

# Polymer translocation in the presence of excluded volume and explicit hydrodynamic interactions

Steve Guillouzic, Gary W. Slater \*

*Ottawa-Carleton Institute for Physics, University of Ottawa, Ottawa, Ontario, Canada, K1N 6N5*

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## Abstract

Molecular Dynamics simulations of polymer translocation are hereby reported. No external force was applied to the polymer during translocation, and the dynamics was dominated by polymer–pore interactions. It was found that hydrodynamic interactions play an important role in the relaxation of the polymer on each side of the membrane but have a negligible impact on the translocation process itself. Also, the scaling laws obtained for the relaxation and translocation times indicate that long translocating polymers may be considered to be following a quasi-equilibrium anomalous diffusion process in the absence of external forces.

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The sequencing of the human genome has marked a very important milestone in human history [1,2]. Indeed, the genetic code that defines our own species is now available, opening the door to a better understanding of our physiology and to a new generation of medical treatments. Up to now, however, only a generic version of the code has been determined. New methods are now being sought in order to allow the sequencing of the entire genome of individuals in relatively short periods of time (days, hours or even minutes instead of years). Such tools would further improve our ability to diagnose and treat illnesses. One of the techniques envisioned for attaining this goal involves polymer translocation, a process by which a polymer crosses a membrane through a small pore [3–7]. Translocation is for instance common in cellular activity, where biological molecules regularly cross nuclear and cellular membranes. It is currently believed that the individual bases of a DNA molecule could be rapidly and sequentially read as the molecule undergoes controlled translocation [8]. Another contemporary area of research where translocation plays a central role is in the development of

genetic treatments, where sequences of DNA must be inserted into individual cells.

The past few years have seen several attempts at modeling polymer translocation [9–11]. In most models, hydrodynamic interactions are neglected and the dynamics of the polymer is projected onto a univariate quantity known as the translocation coordinate  $s$ . This quantity is defined as the instantaneous length (or fractional length) of the linear polymer chain on an arbitrarily chosen side of the pore. The translocation is then assumed to occur on a timescale much larger than the one on which the two polymer arms relax on each side of the pore. This assumption allows the determination of a standard diffusion equation, also known as a Fokker–Planck equation, for  $s$  [10]. The exact form of this equation depends on the details of the dynamics, such as whether or not the polymer is driven by an external force or whether polymer entropy or polymer–pore interactions dominate over one another. The diffusion equation can be used for instance to characterize the translocation time, which is the time required by the polymer to cross the membrane through the pore given some boundary and initial conditions (see Fig. 1). In the absence of external forces, this calculation predicts that the mean translocation time  $\tau_{\text{trans}}$  scales as  $N^2$ , where  $N$  is the number of monomers [12]. This is appar-

\* Corresponding author.

*E-mail address:* [gary.slater@uottawa.ca](mailto:gary.slater@uottawa.ca) (G.W. Slater).

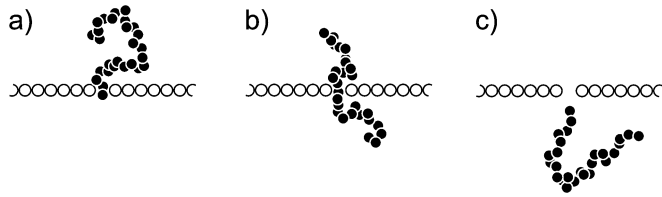


Fig. 1. Schematic representation of the translocation process. (a) The polymer starts on one side of the membrane. Through diffusion and the optional application of an external force, one end of the polymer eventually enters the membrane pore. (b) The polymer then moves back and forth through the pore. Unless it is prevented in one way or another, the polymer may backtrack completely to the original side of the membrane. When this happens, it has to thread again into the pore before proceeding with translocation. (c) The polymer eventually reaches the other side of the membrane. In general, this may require several translocation attempts.

ently the case in any number of dimensions and whether or not excluded volume is taken into account.

However, the relaxation time of polymer chains in solution often scales as  $N^\alpha$  with  $\alpha > 2$ . For phantom chains (i.e., chains without excluded volume interactions), we know that  $\alpha = 2$  without hydrodynamics and  $\alpha = 3/2$  with it [13]. For real self-avoiding chains, on the other hand, these exponents are  $\alpha \simeq 11/5$  and  $\alpha \simeq 9/5$ , respectively, for three-dimensional (3D) systems (note that for two-dimensional (2D) chains, theory predicts  $\alpha = 5/2$  and  $\alpha = 9/4$ , two values that are also larger than 2). Consequently, if the mean translocation time really scaled as  $N^2$  for all polymers, long self-avoiding chains could translocate, even in the absence of any external force, much faster than they relax. This would contradict the instantaneous relaxation assumption of the polymer arms that leads to a standard diffusion equation for the translocation coordinate [12].

This view has been supported by recent Monte Carlo simulations performed by Chuang and coworkers [12]. These authors observed that the mean translocation time of 1D and 2D polymers in the absence of any external force and of hydrodynamic interactions scales with  $N$  in the same way as their relaxation time in free solution, but with a prefactor approximately one order of magnitude larger. In particular, they found that the mean translocation time of self-avoiding chains in 2D scales as  $N^\beta$  with  $\beta \simeq 5/2 = \alpha$ . Following this discovery, they formulated a scaling argument for translocation based on earlier work on the dynamics of individual monomers in polymer coils [14]. They argued that the translocation coordinate  $s$  actually undergoes anomalous diffusion under certain circumstances because the individual monomers do not move freely with respect to one another. This implies that a standard diffusion equation does not always describe adequately the evolution of the translocation coordinate, and it explains why such an equation may lead to an improper scaling relation for the translocation time. In 3D and in the absence of an external force, Chuang and coworkers' argument leads to  $\langle \Delta s^2 \rangle \sim t^{1.12}$  and  $\tau_{\text{trans}} \sim N^{1.8}$  when hydrodynamic interactions are present (i.e., when we use the Zimm exponents for the dynamics of the polymer) and  $\langle \Delta s^2 \rangle \sim t^{0.92}$  and  $\tau_{\text{trans}} \sim N^{2.2}$  when they are not (this corresponds to the Rouse model of chain dynamics), where  $t$  represents time.

These authors also mention that the use of Zimm exponents is probably dubious because the flows must vanish near the wall.

The goal of this Letter is to resolve the controversy and test Chuang et al.'s conjecture. As we shall see, our results indicate that these authors were right and, consequently, that translocation models must take these new elements into account. We thus report on extensive coarse-grained (united atom) Molecular Dynamics simulations that have been performed to establish the relevant scaling relations in the presence of excluded volume *and* explicit hydrodynamics. In these simulations, the monomers, the solvent particles and the membrane particles were represented by identical beads interacting with one another through the pairwise and purely repulsive Lennard-Jones potential

$$V_{\text{LJ}}(r) = \begin{cases} 4\epsilon \left( \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^6 + \frac{1}{4} \right) & \text{if } \frac{r}{\sigma} \leq 2^{1/6}, \\ 0 & \text{if } \frac{r}{\sigma} > 2^{1/6}, \end{cases} \quad (1)$$

where  $\sigma$  is a measure of the size of individual particles,  $\epsilon$  is the interaction energy and  $r$  is the distance between the interacting pair of particles. In addition to the Lennard-Jones interaction, successive monomers in the polymer chain were held together using the finitely extensible non-linear elastic (FENE) potential

$$V_{\text{FENE}}(r) = -\frac{\kappa}{2} \lambda^2 \ln \left( 1 - \frac{r^2}{\lambda^2} \right), \quad (2)$$

where  $\lambda$  is the upper bound for bond length and  $\kappa$  is the spring constant. As is common practice [15], the two parameters in Eq. (2) were set to  $\lambda = 1.5\sigma$  and  $\kappa = 30\epsilon/\sigma^2$ , thus ensuring that the excluded volume of the polymer chain was properly taken into account. A two-dimensional triangular lattice with a nearest-neighbor spacing of  $1 \times \sigma$  was then used for the membrane, and the translocation pore was simply obtained by removing a single bead. Similarly, the solvent was made of  $n \times n \times n$  particles (with  $n$  usually set to 30), of which some were removed to free space for the polymer at the beginning of the simulation. The solvent density was set to  $\rho = 0.85$  by adjusting the size of the box in the direction perpendicular to the membrane. In order to prevent the arms of the polymer on each side of the membrane from interacting (indirectly) through this relatively thin wall, the membrane particles were kept immobile. In addition, the simulations were performed using periodic boundary conditions in all directions. This was particularly critical in the direction perpendicular to the membrane, since it prevented the induction by the translocation process of a pressure difference between the two sides of the membrane. Extensive simulations were carried out for various box sizes  $n$ , and it was found that for sizes  $n \geq 20$ –25, the various parameters studied here remained constant, thus indicating that finite-size effects were negligible (an example is shown in the inset of Fig. 3).

Each simulation of the translocation process was initialized with the middle monomer centered in the membrane pore. It then proceeded with a warm-up period, which duration was determined in preliminary simulations by monitoring the equilibration of temperature and the relaxation of a polymer with the middle monomer permanently held into the pore. During the warm-up period, the middle monomer was constrained to the

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