Reaching to a small target: entropic barriers and rates of specific binding of polymer to substrate

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This paper considers a broadly biologically relevant question of a chain (such as a protein) binding to a sequence of receptors with matching multiple ligands distributed along the chain. This binding is critical in cell adhesion events, and in protein self-assembly. Using a mean field approximation of polymer dynamics, we first calculate the characteristic binding time for a tethered ligand reaching for a specific binding site on the surface. This time is determined by two separate entropic effects: an entropic barrier for the chain to be stretched sufficiently to reach the distant target, and a restriction on chain conformations near the surface. We then derive the characteristic time for a sequence of single binding events, and find that it is determined by the ‘zipper effect’, optimizing the sequence of single and multiple binding steps.

Ordered self-assembly requires the ability to organize and bind many molecules into a coherent structure. In biology, most self-assembling structures rely on specific interactions, matching ligands, and distinct binding sites. The kinetics of self-assembly is a broad and rich topic, which offers a fundamental understanding of processes being used in the construction of structured and functional aggregates.

One such process is the binding of a polymer chain to a sequence of receptor sites on a substrate. In considering adhesion of cells to each other, Jeppesen et al. had this problem for one specific binding site, where ligands tethered to the cell surface by flexible chains could also associate with the matching receptor on the adjacent cell. They found a dependence on the configuration of the polymer tether: in particular, how often the chains entered extended configurations to reach the distant receptors. Their treatment did not extend to an analytical expression of the binding rate, or multiple binding sites. Theoretically solving this problem is one of our main tasks here.

Another example of ‘reaching to a small target’ is the polymer chain that could bind at multiple sites to the same surface, as in Fig. 1. Given a set of binding residues on the polymer chain, and a specifically placed set of receptors on the surface, what is the forward reaction constant of the full binding process? As a step towards the full problem, here we first consider the polymer after an initial binding event to the surface. This graft to the surface is persistent; we regard the tether as fixed. The remaining free chain has a second binding site, which undergoes thermal motion. It is able to bind to a second receptor also on the surface, a fixed distance away from the tethered origin. We calculate the mean time it takes the chain to ‘find’ the target receptor, and discover that it is determined by an activation law where the effective potential barrier is purely entropic, $-T\Delta S$: as such, the explicit temperature disappears from the ‘activation law’ and the mean binding time is proportional to $\exp[a^2/R_g^2]$, with $R_g$ the radius of gyration of the tethered chain.

The search for a small target has already been considered in the context of polymer looping, where the time for two separate monomers on a polymer chain to meet was calculated. Such loops are observed experimentally in chromatin. In fact, our calculation is based on the ideas of Szabo et al., although in their problem of forming a loop the distance to the binding site $a = 0$ and accordingly no activation exponential has been observed. These types of problem are similar to the ‘narrow escape problem’. Here a Brownian particle is confined to a domain whose boundary is entirely reflecting, apart from a small absorbing patch. The ‘narrow escape time’ is the mean first time the particle reaches the absorbing patch and escapes the volume it was diffusing in.

When examining molecules confined to particular regions of space, we must consider carefully how this confinement shows up in a mathematical framework. In the narrow escape problem for diffusing particles, the boundary is considered reflecting, with zero particle flux through the surface – but in polymer physics the ‘hard’ wall has a different effect due to the chain connectivity: the wall imposes an effective repulsive barrier making the monomer density zero on the wall. We discuss the ramifications of these boundary conditions by considering both a tethered polymer chain, comparing it with related problems in the literature.

The chain has a ‘hard’ constraint of the wall to which it is grafted to, but its free end (with the binding ligand) also has a soft constraint on how far it can extend from
the grafted origin. If the chain’s end-to-end distance increases, there will be a resulting reduction in entropy. Associated entropic barriers for activated processes have been investigated in polymer dynamics, and in colloid glassy dynamics. Entropic barriers have an important role to play in cell biology. They show up in polymer translocation through a membrane pore, as well as the mean looping time of a polymer chain. They also play a role in the protein aggregation into amyloids, and in more general protein folding funnel problems.

In this paper, we examine a trade-off in the entropy barrier faced by reaching the distant target against the reduction in confinement. If we make the chain very short, there will be a very small chance of it stretching far enough to reach the receptor site, and the time to reach the receptor will be long. If we make the chain very long, there will no longer be such an entropic penalty for reaching the same receptor. However, the chain will now be able to explore a very large volume, and that reduces the probability that the binding site will hit the target. Once the expression for the average binding time $\tau_{\text{on}}$ is obtained, we find the optimal chain length for the fastest binding time: this turns out to be exactly when the target separation $a$ is equal to the radius of gyration of the chain. Finally, we consider the time of binding to a sequence of receptors, calculating it as a function of chain length, number of binding sites and the distance between them. We find that the presence of binding sites along a chain massively enhances the rate of binding the whole chain. Finally, we consider the time of binding to a sequence of receptors, calculating it as a function of chain length, number of binding sites and the distance between them. We find that the presence of binding sites along a chain massively enhances the rate of binding the whole chain, in a so-called ‘zipper effect’: changing the scaling of mean binding time from an exponential relationship with chain length to a linear function.

DIFFUSION OF A GRAFTED LIGAND

We consider an ideal polymer chain ($N$ segments of length $b$) that is grafted at the origin to a flat surface, where the last ($N$th) monomer is the binding ligand. To find the equilibrium distribution of the chain configuration, we use the Gaussian chain propagator of an ideal chain $G_N(\mathbf{r}, \mathbf{r}_0)$. This is the probability that such a chain begins at $\mathbf{r}_0$ and ends at $\mathbf{r}$, and it satisfies the Edwards equation:

$$
\left( \frac{\partial}{\partial N} - \frac{k_B T}{6} \nabla^2 + \frac{U_e(\mathbf{r})}{k_B T} \right) G_N(\mathbf{r}, \mathbf{r}_0) = \delta(\mathbf{r} - \mathbf{r}_0) \delta(N). \tag{1}
$$

The potential $U_e(\mathbf{r})$ represents any external forces applied to the monomer, and we here will consider the basic problem with $U_e = 0$. We need to implement a boundary condition on the substrate plane $z = 0$. This is a question with a very long history, culminating with the classical work of Edwards and Freed about the ‘chain in a box’. Many aspects of this problem, of a chain near a hard wall, were explored over the years, with seminal contributions being just a few of many important references, all using and exploiting the ‘exclusion’ condition:

$$
G_N(\mathbf{r}_s(\mathbf{r}, \mathbf{r}_0)\big|_{\text{surface}} = 0. \tag{2}
$$

This means, in the case of (1), that no monomer may rest against the wall. Surprisingly, this restriction is not well covered in the literature, and it is difficult to acquire intuition for it. Exclusion seems drastically different from the (correct) reflecting boundary condition we impose on Brownian particles, if they were not connected on the chain. This is a subtle, yet potent effect of chain configurational entropy – understood first by DiMarzio from the point of view of counting restricted chain configurations, and then by Edwards and Freed by looking at the entropic repulsive force arising if we were to push the chain into a wall.

When only one planar wall is present, the solution of the Edwards equation involves one negative chain image. Although we tether the chain at the origin $\mathbf{r} = 0$, it is necessary to insist that the first monomer steps directly away from the surface, so $z_0 = b$, and the image chain starts at $z_0 = -b$. The remaining chain is then of length $N - 1$, but since we must assume $N$ is large, we ignore this:

$$
G_N(\mathbf{r}) = \left( \frac{3}{2\pi N b^2} \right)^{3/2} e^{-\frac{3(z^2 + b^2)}{2N b^2}} e^{-\frac{3(z-b)^2}{2N b^2}} e^{-\frac{3(z+b)^2}{2N b^2}}. \tag{3}
$$

The binding ligand (the $N$th monomer) needs to find a surface receptor placed a distance $a$ from the grafting site, as illustrated in Fig. 2. The receptor zone is assumed hemispherical, with a small radius $\epsilon$. We will now construct an effective radial probability distribution for the distance $\rho$ from the binding site $\mathbf{r}_s$ to the target receptor. That radial probability distribution $P_{\text{rep}}(\rho)$ becomes amenable to the first passage time approach of Szabo et al.

In Eq. (3), the propagator for the position of the chain end is presented using a Cartesian coordinate system

![FIG. 2. A Gaussian chain of $N$ monomers is tethered to a hard wall at the origin. A hemispherical absorbing target of radius $\epsilon$ lies on the surface, a distance $a$ from the tether. We switch from Cartesian coordinates about the tether to spherical polar coordinates about the target, to find the mean first passage time of the end of the chain onto the target.](image)
with the origin at the point of grafting. However, since we are looking for the passage time into a hemisphere centered on a receptor, it useful to shift the to spherical polar coordinates \((\rho, \theta, \phi)\) centered on the target, Fig. 2.

Then we will need to integrate over the two angles, to finally derive the radial probability density about the target receptor, \(P(\rho)\), which will be a function of the receptor position \(a\). Let us choose the target to be in the positive \(x\)-direction relative to the tethered end. Thus we can write the coordinate transformation as

\[
x - a = \rho \sin \theta \cos \phi, \quad y = \rho \sin \theta \sin \phi, \quad z = \rho \cos \theta.
\]

The two scalar products in the combined exponents of Eq. (3) become:

\[
(r \pm b\hat{z})^2 = a^2 + b^2 + \rho^2 + 2a\rho \sin \theta \cos \phi \pm 2b\rho \cos \theta \sin \phi.
\]

The next step of integration over the solid angle on the unit hemisphere is not easy. We need to evaluate

\[
I = \int_0^{\pi/2} d\theta \sin \theta \int_0^{2\pi} d\phi \ e^{-\alpha \cos \phi \sin \theta \pm \beta \cos \theta},
\]

where parameters \(\alpha\) and \(\beta\) involve \(N, b, a\) and \(\rho\). This is solved by realizing that the integrand has a non-trivial axial symmetry. To exploit this symmetry, one needs to transform back into Cartesian coordinates about the target; \(x' = \cos \phi \sin \theta, \quad z' = \cos \theta\), and rotate these new coordinates by an angle \(\varphi = \tan^{-1}(\beta/\alpha) = \tan^{-1} (b/a)\) around the \(y\)-axis. The direction of this rotation depends on the sign of the \(z\)-term in the exponent (i.e. whether we are dealing with the ‘real’ or ‘image’ Gaussian term). The details of this calculation are given in Supplementary part A, including the full expression for the normalized radial distribution function \(P_{eq}(\rho)\). It turns out that a very good approximation exists to that complicated expression, which is nearly accurate except for the region \(a \leq b\). We believe it is safe to assume the receptor site can never be this close to the grafting site, and proceed with the useful approximation:

\[
P_{eq}(\rho) \approx \frac{2b}{a} \sqrt{\frac{N\pi}{6}} \left( \frac{3}{2\pi Nb^2} \right)^{3/2} e^{-\frac{3a^2 + 2b^2}{2Nb^2}} I_1 \left( \frac{3a\rho}{Nb^2} \right),
\]

where \(I_1(\cdot)\) is the the 1st rank modified Bessel function of the first kind, and \(\sqrt{6/\pi} \) is the thermodynamic partition function of a grafted Gaussian chain.

This distribution is plotted in Fig. 3. The probability density goes to zero as \(\rho \to 0\) because of exclusion at the surface, and then peaks before decaying away again. This distribution peak is going to be close to the target distance: \(\rho \approx a\), because the chain is most likely to be found near the tether. The actual peak lies at just less than \(\rho = a\), as a result of averaging over the polar angles, but the difference becomes less significant as \(a \gg R_g\).

One can identify the radial probability density discussed above with an effective radial potential via the Boltzmann factor: \(V_{eff} = -k_B T \ln P_{eq}(\rho)\). The resulting effective potential that the binding ligand on the \(N\)th chain segment experiences is a function of distance from the target receptor, and depends on two relevant length scales in the problem: the chain radius of gyration \(R_g = N^{1/2}b\), and the distance to target \(a\). It is plotted in Fig. 4, for two values of \(a\): one above and one below the \(R_g\). The effective potential has a minimum (seen as the peak of the radial probability distribution), but diverges in the close proximity to the target because of the exclusion boundary condition the wall imposes on the chain: this produces an effective (entropic) repulsion that the ligand has to overcome to reach the target at \(\rho \to 0\). We see in Fig. 4 that this effective energy barrier (between the minimum of \(V_{eff}\) and the value at \(\rho = \varepsilon\)) is \(\sim 2k_B T\) for \(a = 5b\), raising to \(\sim 5k_B T\) for \(a = 20b\), for the chain of 100 monomers.

**MEAN FIRST PASSAGE TIME TO TARGET**

Once we have the equilibrium probability distribution for the single radial variable \(\rho\) (the distance of the dangling ligand from the target receptor), we can use a fa-
mous relation derived by Szabo et al.\(^\text{[3]}\) to find the mean first passage time (MFPT) to an absorbing surface at \(\rho = \varepsilon\). This time is obtained by evaluation:

\[
\tau = 2\pi \int_\varepsilon^\infty d\rho \left[ D\rho^2 P_{eq}(\rho) \right]^{-1} \left[ \int_\rho^\infty d\rho' \rho'^2 P_{eq}(\rho') \right]^2,
\]

where we assume the diffusion coefficient of the free end of the chain, \(D = k_B T / \gamma\), is constant and equal to the diffusion coefficient of a single monomer in solution. In the free particle case, it is necessary to constrain the particle with an upper reflective boundary, but in our case of a Gaussian polymer chain, the entropic spring effect ensures the integrals converge if we take the upper limit to \(\infty\).

Even for the approximate probability distribution given in \(\text{[7]}\), the integral in \(\text{[8]}\) does not have an easy analytical solution. However, much progress can be achieved by noticing that the integrand diverges as \(\rho \to 0\), and so the main contribution to the mean first passage time comes from the region of small \(\rho\). The technical details of this calculation can be found in the Supplementary part \(\text{[3]}\). Expanding the integrand about \(\rho = 0\) and retaining only the leading term, we find that \(\text{[8]}\) reduces to a simple integral

\[
\tau_{on} \approx \frac{2N^2b^4}{9 D} e^{3a^2/2N b^2} \int_\varepsilon^\infty \frac{d\rho}{\rho^3} = \frac{N^2b^4}{9 D \varepsilon^2} e^{3a^2/2N b^2},
\]

where, before we recognize the characteristic length scale \(R_g = N^{1/2}b\), the radius of gyration of an ideal chain.

Equation \(\text{[9]}\) is the first of two main results of this paper. The comparison of the exact numerical integral and the approximation in \(\text{[9]}\) above is shown in Fig. 5 where the mean time of the binding ligand reaching the target receptor is plotted against the ‘size’ of the receptor (measured by the radius of the hemisphere \(\varepsilon\), see the sketch in Fig. 2). The deviations are enhanced in Fig. 5 inset by the logarithmic scale, and are evidently very small for sufficiently small targets.

Clearly, \(\text{[9]}\) is a good approximation, offering a compact analytical expression that we can examine. One can compare it with the average time for a free polymer chain to make a loop by having the last \(N\)th monomer reach a sphere of radius \(\varepsilon\) around the first monomer (the Szabo problem, corresponding to distance \(a = 0\) in our case, and no restricting surface – solved using our method in Supplementary part \(\text{[3]}\):

\[
\tau_{\text{loop}} = \sqrt{\frac{\pi}{54} \left( \frac{Nb^3}{D} \right)^{3/2}},
\]

Also instructive is to compare our expression \(\text{[9]}\) with the average time for a free Brownian particle to escape a closed volume \(V\) through a small hole of size \(s\) (the ‘narrow escape problem’ of Holcman et al.), which is estimated as \(\tau_{\text{esc}} = V / D \varepsilon\). If the volume is replaced by the average extent of chain spreading, \(V = R_g^3\), this matches the Szabo expression \(\text{[10]}\). Both have a different scaling with the size of target, \(1 / \varepsilon^2\) compared to \(1 / \varepsilon^2\) in \(\text{[9]}\). In our case the chain is strongly inhibited from approaching the wall due to the polymer-specific boundary condition; as a result the average time it takes to reach the target is much longer even without the additional exponential factor reflecting the entropic barrier for binding.

The second factor that distinguishes the mean binding time in \(\text{[9]}\) is the exponential factor \(\exp(3a^2/2R_g^2)\). This represents thermal activation over an entropic barrier \(\Delta \tau = k_B T a^2 / 2 R_g^2\), which is essentially the free energy to stretch the chain ends by a distance \(a\). This factor, significantly increasing the time for bridging to a distant target, only arises for the tethered chain (all polymer work on the related narrow escape problems\(\text{[4,5,9,13]}\) has thus far focused on polymers with no attachment to the boundary of the domain, which fundamentally alters the accessibility of the binding site).

**MULTIPLE BINDING SITES**

We can now use the foundation \(\text{[9]}\) to analyze a simplified version of the multiple-site binding problem. Let us consider \(M\) binding sites spaced evenly along a polymer chain of total length \(N\) (so that the ligands are \(\Delta N = N / M\) monomers apart). As in the single site problem, we take the first segment of the chain to be already bound to the surface, so there are \(M\) binding events yet to occur in total. The receptors for these ligands are spaced at equal distances \(\Delta a\) apart in a straight line on a plane reflecting surface, see Fig. 5(a). While it should not be difficult to consider arbitrary positioning of chain binding sites and surface receptors, we use this simplified geometry in the hope of finding a clear analytical result.
the typical time for the pathway with \( n \) double steps, \( \tau_n \),
let us first define the corresponding rates: \( k_1 = 1/\tau_{1a} \) and \( k_2 = 1/\tau_{2a} \). Now consider the following analogy:
Imagining a tank of water with two holes in the bottom, one of which lets water out at a rate \( k_1 \), the other at a rate \( k_2 \). The tank will empty according to the sum of the flow rates through both holes, i.e. it will empty faster than if only one single hole were present. The typical time for the tank to empty is its volume by the sum of the two rates:
\[
\frac{1}{\tau} = \frac{k_1 + k_2}{k_1 + k_2},
\]
while the probability to escape through each of the routes is given by the proportion:
\[
p_{1,2} = \frac{k_{1,2}}{k_1 + k_2}.
\]
When we put a series of such tanks together, see Fig. 6(b), we see the effect of the double steps is merely to bypass the draining time in the intermediary tank. Then, the typical time is just the draining time of a tank multiplied by the number of tanks it has to drain through. The typical time along each pathway is determined by the total number of steps \((m+n)\) along this pathway (single or double), when each step takes the average time \( \tau = (k_1 + k_2)^{-1} \). For instance, for a pathway with \( n \) double steps:
\[
\tau_n = \frac{m + n}{k_1 + k_2} = (m + n) \frac{\tau_{1a}\tau_{2a}}{\tau_{1a} + \tau_{2a}},
\]
\[
\tau = \sum_{n=0}^{M/2} \frac{M - n}{k_1 + k_2} \cdot P(n),
\]
using \((m+n) = M - n\) to eliminate \( m \) and retain only the independent variable \( n \).

The probability \( P(n) \) is proportional to the number of binding paths for a given \( \tau_n \), with the additional bias for the probability of a double step. For a given number of double steps \( n \), we must consider all the possible orderings of the single and double step events. We have to combine this number of binding pathways with a weighting factor, relating to the ‘flow ratio’ discussed above. For a pathway with \( n \) double steps, this probability is given by the binomial distribution:
\[
P(n) = \frac{1}{\binom{m+n}{m} \binom{n}{n} \cdot P_1^n P_2^n},
\]
Mean binding time, $\langle \tau \rangle$ 

The mean time (in units of $b^2/D$, logarithmic scale) to bind the chain of $N = 100$ segments, as a function of the number $M$ of equidistant binding sites. The dashed line marks the case of $M = 1$, when only the $N$th segment has a binding ligand, reaching for a receptor $a = 406$ away. As the number of binding sites along the chain increases, the time to bind the final receptor dramatically reduces. The dots represent the exact expression for $\langle \tau \rangle$ evaluated in Supplementary; the continuous line is the plot of (18), where $\Delta a = a/M$. The agreement is evidently very good.

where we again should eliminate $m$, and where the weighting factors of each escape route are given by (13). Using $p_1 = 1 - p_2$, the normalization constant $Z$ turns out to be:

$$Z = \sum_{n=0}^{M/2} \frac{(M-n)!}{(M-2n)! n!} (1-p_2)^{M-2n} p_2^n = \frac{1 + p_2^{M+1}}{1 + p_2},$$

(17)

The summation of (15) can now be carried out directly, with some algebraic manipulation detailed in Supplementary part C to arrive at the closed-form solution. However, it turns out that a very good approximation to the exact mean binding time $\langle \tau \rangle$ can be constructed by assuming that $p_2 \ll 1$ (i.e. that the double-step binding has a much lower probability). In this approximation, the mean time of binding to a sequence of $M$ receptor sites takes the form:

$$\langle \tau \rangle \approx \frac{1 + 4Me^{\frac{-2\Delta a^2 M}{3a^2 N}}}{(1 + 4e^{-\frac{2\Delta a^2 M}{3a^2 N}})^2} \cdot \frac{4b^4N^2}{9De^2M^2} e^{\frac{2\Delta a^2 M}{N\alpha^2}}.$$  

(18)

This expression is the second main result of our paper. Figures 7 and 8 show the comparison of the approximation in (18) and the exact sum in (15), the latter plotted as discrete points at integer values of $M$. Evidently, the approximation (18) is virtually indistinguishable from the exact average binding time, when the probability of making a double step is small. This approximation is valid when

$$\frac{p_2}{p_1} = \frac{\tau_1a}{\tau_2a} = \frac{1}{4} e^{\frac{-2\Delta a^2}{3a^2 N\alpha^2}} \ll 1,$$

(19)

where $\Delta N = N/M$ is the distance between binding ligands along the chain, so this inequality holds even when $\Delta a \to 0$.

How does adding more binding sites along a chain length influence its time to bind to a surface? Let us consider a chain of fixed length $N$, as usual grafted at the origin. There is a binding ligand on the end of the chain, and (9) gives the mean time for it to bind at a receptor on the surface a distance $a$ away, $\tau_0(N,a)$. Let us now add several more binding ligands on the chain, such that they have $N/M$ monomers in between, and the matching sequence of ordered equidistant receptor sites on the surface, such that they are a distance $\Delta a = a/M$ apart. The resulting decrease in binding time is plotted in Fig. 7. Noting that the binding time is plotted on a logarithmic scale, the decrease is quite dramatic when more binding sites are added to the chain; (18) gives the scaling $\langle \tau \rangle \propto M^{-1} e^{\alpha/M} M$.

We also examine the situation where the binding site density is kept constant, i.e binding sites on the chain are equally spaced, and the matching receptors on the surface are always spaced the same distance $\Delta a$ apart, but vary the total length of the chain. In this case the total chain length $N = M\Delta N$, and the distance to the last receptor is $a = M\Delta a$. The results are plotted in Fig. 8 for the receptor density $\Delta a = 3\Delta b/10 = 6b$. The comparison is made with the mean binding time for the chain with only one binding site at the end, with the chain length and the distance to the single receptor related in the same way: $a = 3\Delta b/10$ away, to illustrate the role of
overall chain length. This time increases almost exponentially, see \[ \tau_{on} \propto N^2 \exp[\alpha N] \]. In contrast, the mean time to bind a sequence of receptors increases only \( \sim \)linearly with the chain length, illustrating that multiple sites massively enhance the binding rate. Note that a non-zero probability to make occasional double steps increases the binding rate even further, comparing with the straight ‘zipper’ sequence – this is illustrated in the inset of Fig. 6.

CONCLUSIONS

Experiments will usually determine the rate constant of a reaction, given by the reciprocal of the binding time. For the single binding event of a tethered ligand:

\[
\kappa_{on} = \frac{1}{\tau_{on}} = \frac{9D\varepsilon^2}{N^2b^4} e^{-3a^2/2Nb^2},
\]

(20)

The rate constant defined by Eq. (20) is Arrhenius in form \( \kappa_{on} = Ae^{-F/k_BT} \) if we take the free energy barrier to be purely entropic: \( F = -T\Delta S \), where

\[
\Delta S = -\frac{3k_B}{2Nb^2}a^2
\]

(21)

is the reduction in entropy for an entropic spring of length \( Nb \) stretched from 0 to \( a \). We might then, naively, believe that the binding time will increase monotonically as the length of chain increases – the entropic penalty will become smaller and smaller.

However, as we find in Eq. (0), there is another competing effect that increases the mean first passage time: as the chain gets longer, the effective volume that the site can explore relative to the receptor volume also increases. If we increase the chain to an infinite length, we actually return to a free particle scenario, and there is not enough confinement for the end of the chain to ever hit the receptor. For two binding sites placed a distance \( a \) apart, we can easily find the optimal length of tether chain for the fastest time to bind:

\[
N^* = \frac{3a^2}{4b^2}, \quad \text{hence} \quad \tau_{on}^* = 0.46 \frac{a^4}{D\varepsilon^2}.
\]

(22)

The difference in scaling of the mean binding time with receptor size \( \varepsilon \) in the tethered chain is an interesting feature, especially when compared with the looping chain or ‘narrow escape’ scenarios (which both have the \( \varepsilon^{-1} \) scaling). When we move from an unrestricted free space to a half-space, the polymer exclusion boundary condition effectively reduces the ways in which the chain can approach the receptor. This effect is purely entropic – it is the reduction in possible ways that the chain can orient itself near the wall that ‘prevents’ the chain from touching the wall. Together with the entropic barrier, this effect determines the binding time of a tethered ligand.

In the problem of multiple binding sites, we find that the addition of intermediary binding sites along a chain length has a dramatic ‘zipper effect’, massively decreasing the time for the chain to bind fully along its length. When we examine the expression in (18), it is important that for large \( \Delta a \) and large \( M \), the dominant binding process is the single-step ‘zipper’ pathway with the mean time \( M\tau_{on} \), as we can see in the inset of Fig. 8. Only occasionally will a chain bind with a double step, and this correction to the binding time also scales linearly with \( M \), see Fig. 8. It is not until receptors are very tightly grouped that double step processes start to become relevant. This is suggestive of reality – if a polymer chain has a specific substrate structure to bind to, then steric effects may well force the polymer to bind in a very conserved and controlled sequence (as in nature), just by virtue of the entropic penalty for binding ‘out of order’.

Here we approached the ‘reaching for the target’ problem in a way completely different from the ‘narrow escape’ problem of Holcman et al. Instead of examining the Smolochowski problem in an effective potential imposed by the constraints, we have generated the mean-field equilibrium probability density \( P_{eq}(\rho) \), and were able to utilize the mean first passage time solution of Szabo et al. It may well be that this approach generates analytical / numerical solutions more rapidly even for the more complex problems involving potential interaction and non-ideal polymer chain, as well as confined Brownian particles, since we are not having to look at the dynamical effects – only at how these affect the equilibrium effective potential.

It would be interesting to apply even this basic solution to a practical problem of amyloid assembly, where the new peptide subunit has to bind to a specific sequence of sites by hydrogen-bonding the \( \beta \)-sheet at the end of the existing filament, and the entropic barriers are explicitly reported.

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Appendix A: Calculation of radial distribution functions

To get an effective propagator in one dimension, we first transform (3) into spherical coordinates:

\[ x - a = \rho \sin \theta \cos \phi, \quad y = \rho \sin \theta \sin \phi, \quad z = \rho \cos \theta. \quad (A1) \]

The two scalar products in the combined exponents of Eq. (3) become:

\[ (r \pm b \hat{z})^2 = a^2 + b^2 + 2a\rho \sin \theta \cos \phi \pm 2b \rho \cos \theta. \quad (A2) \]

The next step of integration over the solid angle on the unit hemisphere is not easy. We need to evaluate

\[ I = \int_0^{\pi/2} d\theta \sin \theta \int_0^{2\pi} d\phi \ e^{-\alpha \cos \phi \sin \theta \pm \beta \cos \theta}, \quad (A3) \]

where parameters \( \alpha \) and \( \beta \) involve \( N, b, a \) and \( \rho \). This is solved by realizing that the integrand has a non-trivial axial symmetry. We transform back into Cartesian coordinates about the target: \( x' = \cos \phi \sin \theta, \quad \phi' = \cos \phi, \) and rotate these new coordinates by an angle \( \varphi = \tan^{-1}(\beta/\alpha) = \tan^{-1}(b/a) \) around the \( y \)-axis. The direction of this rotation depends on the sign of the \( z \)-term in the exponent (i.e. whether we are dealing with the ‘real’ or ‘image’ Gaussian term). This rotation means we are essential integrating \( \exp(-\sqrt{a^2 + b^2} \cdot x) \). However, we must be careful when we define the surface we are integrating over. Since we aren’t integrating over a line in the plane of the surface, the hemisphere appears tilted with respect to the variable of integration \( x \), as in Figure. The surface element is given by \( \psi(x) \sqrt{1 - x^2} \). On the unit sphere \( y = \pm \sqrt{1 - x^2} \), and the element \( ds \) is given by

\[ ds = \sqrt{1 + \left( \frac{\partial y}{\partial x} \right)^2} \ dx = \frac{dx}{\sqrt{1 - x^2}}, \quad (A4) \]

The opening angle of the surface element has the exact expression

\[ \psi(x) = \begin{cases} 2\pi, & -1 \leq x < -\cos \varphi \\ \pi - 2 \sin^{-1} \left( \frac{x \tan \varphi}{\sqrt{1 - x^2}} \right), & -\cos \varphi \leq x \leq \cos \varphi \\ 0, & \cos \varphi < x \leq 1 \end{cases} \quad (A5) \]

The radial probability density is defined according to the normalisation over the allowed half-space:

\[ \int_0^{\infty} d\rho \ 2\pi \rho^2 P_{eq}(\rho) = 1 \quad (A6) \]

where \( 2\pi \rho^2 \) accounts for the area of a hemispherical shell of radius \( \rho \). Using this, we find that the radial probability
density takes the form

\[ P_{eq}(\rho) = \sqrt{\frac{N\pi}{6}} \left( \frac{3}{2\pi Nb^2} \right)^{3/2} e^{-\frac{3a^2 + b^2 + \rho^2}{2Nb^2}} \times \]

\[ \left[ \frac{2Nb^2}{3\rho\sqrt{a^2 + b^2}} \right] \left[ \cosh \left( \frac{3\sqrt{a^2 + b^2}}{2Nb^2} \rho \right) - \cosh \left( \frac{3\rho a}{2Nb^2} \right) \right] + \frac{2b}{a} I_1 \left( \frac{3\sqrt{a^2 + b^2}}{Nb^2} \rho - 4b^2 \pi a^2 \sinh \left( \frac{3\sqrt{a^2 + b^2}}{Nb^2} \rho \right) \right) \].

\[ (A7) \]

Appendix B: Calculation of looping time

Here, we show that the mean looping time of a polymer, as calculated from our method, coincides with the expression derived by Szabo et al. If we consider first the more general problem of a chain with one end ‘tethered’ in place (in reality, since we can change our frame of reference of the polymer, we may do this for the free chain). Then, the distribution of the ‘free end’ is given by

\[ P(r) = \left( \frac{3}{2\pi Nb^2} \right)^{3/2} \exp \left( -\frac{3r^2}{2Nb^2} \right) \]  

\[ (B1) \]

We want to calculate the time for the free end to hit a sphere of radius \( \varepsilon \) centered a distance \( a \) from the first monomer. As in Appendix A, we may transform into spherical polar coordinates and then integrate over the polar angles to obtain a probability distribution over \( r \). This integral is very similar in form to \((A3)\), but with the integration limits extended over the entire unit sphere, and \( \beta = 0 \)

\[ I = \int_0^\pi d\theta \sin \theta \int_0^{2\pi} d\phi \ e^{-\alpha \cos \phi \sin \theta} \]

\[ (B2) \]

Transforming back into Cartesian coordinates, we have

\[ I = 2\pi \int_{-1}^1 dx \ e^{-\alpha x} = \frac{2\pi}{\alpha} \left( e^\alpha - e^{-\alpha} \right). \]

\[ (B3) \]

As such, the resulting radial probability distribution about the target is

\[ P_{eq}(\rho) = \frac{1}{2\pi a \rho} \sqrt{\frac{3}{2\pi Nb^2}} \left( e^{-\frac{2(a-x)^2}{2Nb^2}} - e^{-\frac{2(x+a)^2}{2Nb^2}} \right). \]

\[ (B4) \]

When we use this probability distribution in the expression for mean first passage time

\[ \tau = 2\pi \int_\varepsilon^{\infty} d\rho \left( D\rho^2 P_{eq}(\rho) \right)^{-1} \left[ \int_\rho^{\infty} d\rho' \rho'^2 P_{eq}(\rho') \right]^2, \]

we find that the integral, though not analytically solvable, is dominated by the value of the integrand at small \( \rho \). As \( \rho \to 0 \), the probability distribution tends to a non-zero constant, and so we can make the approximation

\[ \tau_{on} \approx \sqrt{\frac{\pi}{54} \frac{(Nb^2)^{3/2}}{D} \frac{2e^{2\alpha \rho}}{3(\beta + b^2)}} \int_\varepsilon^{\infty} d\rho \frac{\rho^2}{\rho^2} = \sqrt{\frac{\pi}{54} \frac{(Nb^2)^{3/2}}{D\varepsilon} e^{2\frac{\alpha^2}{3}}}. \]

\[ (B5) \]

\[ (B6) \]

From here, it is a matter of setting \( a = 0 \) to recover the Szabo result for the looping time of a polymer in three dimensions, shown in \((10)\).

Appendix C: Calculation of multiple-binding time

Evaluating the sums in \((15)\) requires that we calculate the average \( \langle n \rangle \):

\[ \langle n \rangle = \sum n^2 P(n) \]

The average \( \langle n \rangle = \sum n^2 P(n) \) calculates directly to produce an exact expression

\[ \langle n \rangle = \frac{p_2 ((M - 1)p_2 M + 1 + (M + 1)p_2 M + (M + 1)p_2 + M - 1)}{(p_2 + 1)^2 (p_2 M + 1)} , \]

where \( p_2 = 1 - p_1 \) is the probability of making a double step given in \((13)\). When the probability of making a double step is small, \( p_2 \ll 1 \), then we can expand the average number of double steps \( \langle n \rangle \) in a Taylor series in powers of \( p_2 \), producing

\[ \langle n \rangle = (M - 1)p_2 - (M - 3)p_2^2 + (M - 5)p_2^3 + \ldots \]

\[ = \sum_{n=1}^{M/2} (-1)^{n-1} [M - (2n - 1)] p_2^n \]

\[ (C1) \]

\[ (C2) \]

We arrive at the approximate expression given in \((18)\) by considering the leading order term in the sum, and substituting explicit expressions for \( p_2, k_1 \) and \( k_2 \):

\[ \langle \tau \rangle \approx \frac{p_2 + M(1 - p_2)}{k_1 + k_2} \]

\[ = \frac{1 + 4Mc^2N^2}{9D^2c^2M^2} \frac{Nb^2M^2}{3} e^{-\frac{3a^2M}{2Nb^2}} \]

\[ (C3) \]

which is just \((18)\).