Quantitative approach to facilitated diffusion with intersegmental jumping

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We study the impact of DNA coiling on the search rate of proteins moving along the DNA contour interspersed by three-dimensional (3D) bulk excursions. When the DNA is coiled proteins performing short 3D hops along a DNA segment can be captured by foreign DNA segments that have looped back close to the original segment. These intersegmental jumps are shown to enhance the search rate for a specific site on the DNA by lowering the tendency to resample previously visited sites on the DNA. The model developed here offers a quantitative description of recent single molecule experiments on facilitated diffusion of restriction enzymes EcoRV.

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A single stochastic search mechanism is usually not efficient at optimizing a search process. Thus Brownian motion, whose fractal dimension is \(d_f = 2\), in 1D and 2D leads to significant oversampling in the sense that a given site is revisited many times \(1,2\). Lévy motion with a jump length distribution \(\lambda(x) \simeq |x|^{-1-\alpha}\) \((0 < \alpha < 2)\) has \(d_f = \alpha\) and thus a comparatively reduced degree of oversampling. However, the first arrival of Lévy motion is hampered by leapovers, i.e., frequent overshoots of the target \(3\). In 3D both Brownian and Lévy motions are inefficient at locating a small target. While typical chemical reactants in a liquid environment have no choice but to passively diffuse until mutual encounter \(4,5\) intermittent models combine different search mechanisms \(2,5\).

An important example for intermittent search is facilitated diffusion of DNA binding proteins searching for their specific target binding site on a DNA molecule. In the Berg-von Hippel model \(6\) proteins intermittently diffuse in 3D bulk or along the 1D DNA chain \(7\), the latter mediated by non-specific binding (NSB) \(8\).

Previous approaches to facilitated protein diffusion consider bulk exchange for a straight cylindrical chain \(3,10\); they consider scaling properties in different chain configurations \(11\) without quantitative comparison of the search rates between these; or they reformulate the problem with uncorrelated bulk excursions \(12,13,14,15\). Here we relate a multiparticle picture to single protein jumps along the DNA contour allowing us to consider DNA as a fluctuating chain. Comparison to recent single DNA measurements \(16\) demonstrates that our model quantitatively describes the effect of DNA coiling.

General model. In our description of the target search process, we use the density per length \(n(x,t)\) of proteins on the DNA as the relevant dynamical quantity \((x\) is the distance along the DNA contour). We include 1D diffusion along the DNA with diffusivity \(D_{1d}\), protein dissociation with rate \(k_{\text{ns}}\off\) and (re)adsorption after diffusion through the bulk fluid with diffusion constant \(D_{3d}\). The dynamics of \(n(x,t)\) is thus governed by

\[
\frac{\partial n(x,t)}{\partial t} = \left(D_{1d} \frac{\partial^2}{\partial x^2} - k_{\text{ns}}\off\right) n(x,t) - j(t)\delta(x) + G(x,t) + k_{\text{ns}}\off \int_0^\infty dx' \int_0^\infty dt' W_{\text{bulk}}(x-x',t-t')n(x',t').
\]

Here, \(j(t)\) is the flux into the target site located at \(x = 0\), \(W_{\text{bulk}}(x-x',t-t')\) is the joint probability that a protein returns to the point \(x\) at time \(t\) after leaving the DNA at \(x', t'\) for a bulk excursion. \(G(x,t)\) is the flux onto the DNA of proteins that have not previously been bound to the DNA. \(j(t)\) is determined by imposing the boundary condition \(n(x=0,t) = 0\) at the target. To consider \(W_{\text{bulk}}\) as homogeneous in space and time we made two assumptions that we found to be valid for the system studied in \(16\). First, that the DNA can be treated as being infinitely long when considering the search rate \(17\). Second, that the coiled DNA conformation fluctuates quickly such that subsequent excursion distances \(x-x'\) can be treated as independent.

To proceed, we Laplace and Fourier transform Eq. \(1\):

\[
n(q,u)/W(q,u) - n_0(q) = G(q,u) - j(u)
\]

with \(n(q,u) = \mathcal{L}\{n(x,t)\}; n(q,t) = \mathcal{F}\{n(x,t)\}; n_0(x) = n(x,t=0)\), and

\[
W(q,u) = 1/(u + D_{1d}q^2 + k_{\text{ns}}\off[1 - W_{\text{bulk}}(q,u)]).
\]

We rewrite these equations in the form

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\]

We rewrite these equations in the form

\[
n(q,u) = n_{\text{ns}}(q,u) - j(u)W(q,u)
\]
where the density $n^{ns}(q, u) = W(q, u) |G(q, u) + n_0(q)|$ is the solution of the diffusion problem in absence of the target, i.e., when only NSB between proteins and the DNA occurs. In position space at $x = 0$ one obtains $j(u) = n^{ns}(x = 0, u)/W(x = 0, u)$.

In this study we focus on the long time behavior of $j(t)$ for which the density $n^{ns}(x, t)$ will reach an equilibrium value $n^{eq}_{ns}$. Since, by Tauberian theorems, large $t$ correspond to small $u$ we study the $u \to 0$ behavior of $j(u)$, with $n^{ns}(x, u) \sim n^{eq}_{ns}/u$. For $W_0(x = 0, u)$ we assume that the limit $W(x = 0, u = 0)$ is finite and non-zero; this is true when the distance distribution of bulk excursions is sufficiently long tailed as fulfilled for the $W_0$ encountered below. In practice, being interested in the first arrival at the target, we assume that the protein concentration is sufficiently dilute such that this arrival happens after reaching $n^{eq}_{ns}$ (‘rapid equilibrium’) but still with many searching proteins. Thus $j(u) \sim k_{1d}n^{eq}_{ns}/u$, and therefore at long times the stationary current $j_{stat} \sim k_{1d}n^{eq}_{ns}$ into the target is reached. Here we introduced $k_{1d}^{-1} = W(x = 0, u = 0)$:

$$k_{1d}^{-1} = \int_{-\infty}^{\infty} dq \frac{1}{2\pi D_1 q^2 + k_{off}(1 - \lambda_{bulk}(q))}. \quad (5)$$

$\lambda_{bulk}(x) = W_{bulk}(x, u = 0)$ is the distribution of relocation lengths along the DNA after a single 3D excursion. We express our results in terms of the association rate $k_{on} = j_{stat}/n_{bulk} = k_{1d} K_{ns}$

$$to the target where $n_{bulk}$ is the density of unbound proteins in the bulk (at non-specific equilibrium). The constant of NSB per length of DNA is $K_{ns} = n^{eq}_{ns}/n_{bulk}$. In terms of the total volume concentration of proteins $n_{total} = n_{bulk} + n^{total}_{DNA} n^{eq}_{ns}$ where $n^{total}_{DNA}$ is the total length of DNA divided by the volume of the entire system, we have $j_{stat} \sim k_{on} n_{total}/(1 + K_{ns} n^{total}_{DNA})$. The rate $k_{on}$ is related to the mean first arrival time for the steady state association. Namely $k_{on} n_{bulk}$ is the probability per time for protein association with the target. Thus the (survival) probability that no protein has arrived at the target yet is $P_{surv}(t) = \exp(-k_{on} n_{bulk} t)$, and the average target search time is $T = 1/(k_{on} n_{bulk})$. The flux $j(t)$ being linear in the protein concentration $n_{total}$ implies that for sufficiently low $n_{total}$ the steady state is reached well before the first protein actually binds to the specific target (note that in vivo protein concentrations can be as low as nanomolar).

**Straight rod configuration (Fig. 7).** Consider first stretched DNA corresponding to a cylinder of radius $r_{int}$ (the range of non-specific interaction), with NSB reaction rate $k^{ns}_{on}$ at the boundary: the flux of proteins, per length of DNA, onto the DNA is $k^{ns}_{on}$ times the bulk concentration next to the DNA. This implies that at equilibrium of NSB, $n^{ns}_{eq} k_{off} = n_{bulk} k^{ns}_{on}$ such that $K_{ns} = k^{ns}_{on}/k_{off}$. In this limit the protein can rebind quickly after unbinding. This leads to oversampling and a lowered value of $k_{on}$ compared to Eq. 10. $l_{sl}$ can be interpreted as an effective sliding length including immediate rebinding.

To find the distribution $W_{bulk}(x, t)$ for return to the DNA of a protein released at the DNA at $x = 0$ and $t = 0$, we solve the cylindrical diffusion equation for the probability density $P(x, r, t)$ of the protein’s position

$$\frac{\partial P}{\partial t} = D_{3d} \left( \frac{\partial^2 P}{\partial x^2} + \frac{1}{r} \frac{\partial P}{\partial r} \right)$$

where $r$ measures the distance to the cylinder axis. The reactive boundary condition for the probability flux out of the cylinder boundary is

$$-2\pi r_{int} D_{3d} \left. \frac{\partial P}{\partial r} \right|_{r=r_{int}} = -k^{ns}_{on} P|_{r=r_{int}} \delta(t) \delta(x). \quad (8)$$

The initial distribution outside the cylinder is $P(r, t)|_{t=0} = 0$. From the solution of this problem we obtain $W_{bulk}$ as $k^{ns}_{on} P|_{r=r_{int}}$ in terms of modified Bessel functions $K_{\nu}$ with $\tilde{q} = \sqrt{q^2 + u}$

$$W_{bulk}^{cyt}(q, u) = \left(1 + \frac{2\pi D_{3d} \tilde{q} r_{int} K_{\nu}(\tilde{q} r_{int})}{k^{ns}_{on} K_{\nu}(\tilde{q} r_{int})} \right)^{-1}. \quad (9)$$

With these ingredients one can evaluate numerically the search rate to reach the specific target on a straight DNA, as given by Eq. 3. However, some limits allow analytic approximation for the integral in Eq. 3: for $k^{ns}_{on} \ll D_{3d}$ one may take $1 - \lambda_{bulk}(q) \approx 1$, and thus $k_{1d}^{-1} \approx (2\sqrt{D_{1d} k_{off}})^{-1}$. One finds the association rate

$$k_{on} = 2\pi l_{sl} k^{ns}_{on}, \quad (10)$$

where $l_{sl} = \sqrt{D_{3d} l_{off}}$ is the so-called sliding length of a protein during a single NSB period. Eq. 10 states that each time a protein, with rate constant $k^{ns}_{on}$, binds to the DNA within a distance $l_{sl}$ from the target it is able to “slide” onto the target. Note that in this $k_{on} \ll D_{3d}$ limit the search rate $k_{on}$ is independent of the DNA conformation. In the opposite limit $k^{ns}_{on} \gg D_{3d}$ one may approximate $1 - \lambda_{bulk}(q) \approx 2\pi D_{3d} (k^{ns}_{on}/\ln[l_{sl}/r_{int}])$ where $l_{sl} = \sqrt{k^{ns}_{on}/(2\pi D_{3d} l_{off})}$. This produces the result

$$k_{on} \approx 4\pi D_{3d} l_{off} / (\ln[l_{sl}/r_{int}])^{1/2}. \quad (11)$$

In this limit the protein can rebind quickly after unbinding.
approach here allows to explicitly consider coiled DNA. However, the
eq 0 \) and denoting the probability that the protein has bound to this DNA before time \( t \) by \( J_{\text{single}}(t) \), then the probability that it has not bound to any of \( N \) pieces of DNA is (using the assumed independent interactions) \( P_{\text{surv}}(t) = [1 - J_{\text{single}}(t)]^N \). Taking the limit of \( V, N, L \to \infty \) for fixed \( l_{\text{DNA}} = NL/V \) we get \( P_{\text{surv}}(t) = \exp [-J_{\text{cap}}(t)] \), where

\[
W_{\text{bulk}}(q, t) = W_{\text{bulk}}^\text{cyl}(q, t) P_{\text{surv}}^\text{foreign}(t) - \frac{d P_{\text{surv}}(t)}{dt} \delta_{q,0} \int_t^\infty W_{\text{bulk}}^\text{cyl}(q = 0, t') dt'.
\]

The first term on the right hand side stands for proteins that return to the original segment without being captured by foreign segments. Those are represented by the second term, where the factor \( \delta_{q,0} \) is a result of the assumption that a capture by foreign DNA segments leads to a long relocation measured along the DNA contour. These relocations only contribute close to \( q = 0 \) in Fourier space. Exploiting the reasoning behind the approximation that led to Eq. (10) we discard them from \( W_{\text{bulk}} \) when the integral in Eq. (13) is calculated. However, even numerically this integral is difficult to handle. A good approximation can be found noting that by Tauberian theorems the Laplace inversion for \( J_{\text{cap}}(u) \) can be divided into three regimes when \( k_{\text{on}}^{\text{ns}} \gg D_{3d} \):

\[
J_{\text{cap}}(t) = \begin{cases}
k_{\text{on}}^{\text{ns}} l_{\text{DNA}}t & , t \ll \frac{D_{3d}^2}{k_{\text{on}}^{\text{ns}}} \\
4D_{3d} r_{\text{cap}} \sqrt{\pi D_{3d} t} & , t \ll \frac{r_{\text{cap}}^2}{D_{3d}} \\
\frac{\pi D_{3d} l_{\text{DNA}}}{\ln(D_{3d} l_{\text{DNA}})} r_{\text{cap}} t & , t \gg \frac{r_{\text{cap}}^2}{D_{3d}}
\end{cases}
\]

The first regime corresponds to reaction limited binding and is very brief for large \( k_{\text{on}}^{\text{ns}} \). We discard this regime and ignore the slowly varying logarithm in the last regime, to approximate \( P_{\text{surv}}^\text{foreign} \) by

\[
P_{\text{app}}(t) = \exp \left[-4D_{3d} r_{\text{cap}} \sqrt{\pi D_{3d} t} - k_{\text{cap}} t \right].
\]

The value of \( k_{\text{cap}} \) is fixed self-consistently by the condition that the total amount of proteins returning to the original segment is the same as for \( P_{\text{surv}}^\text{foreign} \), i.e.

\[
\int_0^\infty dt W_{\text{bulk}}^\text{cyl}(q, t) \left[P_{\text{surv}}^\text{foreign}(t) - P_{\text{app}}(t) \right] = 0.
\]

We solved this equation numerically. But when a value for \( k_{\text{cap}} \) has been obtained then the choice of \( P_{\text{app}} \) in Eq. (15) is very convenient. In fact it can be written

\[
P_{\text{app}}(t) = \int_0^\infty ds e^{-s/(s+k_{\text{cap}})} \frac{a}{2\sqrt{\pi s^3}} e^{-a^2/(4s)},
\]

where \( a = 4\sqrt{\pi r_{\text{cap}}} l_{\text{DNA}} \sqrt{D_{3d}} \). When inserted into Eq. (15) in Laplace space we need to evaluate numerically only one integral to obtain \( W_{\text{bulk}}(q, u) \), namely

\[
W_{\text{bulk}}(q, u) = \int_0^\infty ds a e^{-a^2/(4s)} W_{\text{bulk}}^\text{cyl}(q, u + s + k_{\text{cap}}).
\]

The term with \( \delta_{q,0} \) was already discarded here. Eq. (18) generalizes the straight rod result (9). In the limit \( D_{3d} \gg k_{\text{on}}^{\text{ns}} \) it is consistent with the approximation \( 1 - \lambda_{\text{bulk}}(q) \approx 1 \) leading to the expected result (10) for that case.
In above analysis we assumed that the density of foreign segments is uniform in space. Although this is not true for a relaxed coil (the density decreases on a scale of the persistence length of the DNA) we argue that this is not important for evaluating the search rate: in fact, if the protein diffuses far away from the original segment it will most likely perform a long relocation measured along the DNA contour. Again it does not matter for the search rate how we bookkeep these long relocations.

To estimate the density $I_{DNA}$ for a random relaxed coil we employ the Worm Like Chain model. A good approximation for the probability density for a point a contour distance $s$ away from another point to loop back is

$$j_M = \left( \frac{3}{4 \pi s l_p} \right)^{3/2} \exp \left( - \frac{8 s^2}{3 l_p^2} s^2 \right). \quad (19)$$

For a target in the middle of a chain of length $L$, we find the DNA density $I_{DNA} = \int_0^{L/2} ds j_M$ around the target.

The theory presented here was shown in Ref. [16] to quantitatively describe recent experimental data obtained from an optical tweezers setup by which the search rate $k_{on}$ at various degrees of DNA coiling could be measured. The relative increase $R$ of $k_{on}$ in the maximally relaxed DNA configuration compared to $k_{on}$ in the stretched state, for DNA length $L = 6538$ base pairs, was measured to be around 1.1 to 1.3 in buffers with salt concentrations of 5 mM MgCl$_2$ and 0 to 25 mM for NaCl.

This relative increase $R$ compared well with the theory presented here using estimates of $I_{DNA}$ based on Eq. (19) giving $1/\sqrt{I_{DNA}} \sim 500$ bp, and a value $v_{sl} \sim 100$ bp based on a quantitative analysis of experiments suggesting effective sliding lengths of this size. Numerical analysis of the theory presented here showed that $R$ depends significantly only on $I_{DNA}$ and $v_{sl}^2$ for realistic ranges of the remaining parameters. At physiological salt (100 mM NaCl) an increase of $R \approx 1.7$ was found experimentally. This observation agrees well with the increased DNA density expected due to attraction between segments induced by the 5 mM divalent Mg$^{2+}$ ions at this NaCl concentration, see Ref. [10] for details. We are not aware of a theory to calculate $I_{DNA}$ under such attraction. However, the value $1/\sqrt{I_{DNA}} \sim v_{sl}^2$ needed to obtain $R \approx 1.7$ at this salt conditions appears reasonable.

We presented a model for facilitated diffusion that is useful to calculate the search rate of DNA binding proteins for their specific binding site on a fluctuating DNA coil with variable DNA density. This model represents a convenient way to rephrase the Berg-von Hippel theory with the additional advantage that it interpolates between stretched and coiled DNA configurations. In the development of this theory a number of assumptions were made, in particular that of sufficiently fast local relaxation of the DNA configuration. This assumption was found to be satisfied for the protein EcoRV used in [10], but it will not hold universally. It would therefore be beneficial to generalize the theory to slowly fluctuating or static DNA configurations.

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[19] Eq. (47) generalizes Smoluchowski’s result $k_{on} = 4 \pi D_{3d} a b$ for pure 3D search for a target of size $b$. The effective target size in Eq. (47) is often called antenna length.
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