the polymer as a function of time for each size considered in our study. The parameter diffusion coefficient is defined as the amount of polymer diffused in a surface of square lattice constant per unit MC step time, and it is calculated from the plot of MSD versus time in an obstacle-free environment. And then, we plot the log-log plot of diffusion coefficient \(D\) against the polymer size \(N\), as shown in Fig. 9, to examine the interplay between the quantities \((D\) and \(N\)). In this manner, in an obstacle free environment, the study result for the interplay between \(D\) and \(N\) can be
expressed as $D \sim N^{-0.92 \pm 0.01}$ which is line with the scaling law of Rouse model which can be expressed by Eqn. 12. As it is presented in the figure, one can observe that the rate of diffusion ($D$) decreases as the polymer size ($N$) increases, as expected.

Moreover, from our recent study of linear polymers[21] and our present study of ring polymers in the same system, we observed that the two types of polymers obey the same law, which is in line with previous studies[43, 44].

### 4 CONCLUSION

Ring polymer translocation through a nanopore in a populated area with the same concentration of crowding agents ($\phi$) on both sides of an impenetrable biomembrane has been investigated. To achieve the goal, we manipulated the Monte Carlo method with the Bond Fluctuation Model in two dimensions ($2D$). The radius of gyration scaling relation of a ring polymer with the size of the polymer $N$ is highly influenced by the density of the crowding agents, $\phi$. Moreover, we observed how the scaling relation of the average square radius of gyration ($\langle R_g^2 \rangle$) with polymer size $N$ depends on the obstacle concentration. We have also observed the interplay between the escape time and the size of the polymer. According to our simulation result, $\phi$ also has a great impact on the relation of $\tau$ and $N$, in an environment that is crowded by other macromolecules, the presence of the other macromolecules results in the broken of the universal power-law relation of $\tau$ and $N$, which can be expressed as $\tau \sim N^{2.50}$.

We also discovered a nonmonotonic relationship between translocation time and pore size. The study also shows a preference for polymer translocation toward disordered obstacles.

### References


