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Polymer translocation

The polymer translocation is a dynamic process in which a polymer pass through an hole whose size is generally much smaller than the average extension of the polymer. With the advent of nano-technologies it is possible to build up impenetrable walls with nano-holes in it but the polymer translocation is also an important biological process related to the migration of DNA and RNA molecules from one region to another of the cell, generally by passing through a narrow pore of the nuclear membrane[**?**]. Translocation processes may also have practical applications such as the possibility of reading the DNA or RNA sequence by passing it through an artificial nano-pore or α-hemolysin channel [**?**]. For the polymer moving through the pore the number of available configurations decreases. Hence, in *in vitro* experiments the polymers that are typically DNA or RNA i.e. negatively charged molecules, are driven across the membrane with the help of external electric fields. when the polymer is in the pore the membrane current, produced mainly by small ions present in the system, decreases significantly. It is then possible to measure the translocation time by looking the time the current is blocked in the pore.

Translocation of a polymer involves both considerations on the interactions at molecular level between the elementary units making the polymer (monomers) and the molecules of the channel as well as macroscopic factors such as the statistics and dynamics of the long polymer. In a coarse grained description the macromolecule is described by a sequence of beads connected together sequentially in order to form a chain (see Chapter on polymers) while the membrane with the pore can be described as an impenetrable, non fluctuating, wall with a small hole in it. Within this framework one can add the following simplifications (Sung and Park 1996):

1. The thickness of the wall is negligible and the pore is small enough to allow only a single monomer passage at once.

2. The interaction of the polymer segments with membrane is considered to be only of steric origin, i.e. the monomers cannot cross the wall except through the pore (excluded volume interaction).

Given the hypothesis above the process is essentially 1D and can be described by a single variable s representing the monomer number at the pore. This variable indicates how far the polymer has progressed and it is called *translocation coordinate*. Another important hypothesis is the following:

Hypothesis 0.0.1. The translocation process is very slow compared to the equilibration process of the polymer. In other words the time scale over which the position s varies in an appreciate way is much bigger than the time scale over which the whole polymer relaxes.

If this is the case the polymer segments on both sides of the membrane have time to equilibrate and at each stage of the translocation process the statistics of the segments will be governed by the equilibrium Boltzmann weight. We now first compute the free energy due to the equilibrated part of the process. Suppose that at given time t the monomer at the pore is the s-th monomer. If the total length of the polymer is L there will be a segment of length s in region II (trans) and $N - s$ in region I (cis). Because of the presence of the hard wall the two segments are independent and the free energy of the system is simply given by the sum of the free energies of the two segments. If

there are no interactions other than the steric repulsion with the wall, the free energy of a polymer of length s anchored through a monomer to a wall is simply given by the entropic term

$$F_s(T) = -k_B T \log \left[q_{eff}(T)^s s^{\gamma_1 - 1} \right] \tag{1}$$

where $q_{eff}(T)$ is the exponential part of the entropy and is related to the effective coordination number per monomer whereas is the so called surface entropic correction exponent. The total free energy is then given by

$$
\begin{aligned}
F(s, N; T) &= F_s^{II}(T) + F_{N-s}^I(T) \\
&= k_B T \left((1 - \gamma_1^{II}) \log s + (1 - \gamma_1^I) \log(N - s) \right. \\
&\quad - \left. s \log q_{eff}^{II}(T) + (s - N) \log q_{eff}^I(T) \right)
\end{aligned} \tag{2}
$$

where the superscripts indicates the region in which the segment is located. Taking only the s dependent part we have

$$F(s, N, T) = k_B T \left((1 - \gamma_1^{II}) \log s + (1 - \gamma_1^{II}) \log(N - s) + s \log(q_{eff}^I(T)/q_{eff}^{II}(T)) \right) \tag{3}$$

In general $\gamma_1^{II} = \gamma_1^I = \gamma_1$ giving

$$F(s, N, T) = k_B T \left((1 - \gamma_1) \log(s(N - s)) + s \log(q_{eff}^I(T)/q_{eff}^{II}(T)) \right). \tag{4}$$

If there is no external field or the solvent conditions in the two regions are equal then $q_{eff}^I(T) = q_{eff}^{II}(T)$ and

$$F(s, N, T) = k_B T(1 - \gamma_1) \log(s(N - s)). \tag{5}$$

This is the so called (*unbiased translocation*) problem. For Gaussian (random walk) chains $\gamma_1 = 1/2$, whereas for self-avoiding chains $\gamma_1 \simeq 0.69$. Let us focus for simplicity to the Gaussian case. Hence

$$F(s, N, T) = \frac{k_B T}{2} \log(s(N - s)). \tag{6}$$

This means that there is a symmetric barrier of entropic origin that for a long chain is nearly flat except near $s = 1$ or $s = N$. We can now model the unbiased translocation process as a 1D stochastic process with potential barrier given by (6). As the monomer moves forward or backward through the pore a distance a (of the order of the typical separation size between contiguous monomers) the relevant monomer number increases or decreases by unity in a random manner. Moreover , because of hypothesis (0.0.1), the monomer at the pore experiences a mean force that can be obtained from the variations of the free-energy $F(s, T)$. Treating s as a continuous variable we can then construct a Langevin equation for $s(t)$ in the over-damped limit as

$$\Delta s = -\frac{1}{\gamma m} \frac{\partial F}{\partial s} \Delta t + 2 D^{1/2} \Delta W \tag{7}$$

where $\Delta W(t)$ are the increments of a Wiener process with variance equal to $m k_B T$. To this Langevin equation it corresponds the Fokker-Planck equation:

$$\frac{\partial p(s, t)}{\partial t} = \frac{\partial}{\partial s} \left[\frac{1}{\gamma m} \frac{\partial F}{\partial s} p(s, t) \right] + \frac{\partial^2}{\partial s^2} D \left(p(s, t) \right) \tag{8}$$

where D is the chain diffusivity during translocation. In principle $D = D(s)$ but let us assume for simplicity that the diffusion coefficient is constant during the translocation. In this case, dividing and multiplying by $k_B T$ the first term of the left hand side, and remembering that $D = k_B T/(m\gamma)$ we get

$$\frac{\partial p(s, t)}{\partial t} = D \frac{\partial}{\partial s} \left(\frac{1}{k_B T} \frac{\partial F}{\partial s} p(s, t) + \frac{\partial}{\partial s} p(s, t) \right) \tag{9}$$

that can be written as

$$\frac{\partial}{\partial t}p(s,t) = \hat{L}_{FP}(s)p(s,t) \tag{10}$$

where

$$\hat{L}_{FP}(s) = D\frac{\partial}{\partial s}e^{-F(s)/k_BT}\frac{\partial}{\partial s}e^{F(s)/k_BT} \tag{11}$$

Clearly the translocation time depends on the way we define the boundary and initial conditions of the process. To our purposes we consider the following conditions

Boundary conditions we consider a process in which the first monomer can never be withdrawn from the pore, and that after the Lth monomer crosses the wall, the polymer will no longer return to it. These physical conditions corresponds in assigning the reflecting and adsorbing BCs, respectively, at $s=1$ and $s=N$:

$$j(s=1,t|s_0,0) = 0, \qquad p(s=N,t|s_0,0) = 0. \tag{12}$$

Initial conditions The translocation process starts when the first monomer is at the pore while the rest of the chain is in the *cis* region. This corresponds to consider the initial condition

$$p(s,t \to 0|s_0,0) = \delta(s-1). \tag{13}$$

With these condition the average translocation time $\langle \tau_T \rangle$ corresponds to the MFPT $T_1(1)$ of the process.

From section **??** we know that the MFPT can be obtained by solving the ODE

$$\hat{L}_{s_0}^{\dagger}T_1(s_0) = -1 \tag{14}$$

where

$$\hat{L}_{s_0}^{\dagger} = De^{F(s0)/k_BT}\frac{d}{ds_0}e^{-F(s_0)/k_BT}\frac{d}{ds_0}. \tag{15}$$

We then have

$$D\frac{d}{ds_0}e^{-F(s_0)/k_BT}\frac{d}{ds_0}T_1(s_0) = -e^{-F(s_0)/k_BT} \tag{16}$$

To obtain a formal solution we first integrate both terms of the above equation in the interval $[s_0,s] = [1,s]$. This gives

$$e^{-F(s)/k_BT}\frac{d}{ds}T_1(s) - e^{-F(1)/k_BT}\frac{d}{ds}T_1(1) = -\frac{1}{D}\int_1^s e^{-F(s')/k_BT}ds' \tag{17}$$

On the other hand $\frac{d}{ds}T_1(1) = 0$ and by integrating both terms once more between the extremes $[1,N]$ we get

$$T_1(N) - T_1(1) = -\frac{1}{D}\int_1^N e^{-F(s)/k_BT}\left(\int_1^s e^{-F(s')/k_BT}ds'\right)ds \tag{18}$$

and since $T_1(N) = 0$ we have

$$T(1) = \frac{1}{D}\int_1^N dse^{F(s)/k_BT}\int_1^s ds'e^{-F(s')/k_BT}. \tag{19}$$

Let us first consider the case in which $q_{eff}^I(T) = q_{eff}^{II}(T)$ and F does not depend on s (no entropic barrier). Remember that the entropic potential is almost everywhere flat except that close to the two BCs. We then have

$$T_1(1) = \langle \tau_T \rangle = \frac{(N-1)^2}{2D} \sim \frac{L^2}{2D}. \tag{20}$$

If on the other hand there is still no external force but the entropic barrier is present and given by (5) then

$$
\begin{aligned}
T_1(1) &= \frac{1}{D} \int_1^N ds \sqrt{s(N-s)} \int_1^s ds' \frac{1}{\sqrt{s'(N-s')}} \\
&= \frac{1}{D} \int_1^N ds \sqrt{s(N-s)} \left[\arctan\left(\frac{s'-N/2}{\sqrt{s'(N-s')}} \right) \right]_{s'=1}^{s'=s} \\
&= \frac{1}{D} \int_1^N ds \sqrt{s(N-s)} \arctan\left(\frac{s-N/2}{\sqrt{s(N-s)}} \right) \\
&\quad - \frac{1}{D} \int_1^N ds \sqrt{s(N-s)} \arctan\left(\frac{1-N/2}{\sqrt{N-1}} \right) \\
&= 0 - \frac{1}{D} \int_1^N ds \sqrt{s(N-s)} \arctan\left(\frac{1-N/2}{\sqrt{L-1}} \right) \\
&= -\left[\frac{1}{2D} \arctan\left(\frac{1-N/2}{\sqrt{N-1}} \right) \left[s\sqrt{Ns-s^2} - \frac{1}{2}L\sqrt{Ns-s^2} + \frac{1}{4}N^2 \arctan\left(\frac{s-1/2\,N}{\sqrt{-s^2+Ns}} \right) \right] \right]_1^N \\
&= \frac{1}{4D} \arctan\left(\frac{N/2-1}{\sqrt{N-1}} \right) \left(2\sqrt{N-1}(N-2) + L^2 \arctan\left(\frac{N/2-1}{\sqrt{N-1}} \right) \right) \\
&\sim \frac{\pi^2}{16} \frac{N^2}{D} = \frac{\pi^2}{8} \left(\frac{N^2}{2D} \right)
\end{aligned}
\tag{21}
$$

While the length scaling behaviour of the translocation time of flexible chain is the same as that of the rigid chain (eq. 20) (no entropic term), the prefactor of $\pi^2/8$ indicates that the chain flexibility (i.e. with the logarithmic potential barrier) retards translocation only by $\sim 20\%$. More strikingly, there is little difference in the distribution of times with or without an entropic barrier.

Note. The version with no entropic barriers corresponds to the passage of a polymer through a ring. Indeed in this case although the polymer must pass through a constricted space, its free ends may be have any possible configuration.

Remark. For a polymer chain of N beads it is known that

$$
D \sim N^{-\sigma}
\tag{22}
$$

whit $\sigma = 1$ for Rouse dynamics and $\sigma = 1/2$ if hydrodynamic interactions are included (Zimm model). Since, by Rouse dynamics, $D \sim N^{-\sigma}$ We then have

$$
\langle \tau_T \rangle \sim \frac{\pi^2}{16} N^2 \sim N^{2+\sigma}
\tag{23}
$$

Hence, the translocation time is proportional to $N^{2+\sigma}$ and, interesting enough, with $\sigma = 1$ (Rouse dynamics) this scaling behaviour is identical to that of chain reptation time in entangled polymer systems [**?**, **?**].

0.0.1   External field

Suppose now that the polymer is negatively charged (as DNA for example) and that in the trans region a uniform electric field is present. In this case if in region II there are s monomers there will be an energy term of the order $-eEs$. This would corresponds to a Boltzmann factor $\exp(\beta eEs)$ and to a free energy term $f_E^{II} = -eEs$. In other words in region II there is a chemical potential $\mu^{II} = -eE$ and the full free energy is given by

$$
F(s, N|T) = k_B T(1-\gamma_1) \log(s(L-s)) + s\Delta\mu + const.
\tag{24}
$$

with $\Delta\mu = \mu^{II} - \mu^{I} = \mu^{II} = -eE$. For the Gaussian case

$$F(s, N|T) = \frac{k_B T}{2} \log(s(L-s)) + s\Delta\mu. \tag{25}$$

In this case the MFPT is given by

$$T_1(1) = \frac{1}{D} \int_1^N ds e^{s\Delta\mu/k_B T} \sqrt{s(N-s)} \int_1^s ds' \frac{e^{-s\Delta\mu/k_B T}}{\sqrt{s'(N-s')}} \tag{26}$$

where, again, the independence of D from the coordinate s is considered. If we neglect the entropic term with respect to the chemical potential term equation above simplifies to

$$T_1(1) = \frac{1}{D} \int_1^N ds e^{s\Delta\mu/k_B T} \int_1^s ds' e^{-s\Delta\mu/k_B T} \tag{27}$$

0.0.2 Limitations

There are several limitations in analysis presented above. Let us list some of these

$D = D(s)$ As we said before in principle the diffusion constant depends on the size s of the translocated chain.

Two time scales failure The analytical considerations described in previous sections rests on hypothesis 0.0.1, i.e. on the assumption that translocation is slow. In particular it should be slow enough that the two polymeric segments on the two regions are in equilibrium at each value of s. The minimal requirement is that the typical translocation time τ should exceed the equilibration time τ_{eq} of a polymer. For a chain of finite size it is always possible to achieve this limit by designing a pore with large friction coefficient. This seems to be the case of the experiments in [**?**]. On the other hand for sufficiently big values of N ($L = Nb$) this assumption fails because the equilibration time depends strongly on N. Indeed the equilibration time of a free polymer may be estimated as the time required for it to diffuse for a distance of the order of a typical size , say the mean radius of gyration, R_g. Under Rouse dynamics (ignoring hydrodynamic effects) the diffusivity of the center of mass of a N-monomer polymer is reduced to D/N where D is the diffusion constant of a single monomer. This will then give an equilibration time of order $R_g^2 N/D$. For Gaussian chains $R_g^2 \sim N$ and the equilibration time is of the same order (N^2/D) as the MFPT obtained with the simple theory of Brownian translocation dynamics. Hence the equilibrium assumption is marginally (in)valid in this case. For self-avoiding polymers $R_g \sim N^\nu$ where $\nu = 3/4$ id $d = 2$ and $\nu = 0.5889$ in d=3. The resulting relaxation time scales as $N^{1+2\nu}/D$ and is now longer than the translocation time ($\sim N^2/D$) by Brownian dynamics. Consequently the approximations involved are not self consistent for N big enough.

In the last years [] there have been many studies on polymer translocation mainly based on numerical simulations in which the size N of the polymer has increased in order to explore the regime in which the two time scales are comparable. In particular it has been shown that for $N >> 1$ the equilibration process tends to slow down the translocation one and the stochastic forces acting on s are somehow anti-correlated. This gives rise to a process $s(t)$ that display an *anomalous diffusion* behaviour i.e. with $Var\{s(t)\} \simeq t^\alpha$ with $\alpha = \frac{2}{1+2\nu} \simeq 0.8$. In other words the process is *sub-diffusive*. Moreover it has been shown that

$$T_1(1) = \langle \tau_T \rangle \simeq N^{1+2\nu} \tag{28}$$

More recently Kardar et al [**?**] have shown by numerical simulations that indeed the process is sub-diffusive. In the numerical experiment the polymer was first normalized by keeping fixed the middle monomer at the pore and then released this constraint by letting to translocate in both

directions. This corresponds to take two absorbing BC $p(1,t|s_0,0) = p(N,t|s_0,0) = 0$ and to consider as the initial condition $p(s,0|s_0,0) = \delta(s-s_0) = \delta(s-N/2)$. In this situations they have estimated not only the average translocation time but also the distribution $p(s,t|0,N/2)$ and the distribution $w(t|N/2)$. In addition to the sub-diffusive behaviour they also found that if the quantity $w(t,|N/2)T_1(N/2)$ is plotted versus $t/T_1(N/2)$ it does not depend on N and for large time it decays exponentially. Moreover the probability distribution $p(s,t|N/2,0)$ follows, for times smaller than the average translocation time, is a Gaussian with $Var(s) \sim T^\alpha$ ($\alpha \simeq 0.8$). However, for times larger then $\langle\tau_T\rangle$ the $p(s,t|N/2,0)$ restricted to the set of polymers that are still non translocated, has a non trivial form that fits well with $A\sin^k[s\pi/(N+1)]$, $k = 1.44$. It is interesting to notice that there exists a way, based on the theory of fractional FP equations, to explain the sub-diffusive character of the process. This theory, however, is not consistent with the exponential decay and with the anomalous behaviour of the $p(s,t|N/2,0)$ in the large time limit.

How can we study a anomalous diffusion processes in presence of two absorbing boundaries ? (TODO)