Free Energy Evaluation in Polymer Translocation via Jarzynski Equality

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Abstract

We perform, with the help of cloud computing resources, extensive Langevin simulations which provide free energy estimates for unbiased three dimensional polymer translocation. We employ the Jarzynski equality in its rigorous setting, to compute the variation of the free energy in single monomer translocation events. In our three-dimensional Langevin simulations, the excluded-volume and van der Waals interactions between beads (monomers and membrane atoms) are modeled through a repulsive Lennard-Jones (LJ) potential and consecutive monomers are subject to the Finite-Extension Nonlinear Elastic (FENE) potential. Analysing data for polymers with different lengths, the free energy profile is noted to have interesting finite size scaling properties.
I. INTRODUCTION

The process of polymer translocation occurs in many biological and biotechnological phenomena. It has received great attention in both experimental and theoretical studies in recent years due to its important role in many crucial biological processes, such as mRNA translocation across a nuclear pore complex [1], drug delivery [2], injection of DNA from a virus head into a host cell and gene therapy [3, 4]. However due to the complexity of the interactions involved, especially between the pore and the membrane, computer simulations have been widely used as a fundamental research tool. Most of the numerical studies can be classified into the topical issues of (i) translocation driven by chemical potential gradients [5–10], (ii) translocation driven by external forces [11], and (iii) unbiased translocation [12, 13].

The first observation of polymer translocation was done experimentally by Kasianowicz et al. [5], using ssDNA fragments driven through a narrow α-hemolysin nanopore in a biomembrane by application of an external voltage. Kasianowicz et al. [5] observed that the mean translocation time, $\langle \tau \rangle$, scales linearly with polymer length, $N$, and inversely with the potential difference across the pore. Putting together the Fokker-Planck approach and classical nucleation theory, Sung and Park [14] and Muthukumar [15] theoretically predicted that the translocation time scales with polymer chain length $N$ as $\langle \tau \rangle \sim N$ for driven translocation and $\langle \tau \rangle \sim N^2$ for the case of nondriven translocation. In 2002, Chuang et al. [16] pointed out that the estimate of the translocation time, $\tau_{\text{trans}} \sim N^2$, based on the Fokker-Planck equation for the first-passage time over the membrane entropic barrier couldn’t be correct since $\tau_{\text{trans}}$ cannot be smaller than the Rouse time, which scales as $\tau_R \sim N^{1+2\nu}$. This prediction was confirmed for many simulations in 2D and in 3D and had a special attention in Ref. [17], where polymers with a relatively large number of monomers have been studied.

From the statistical physics point of view, the polymer translocation problem can be seen as a kind of tunneling process over an entropic barrier as pointed out by Muthukumar [15]. The entropic barrier results from the decrease in the number of allowed conformations which takes place in the presence of the membrane. For a polymer of length $N$, with one end fixed on a wall, the total number of conformations, $Z$, can be written as $Z(N) = \bar{z}^N N^{\gamma - 1}$, where $\bar{z}$ is essentially the effective coordination number for the orientation of the adjacent bonds, and $\gamma$ is a scaling exponent. This exponent depends on the nature of the polymer and the background fluid, and also on boundary conditions related to the specific membrane geom-
etry. The parameter $\Xi$ can be written as $\exp(-\mu/k_BT)$, where $\mu$ is the chemical potential.

The Helmholtz free energy $F_N$ of the chain is related to the partition function $Z(N)$ as $F_N = -k_BT \ln Z(N)$. We have, then,

$$\frac{F_N}{k_BT} = \frac{\mu N}{k_BT} - (\gamma - 1) \ln(N) .$$  \hspace{1cm} (1)

In the translocation problem, the polymer chain undergoes translocation through the hole from region I (cis) to region II (trans). In a intermediate state during the translocation, let there be $m$ segments in the region II and $N - m$ segments in the region I. The total partition function will be the product of the partition functions for the two tails, $Z = Z_I(N-m)Z_{II}(m)$, and in the same way as before, the free energy of the chain $F(m)$, with $m$ monomers in the region II can be written as:

$$\frac{F(m)}{k_BT} = (1 - \gamma'_2) \ln(m) + (1 - \gamma'_1) \ln(N-m) - m \frac{\Delta\mu}{k_BT} ,$$  \hspace{1cm} (2)

where $\gamma'_1$ and $\gamma'_2$ are the values of $\gamma'$ in the regions I and II, respectively, and $\Delta\mu \equiv \mu_1 - \mu_2$ is the chemical potential difference across the membrane. In our study, we focus on a homopolymer surrounded by some homogeneous solution. We take, thus, $\gamma'_1 = \gamma'_2 = \gamma = 0.5$ and $\Delta\mu = 0$.

It is important to observe that this approach employs the quasi-equilibrium approximation once it is assumed that unbiased translocation is sufficiently slow, so that the sections of the polymer outside the nanopore remain in conformational equilibrium. The validity of the quasi-equilibrium approximation for polymer translocation has been challenged in both nondriven [13, 18] and driven [19–21] translocation. Some authors have suggested that polymer translocation is a strong non-equilibrium process and having this in mind they have proposed alternative descriptions [22–24]. Unfortunately, these methods are essentially based on Monte Carlo and molecular dynamics for short polymer chains. Since it is a difficult task to derive analytical expressions for free energy in the translocation problem, the use of numerical simulations within a cloud computing framework, together with modern non-equilibrium theorems comes as a promising way to pursue.

In this article we provide numerical evaluations of the free energy in the polymer translocation problem via the Jarzynski Equality. With the help of cloud computing resources [25] we have been able to introduce statistical ensembles and study polymer chains which are considerably larger than the ones usually taken in the literature. In Sec. II, we briefly review
the Jarzynski Equality and its applications. In Sec. III, we discuss the numerical details related to the Langevin simulations. In Sec. IV, we apply the Jarzynski Equality to the problem of polymer translocation, where we then obtain free energy profiles. Finally in Sec. V, we summarize our results and point out directions of further research.

II. JARZYNSKI EQUALITY

C. Jarzynski derived, in a straightforward and seminal paper [26], a relation between the path dependent work and the path independent free energy change of a thermodynamical system, as given from the following sum rule,

$$\int_{-\infty}^{\infty} dW \rho(W) e^{-\beta W} = \langle e^{-\beta W} \rangle = e^{-\beta \Delta F} ,$$

(3)

where $\rho(W)$ denotes the probability density function of the work $W$ that is performed on the system, and $\Delta F = F_f - F_i$, denotes the difference between the free energies $F_i$ and $F_f$ of the initial thermal equilibrium state and the final thermal equilibrium state of the system, respectively. It is important to emphasize that the non-equilibrium processes involved in the definition of the Jarzynski equality all start at some well-defined equilibrium thermodynamic state with temperature $T = (k_B \beta)^{-1}$. The processes are guided by the action of forces related to the time-dependent parameters that characterize the Hamiltonian of the system.

The Jarzynski equality provides a way to compute the equilibrium quantity $\Delta F$ from an ensemble of finite-time, nonequilibrium measurements of the work done on the system, as given by the statistical average $\langle e^{-\beta W} \rangle$. Any application of the Jarzynski equality requires repeating experiments (real or numerical) with the same protocol a great number of times in order to generate sufficient statistics. Some care is necessary when working with the Jarzynski equality since the work average can have a very slow convergence, in particular if we deal with macroscopic states.

The validity of this equality, having in mind determinations of the free energy change $\Delta F$ was sucessfully demonstrated in various experimental systems such as, for instance, classical oscillators [27, 28] and single molecules [29]. In a particular class of single-molecule experiments suggested by Hummer and Szabo [30], where the end-to-end distance of the molecule is controlled by means of optical traps, the molecule is attached to a glass slab on one end and a polystyrene bead on the other, which in turn interacts with the external laser
trap through an effectively harmonic potential. In this case, the external control parameter in the Jarzynski equality specifies the position of the confining potential. The central idea of this paper is to use the Jarzynski Equality approach in the polymer translocation problem, as it will be discussed in detail in Sec. IV.

III. COMPUTATIONAL STRATEGY

In our three-dimensional Langevin simulations, the excluded-volume and van der Waals interactions between beads (monomers and membrane atoms) separated by a distance \( r \) are modeled through a repulsive Lennard-Jones (LJ) potential \( U_{\text{LJ}}(r) \) with cutoff at length \( 2^{1/6}\sigma \), where \( \sigma \) is the bead diameter:

\[
U_{\text{LJ}}(r) = \begin{cases} 
4\epsilon[(\sigma/r)^{12} - (\sigma/r)^{6}] + \epsilon, & \text{if } r \leq 2^{1/6}\sigma, \\
0, & \text{if } r > 2^{1/6}\sigma.
\end{cases}
\] (4)

Besides the LJ potential, consecutive monomers are subject to the Finite-Extension Nonlinear Elastic (FENE) potential,

\[
U_F(r) = -\frac{1}{2}kR_0^2\ln[1 - (r/R_0)^2].
\] (5)

From the above definition, it is clear that the FENE potential does not allow the distance between consecutive monomers to become larger than \( R_0 \).

We have studied polymers with sizes up to 100 monomers, which translocate through a pore created by the remotion of a single atom at the center of an 80 x 80 monoatomic square lattice membrane similar to the one shown in Fig. [1]

The translocation process can be dynamically described by the following Langevin equations,

\[
m\frac{d^2\vec{r}_i}{dt^2} = -\sum_{j\neq i}\vec{\nabla}_{r_i}[U_{\text{LJ}}(r_{ij}) + U_F(r_{ij})] - \xi \frac{d\vec{r}_i}{dt} + \vec{F}_i(t),
\] (6)

where \( r_{ij} = |\vec{r}_i - \vec{r}_j| \), \( \xi \) is the dissipation constant and \( \vec{F}_i(t) \) is a gaussian stochastic force which acts on the monomer with label \( i \), being completely defined from the expectation values

\[
\langle \vec{F}_i(t) \rangle = 0,
\]

\[
\langle [\hat{n} \cdot \vec{F}_i(t)][\hat{n}' \cdot \vec{F}_j(t')] \rangle = 2\hat{n} \cdot \hat{n}' k_B T \xi \delta_{ij} \delta(t - t').
\] (7)
Above, $\hat{n}$ and $\hat{n}'$ are arbitrary unit vectors, and $k_B$ and $T$ are the Boltzmann constant and the temperature, respectively. By means of a suitable regularization of the stochastic force, we have implemented a fourth-order Runge-Kutta scheme for the numerical simulation of the Langevin Equations (6). Our simulation parameters are: $\epsilon = 1.0$, $\sigma = 1.0$ (\(\sigma\) is also identified with the membrane lattice parameter), $\xi = 0.7$, $k = 7\epsilon/\sigma^2$, $R_0 = 2\sigma$, $k_B T = 1.2\epsilon$. The simulation time step is taken as $3 \times 10^{-3} t_{LJ}$, where $t_{LJ} \equiv \sqrt{m\sigma^2/\epsilon}$ is the usual Lenard-Jones time scale. In the most general case, the initial configuration of the polymer has $m$ monomers on the trans-side of the membrane and $N - m$ on the cis-side. Translocation is allowed to start only after an initial stage of thermal equilibrium is reached for the whole polymer.

IV. FREE ENERGY EVALUATIONS

In order to get an operational understanding of the Jarzynski equality in the polymer translocation context, let us consider a situation where the monomer position at the pore is determined by an arbitrary potential that acts like an optical trap. This potential, for our purposes, is a time-dependent modulated well, $U(r, t)$, which induces the translocation of a single monomer,

$$U(r, t) = A e^{-br^2} (\sin[c(z - \pi vt/c)])^2,$$

(8)
where $A$, $b$ and $c$ are constants and $v$ is the speed of the minimum potential location along the $\hat{z}$ direction (perpendicular to the membrane plane).

We show, in Fig. 2, snapshots of the time dependent potential at four time instants. A monomer is initially placed at the pore, and there it remains, due to the existence of a surrounding large potential barrier. The potential well then starts to move, dragging the monomer attached to it. At any given time instant $t$, a single monomer is trapped by this potential and the whole process is completed when the time dependent potential gets back to its original state, now with a different monomer at the pore position. A single monomer translocation is accomplished at time $t = 1/v$.

It is important to note that while dealing with expectation values such as

$$\langle e^{-\beta W} \rangle \approx \frac{1}{N} \sum_{i=1}^{N} e^{-\beta W_i}$$

in the Jarzynski Equality, some special care is in order, since the large fluctuations displayed by $W$ enforces us to employ large statistical ensembles, which we have been able to produce thanks to a well-established cloud computing framework. Also, it is worth of remarking that the single monomer translocation event is a convenient choice to deal with, related to amounts of $W$ that are not large enough to ruin the precision of our statistical averages.

The work $W$ which is used in the Jarzynski equality is obtained by means of the following procedure:

(i) After the thermalization process, we turn off the stochastic and dissipation forces, so that only conservative forces play a role in the system and, consequently, the total energy is independent of the path. In this case, we can assure that,

$$\langle e^{-\beta W} \rangle = \langle e^{-\beta \Delta E} \rangle = e^{-\beta \Delta F}.$$  \hspace{1cm} (10)

(ii) The time-dependent potential starts to act at $t = 0$ and then stops when the monomer that follows the one that was previously attached to the pore reaches the same location, i.e. the pore.

Once we have established the procedure for the computation of free energy variations, we are now able to perform our simulations, which are run as follows. First, we fix the size $N$ of the polymer, say $N = 50$, where initially half of the monomers are located in both sides of the membrane ($m = 25$) in a situation of thermal equilibrium. After a period of time $t = 1/v$, the translocation of a single monomer is deterministically driven towards the
FIG. 2: (a) At $t_a$, soon after thermalization, the polymer has a monomer attached to the pore, preventing other monomers from translocating. (b) At $t_b$, the monomer which was previously attached to the pore moves along with the potential well, which in its turn develops a smaller right peak. (c) At $t_c$, the right monomer is free, while the left one is imprisoned by the potential. (d) At $t_d$, the left monomer is finally brought the pore, ending the single-monomer translocation induced by the action of the time-dependent potential.

trans side of the membrane, so that the polymer ends up having $m = 26$ monomers in that region. This procedure is repeated for 100 independent realizations, in such a way that each one of these realizations takes the time interval $t = 400\ (v = 2.5 \times 10^{-3})$ to be completed. From (10), we obtain the variation of free energy for each individual translocation. This algorithm is repeated to generate the free energy profiles shown in Fig. 3, related to the whole process of translocation.

Fig. 3 illustrates the comparison, for a polymer of size $N = 50$, between the cases of two different translocation velocities, $v = 5 \times 10^{-3}$ and $v = 2.5 \times 10^{-3}$. Our application of the Jarzynsky Equality is clearly validated, once we have found that both travel velocities of the
FIG. 3: The behavior of the free energy obtained through Langevin simulations, for velocities $v = 5 \times 10^{-3}$ and $v = 2.5 \times 10^{-3}$. In both cases, the size of the polymer was set to $N = 50$. The solid line, which yields a reasonable account of the data is obtained for a scaling exponent $\alpha = 1.53$, as defined in Eq. (11).

potential lead to compatible free energy profiles; the case of smaller translocation velocity yields smaller fluctuations, as expected.

We have found, as also shown in Fig. 3, that the free energy can be reasonably approximated as

$$\frac{F}{k_B T} \approx A[(N - m)^\alpha - \left(\frac{N}{2}\right)^\alpha],$$

where $A$ and $\alpha$ are fitting constants. Good interpolations are obtained for the parameter values $A = 1.0$ and $\alpha = 1.53$.

The Jarzynski Equality-based procedure for obtaining free energy variations has been carried out for polymers of sizes $N = 50$, 70 and 100, with a potential moving with velocity $v = 2.5 \times 10^{-3}$. The corresponding results are displayed in Fig. 4 in which, furthermore, we check the finite size scaling behavior of the free energy indicated from Eq. (11).

It is interesting to compare the results of Fig. 4 with the free energy profile put forward by Muthukumar, as given in Eq. (2). One clearly observes that the free energy curve proposed on purely theoretical grounds by Muthukumar decays not so fastly as ours do.
FIG. 4: In (a) we plot the free energy profiles obtained via Jarzynski Equality as a function of the trans-side monomer concentration. We have worked with the polymer sizes \( N = 50, 70 \) and 100. In (b) a clear finite-size scaling collapse is shown for the free energy values when they are rescaled by the size dependent factor \( N^{1.53} \).

In our model, the polymer is considered to be a self-avoiding chain having short-distance monomer-to-monomer and monomer-to-membrane interactions - this is also the point of view taken by Muthukumar [15]. Note, however, that our model includes, *ab-initio*, the vibrating degrees of freedom, a point not considered in the original Muthukumar formulation. The thermal effects associated to vibrations are likely, as suggested by our results, to strongly affect the free energy profile of the translocating polymer.

The collapse of the free energy profiles into a single curve, due to finite-size scaling effects, is a central result of our work. We call attention to a suggestive agreement between our results and the ones of Ref. [32], in which the free energy of a polymer interacting with a
FIG. 5: (a) The numerical data reported in Fig. 4(a) of Ref. [32] is (b) alternatively plotted taking into account a rescaling $N^{1.53}$ factor. The collapse is in fact similar to the one shown in our Fig. 4. We note that there is a clear anomaly of unknown origin for the case $N = 31$.

membrane is determined through histogram methods - a completely different methodological procedure – for relatively small polymer chains ($N \leq 41$). The results shown in [32] indicate that as the chain length increases the free energy curve no longer displays the profile originally predicted by Muthukumar. Moreover, we have checked that the free energy data reported in Ref. [32] have a finite- size scaling collapse similar to the one obtained here, as one can see from Fig. 5 (there seems to be, however, some anomaly with the data for polymers of size $N = 31$).
V. CONCLUSION

We have investigated, taking the Jarzynski Equality as a fundamental tool, the free energy profiles for the problem of unbiased three-dimensional polymer translocation. The use of a large cloud computing resource has allowed us to work with polymers and statistical ensembles of sizes which go reasonably beyond the ones commonly found in the literature of the subject. In our Langevin simulations, the use of the Jarzynski Equality has been implemented by means of a weakly invasive time dependent potential that behaves like an optical trap pulling monomers along a single monomer translocation event.

Our results show that the Muthukumar’s educated guess (2) for the free energy profile does not account with the behavior derived from Langevin simulations. As a clear result, we note that the larger is the size of the polymer the steeper the free energy becomes. Another important remark is the finite-size scaling collapse obtained for our data and for the one reported in Ref. [32] for small polymer sizes, when the free energy is rescaled by the factor $N^{1.53}$. A challenging statistical mechanics problem, of course, is to understand the finite-size scaling properties of the free energy discussed in Sec. IV.

An interesting question, which is actually open to further study, is whether the Fokker-Planck approach originally devised by Muthukumar [15] can lead to relevant results, if more realistic free energy profiles are taken into account. A motivating work, in this direction of research, is related to the discovery of free energy oscillations due to pore thickness effects [24]. Fluctuations arising from the delay due to the interactions with the membrane atoms are not captured in our study because of the one-atom-thick membrane used in our simulations. Also, we have not considered in this work situations where the initial monomer position would be slightly displaced from the membrane pore, in order to provide a more detailed account of the free energy variations as monomers cross the membrane pore. As a matter of principle, all of the aforementioned problems can be numerically studied along lines which have been addressed in the present paper.

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