DNA-Protein Binding Rates: Bending Fluctuation and Hydrodynamic Coupling Effects

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Abstract

We investigate diffusion-limited reactions between a diffusing particle and a target site on a semiflexible polymer, a key component of DNA-protein interaction and polymerization of cytoskeletal filaments. Our theory focuses on two competing effects: internal polymer fluctuations, which speed up association, and hydrodynamic coupling between the particle and chain, which inhibits association. Internal polymer motion is described using a mean field dynamical theory, while the hydrodynamic coupling between polymer and particle is incorporated through a simple heuristic approximation. Both of these we validate through comparison with Brownian dynamics simulations. Neither of the effects has been fully considered before in the biophysical context, and we show they are necessary to form accurate estimates of reaction processes. The association rate depends on the stiffness of the polymer and the particle size, exhibiting a maximum as a function of persistence length and a minimum with particle radius. In the parameter range relevant to DNA-protein binding, the rate increase is up to 100% compared to the Smoluchowski result for simple center-of-mass motion. The quantitative predictions made by the theory can be tested in single molecule experiments.
1 Introduction

Reactions between semiflexible polymers and small molecules are ubiquitous in cells, playing a crucial role in a large number of biological processes: examples include the interaction of gene-regulating proteins with specific target sites on DNA, and the polymerization of DNA or structural proteins such as actin and tubulin. Many of these reactions are diffusion-limited—the activation energy is negligible compared to the thermal energy $k_B T$—so the overall association speed therefore depends on the rate at which the reactive molecules approach each other.

DNA-protein interaction has been the most widely studied process of this type (1, 2), attracting attention since the first measurement of the reaction rate between the Lac repressor and operator (3) revealed that it far exceeds the 3D diffusion limit. The quest to identify the underlying mechanism culminated in the seminal idea of facilitated diffusion by Berg, Winter, and von Hippel (4, 5, 6), but the general description of DNA-protein interaction is still far from complete. Although recent single molecule experiments show evidence that certain proteins indeed make use of facilitated diffusion (7, 8), the majority of measured reaction rates for DNA-binding proteins are on the order of the Smoluchowski result for 3D diffusion (1, 9). Thus recent years have seen extensive theoretical efforts (10, 11, 12, 13, 14) revisiting the underlying assumptions of facilitated diffusion, and examining it anew in response to experimental advances.

In the current work we focus on two aspects that enter into any theory of facilitated diffusion (or polymerization): for a bimolecular reaction involving a specific site on the semiflexible polymer and a free particle, how does the association rate depend on (i) the conformational fluctuations of the polymer contour in solution; (ii) the long-range hydrodynamic coupling between the polymer and the particle. Understanding these two intimately linked effects is necessary for any quantitative prediction of empirical rates, but they have been largely neglected in the context of DNA-protein association. Diffusion-controlled reactions with targets on flexible polymers are a well-established subject in polymer physics, with general analytical frameworks developed by Wilemski and Fixman (15, 16), and Szabo, Schulten, and Schulten (17) decades ago. Using the Wilemski-Fixman approach and a Gaussian model for circular polymers, a study by Berg looked at the influence of internal DNA motion on the binding of proteins (18). But little is known about the role of chain stiffness, and both Berg’s study and the classic polymer reaction rate theories do not include hydrodynamics. This is a significant oversight, because solvent-mediated interactions modify not only the approach of the particle to the target site, but also the fluctuation of the entire polymer contour, and thus all time scales involved in the dynamics. Moreover, the two effects are in opposition: polymer fluctuations lead to the target site exploring a larger configurational space than simple center-of-mass diffusion, and hence the association rate is enhanced; the hydrodynamic coupling between the particle and coil, on the other hand, reduces their relative mobility, decreasing the rate. The observed binding rate is a subtle competition between these two phenomena. As experiments are providing an ever more detailed picture of biological reactions at the single molecule level, we need theories that begin to grapple with the full complexity of polymer-particle diffusive motion.

The paper is organized as follows: in Sec. 2 we briefly describe the Brownian dynamics (BD) simulation method; this is used to independently test the theoretical description of
polymer–particle dynamics in Sec. 3. The latter is divided into three parts: Sec. 3.1 presents a short review of the mean field theory for semiflexible polymers, which gives an accurate description of the internal fluctuations of the chain; Sec. 3.2 considers the hydrodynamic coupling between the free particle and the polymer coil; finally Sec. 3.3 describes the renewal approach used to derive first passage times and association rates. The detailed validation of the theory through BD simulation results is presented in Sec. 4. We then investigate how the mechanical characteristics of the semiflexible polymer—the contour and persistence lengths—affect the reaction rate. Ultimately our theory yields quantitative predictions that can be tested empirically, and Sec. 5 summarizes the main results and offers suggestions for future experiments.

2 Brownian dynamics simulations

To simulate a polymer in solution we adopt a standard Brownian dynamics (BD) scheme (10), modeling the polymer as a chain of \( M \) beads of radius \( a \). For the low Reynolds number regime, the Langevin equation governing the time evolution of the position \( \mathbf{r}_i \) of bead \( i \) is given by

\[
\frac{d\mathbf{r}_i(t)}{dt} = \sum_{j=1}^{M} \vec{\mu}_{ij} \cdot \left( -\frac{\partial U(\mathbf{r}_1, \ldots, \mathbf{r}_M)}{\partial \mathbf{r}_j} \right) - \mathbf{f}_j(t) + \xi_i(t). \tag{1}
\]

The long-range hydrodynamic interactions—the fact that a force \( \mathbf{f}_j \) acting on bead \( j \) creates a flow-field affecting the motion of bead \( i \)—are described by the Rotne-Prager mobility matrix \( \vec{\mu}_{ij} \) (20):

\[
\vec{\mu}_{ij} = \mu_0 \delta_{ij} \mathbf{1} + (1 - \delta_{ij}) \vec{\mu}(\mathbf{r}_{ij}), \tag{2}
\]

\[
\vec{\mu}(\mathbf{r}_{ij}) = \frac{1}{8\pi\eta r_{ij}} \left[ \mathbf{1} + \frac{\mathbf{r}_{ij} \otimes \mathbf{r}_{ij}}{r_{ij}^2} \right] + \frac{a^2}{4\pi\eta r_{ij}^3} \left[ \frac{1}{3} r_{ij}^2 - \frac{r_{ij} \otimes r_{ij}}{r_{ij}^2} \right], \tag{3}
\]

where \( \mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j \), \( r_{ij} = |\mathbf{r}_{ij}| \), \( \mathbf{1} \) is the 3 × 3 identity matrix, and \( \mu_0 = (6\pi\eta a)^{-1} \) is the Stokes self-mobility of a sphere of radius \( a \) in a solvent of viscosity \( \eta \). The stochastic contributions \( \xi_i(t) \) to the equation of motion are assumed to be Gaussian random vectors which are hydrodynamically correlated according to the fluctuation-dissipation theorem:

\[
\langle \xi_i(t) \otimes \xi_j(t') \rangle = 2k_B T \vec{\mu}_{ij} \delta(t - t'). \tag{4}
\]

The inter-bead potential \( U = U_{WLC} + U_{LJ} \) determining the configuration-dependent forces, where

\[
U_{WLC} = \frac{\gamma}{4a} \sum_{i=1}^{M-1} (r_{i+1,i} - 2a)^2 + \frac{\kappa}{2a} \sum_{i=2}^{M-1} (1 - \cos \theta_i),
\]

\[
U_{LJ} = w \sum_{i<j} \Theta(2a - r_{ij}) \left[ \left( \frac{2a}{r_{ij}} \right)^{12} - 2 \left( \frac{2a}{r_{ij}} \right)^{6} + 1 \right], \tag{5}
\]

\[
\mathbf{f}_j(t) = \sum_{i=1}^{M} \vec{\mu}_{ij} \cdot \left( -\frac{\partial U(\mathbf{r}_1, \ldots, \mathbf{r}_M)}{\partial \mathbf{r}_j} \right) - \mathbf{f}_j(t).
\]
consists of a shifted harmonic potential between adjacent beads of strength $\gamma = 200 k_B T / a$, a bending potential of strength $\kappa = l_p k_B T$ between adjacent bonds, and a pairwise truncated Lennard-Jones potential $U_{\text{LJ}}$ of strength $w = 3 k_B T$. Here $\theta_i$ is the angle between the bond vectors $\mathbf{r}_{i,i-1}$ and $\mathbf{r}_{i+1,i}$. The first term in the worm-like chain potential $U_{\text{WLC}}$ keeps the contour length $L$ approximately fixed, while the second one with modulus $\kappa$ takes care of the bending stiffness of the chain. The repulsive Lennard-Jones potential $U_{\text{LJ}}$ prevents significant bead overlap, which is a source of numerical instabilities. In Sec. 4.3 where we model the motion of a free particle (i.e. a protein or free monomer) relative to the polymer chain, the particle is represented by an additional bead, not connected to the polymer chain, and subject only to hydrodynamic interactions between the particle and the chain. To avoid numerical instabilities in situations where the free particle overlaps with the polymer, in this case we use the Rotne-Prager-Yamakawa tensor (21), which modifies Eq. 3 for overlapping beads:

$$\mu(\mathbf{r}_{ij}) = \mu_0 \left[ \left( 1 - \frac{9r_{ij}}{32a} \right) \mathbf{1} + \frac{3r_{ij}}{32a} \mathbf{r}_{ij} \otimes \mathbf{r}_{ij} \right] \text{ if } r_{ij} \leq 2a.$$ (6)

Eq. (4) is discretized and integrated numerically using the Euler algorithm. The correlated stochastic contributions of Eq. (4) are obtained from uncorrelated Gaussian noise by means of a Cholesky decomposition of the hydrodynamic matrix $\mu_{ij}$. In all the results below, lengths are measured in units of $a$, energies in units of $k_B T$ and time in units of $\tau = a^2 / (k_B T \mu_0)$. The time step is $\Delta t = 3 \times 10^{-4} \tau$, and a typical simulation lasts $10^9$ steps, after an initial thermalization period of $10^6 - 10^7$ steps. To reduce computational costs the Cholesky decomposition is only performed every 5 time steps. For a given chain length $L = 2a(M-1)$ and persistence length $l_p$, the quantities of interest are averaged over $25 - 2500$ different trajectories until the convergence is satisfactory.

3 Theory

3.1 Mean field theory for semiflexible polymer dynamics

We briefly review the mean field theory for the dynamics of semiflexible polymers discussed in detail in Ref. (22). In that earlier study the model was shown to provide an accurate description of internal polymer kinetics, validated through extensive comparisons with BD simulations. Moreover, the theory can be independently tested by comparison to recent fluorescence correlation spectroscopy experiments: without any fitting parameters, it exhibits excellent agreement for the mean square displacement (MSD) of tagged ends of single dsDNA fragments diffusing in solution (23, 24).

The simplest description of a semiflexible polymer is the worm-like chain model: the polymer is represented by a continuous, differentiable space curve $\mathbf{r}(s)$ of contour length $L$, where the arc-length variable $s$ ranges from $-L/2$ to $L/2$. The associated elastic energy $U_{\text{WLC}}$, the continuum analogue of Eq. (3) is given by (25):

$$U_{\text{WLC}}[\mathbf{r}(s)] = \frac{\kappa}{2} \int_{-L/2}^{L/2} ds \left( \frac{\partial u(s)}{\partial s} \right)^2.$$ (7)
The bending rigidity is \( \kappa = l_p k_B T \), and the tangent vector \( \mathbf{u} = \partial \mathbf{r} / \partial s \) is constrained by local inextensibility to unit length, \( \mathbf{u}^2(s) = 1 \) at each \( s \). Since this constraint leads to nonlinear equations of motion, an alternative, approximate model is required. Within the mean field theory approach \([26, 27]\) the local constraint is relaxed and replaced by the global and end-point conditions \( \langle \int ds \mathbf{u}^2(s) \rangle = L \) and \( \langle \mathbf{u}^2(\pm L/2) \rangle = 1 \). The result is a Gaussian mean field Hamiltonian which incorporates a finite extensibility in addition to the bending term:

\[
U_{\text{MF}}[\mathbf{r}(s)] = \frac{\epsilon}{2} \int_{-L/2}^{L/2} ds \left( \frac{\partial \mathbf{u}(s)}{\partial s} \right)^2 + \nu \int_{-L/2}^{L/2} ds \mathbf{u}^2(s) + \nu_0 (\mathbf{u}^2(L/2) + \mathbf{u}^2(-L/2)), \tag{8}
\]

where \( \epsilon = 3l_p k_B T/2 \), \( \nu = 3k_B T/4l_p \), and \( \nu_0 = 3k_B T/4 \). In this form the Gaussian model exactly reproduces various lowest-order equilibrium averages of the worm-like chain, most importantly the tangent-tangent correlation function, and other derived quantities such as the mean square end-to-end distance.

The dynamic theory for the Gaussian semiflexible polymer is based on the hydrodynamic pre-averaging approach of Ref. \([28]\), analogous to that used for the Zimm model \([29]\) in the case of flexible chains. The time evolution of a point \( s \) on the polymer contour is governed by the Langevin equation:

\[
\frac{\partial}{\partial s} \mathbf{r}(s,t) = -\int_{-L/2}^{L/2} ds' \overline{\mathbf{\mu}}_{\text{avg}}(s, s') \frac{\delta U_{\text{MF}}}{\delta \mathbf{r}(s', t)} + \xi(s, t),
\]

\[
\langle \xi(s, t) \otimes \xi(s', t') \rangle = 2k_B T \overline{\mathbf{\mu}}_{\text{avg}}(s, s') \delta(t - t'). \tag{9}
\]

Here we use the pre-averaged mobility tensor \( \overline{\mathbf{\mu}}_{\text{avg}}(s, s') \), which is obtained from the standard Rotne-Prager tensor by averaging over all equilibrium configurations of the polymer. As seen in Eq. \(8\) the original Rotne-Prager mobility involves a dependence on the spatial distance between polymer points, and hence on the specific configuration of the chain. This would lead to nonlinear equations of motion, a problem which is resolved in the pre-averaging approximation, where the mobility depends only on the arc-length coordinates \( s \) and \( s' \). For the mean field model of Eq. \(8\) the pre-averaged mobility has the form \([28]\):

\[
\overline{\mathbf{\mu}}_{\text{avg}}(s, s') = 2a \mu_0 \delta(s - s') + \frac{\Theta(|s - s'| - 2a)}{\eta \sqrt{6 \pi \sigma(|s - s'|)}} \exp \left( -\frac{6a^2}{\sigma(|s - s'|)} \right) \mathbf{1}, \tag{10}
\]

where \( \sigma(l) = 2l_p l - 2l_p^2 (1 - \exp(-l/l_p)) \). The microscopic length scale \( a \) in the continuum theory corresponds to the monomer radius in the discrete BD simulations, and the unit step function \( \Theta \) in Eq. \(10\) serves as a short-distance cutoff for the hydrodynamic interactions.

The pre-averaged Langevin equation can be solved through a normal mode decomposition, with the eigenmodes fulfilling free-end boundary conditions at \( s = \pm L/2 \). This reduces Eq. \(9\) to a set of ordinary differential equations coupled by a hydrodynamic interaction matrix; the diagonalization of this matrix yields simple Langevin equations for the decoupled normal mode amplitudes \( P_n(t) \) (with stochastic contributions \( Q_n(t) \)):

\[
\frac{\partial}{\partial t} P_0(t) = Q_0(t), \quad \frac{\partial}{\partial t} P_n(t) = -\Lambda_n P_n(t) + Q_n(t), \quad n = 1, \ldots, N,
\]

\[
\langle Q_n(t) Q_m(t') \rangle = 2k_B T \delta_{nm} \delta(t - t') \Theta_\delta
\]

\[
\Theta_\delta = \begin{cases} 1, & \text{for } s, s' \text{ connected}, \\
0, & \text{otherwise} \end{cases}
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The vectors $P_n(t)$ and $Q_n(t)$ are related to $r(s, t)$ and the stochastic velocities $\xi(s, t)$ through the expansions $r(s, t) = \sum_{n=0}^{N} P_n(t)\Psi_n(s)$ and $\xi(s, t) = \sum_{n=0}^{N} Q_n(t)\Psi_n(s)$, where the scalar functions $\Psi_n(s)$ are the decoupled normal modes. The modes are ordered in such a way that the eigenvalues $\Lambda_n$ (inverse relaxation times) increase with $n$. Following Ref. (22), we set the high-frequency cutoff $N$ for the mode number to $N = [L/8a] + 1$, which was shown to give good agreement at short times with BD simulations. At longer times, where the polymer fluctuations are at length scales much larger than the monomer radius $a$, the dynamics does not depend on the precise choice of the cutoff. $\Lambda_n$ and the fluctuation-dissipation parameters $\Theta_n$ can be directly derived from the tensor $\overline{\mu}_{\text{avg}}$ evaluated numerically in the normal mode basis. Full details of this procedure, together with the explicit form of the normal modes $\Psi_n(s)$, are given in Ref. (22).

Eq. (11) for a given mode $n$ can be mapped onto the well-known problem of a particle diffusing with friction constant $\zeta$ in a harmonic potential of strength $\kappa$ centered at $x = 0$. We identify the mode amplitude $P_n(t)$ with the position $x$ of the particle and set $\Lambda_n = k/\zeta$, $\Theta_n = 1/\zeta$. This allows us to calculate the explicit form of the Green’s function for the diffusive process, in other words the transition probability $P(P_n(t), P_n(0); t)$ for observing the amplitude $P_n(t)$ after time $t$, starting from the initial amplitude $P_n(0)$:

$$P(P_n(t), P_n(0); t) = (2\pi\sigma_n^2(t))^{-3/2} \exp\left(-\frac{(P_n(t) - M_n(t))^2}{2\sigma_n^2(t)}\right).$$

The probability has the form of a spreading Gaussian, with time-dependent mean $M_n(t)$ and variance $\sigma_n^2(t)$ given by:

$$M_0(t) = P_0(0), \quad M_n(t) = P_n(0)e^{-\Lambda_nt}, \quad \forall n > 0, \quad (13)$$

$$\sigma_0^2(t) = 2LD_{\text{pol}}t, \quad \sigma_n^2(t) = k_B T\Theta_n\Lambda_n^{-1}\left(1 - e^{-2\Lambda_nt}\right), \quad \forall n > 0. \quad (14)$$

Here $D_{\text{pol}} = \Theta_0\Psi_0(s)^2$ denotes the center-of-mass diffusion constant of the polymer coil. Modes with different mode number $n$ evolve independently of each other. Transition probabilities between different polymer configurations, each of them corresponding to a certain (unique) set of normal mode amplitudes $\{P_n(t)\}$, are therefore expressed as the product of the transition probabilities for the individual modes. As we are interested in the motion of a single point $s$ on the polymer contour, the integrations over initial configurations with $r(s, 0) = r_0$ and final configurations with $r(s, t) = r$ can be readily performed. The result is a Gaussian Green’s function specifying the conditional probability that point $s$ reaches spatial position $r$ in time $t$ given that it starts at $r_0$:

$$G(r, r_0; t) = (2\pi V(t))^{-3/2} \exp\left(-\frac{(r - r_0)^2}{2V(t)}\right), \quad (15)$$

$$V(t) = 2D_{\text{pol}}t + 2k_B T\sum_{n=1}^{N-1} \frac{\Theta_n}{\Lambda_n} (1 - e^{-\Lambda_nt})\Psi_n(s)^2. \quad (16)$$

For $t \gg \Lambda_1^{-1}$ the variance $V(t) \approx 2D_{\text{pol}}t$ and hence the Brownian diffusion of the polymer’s center-of-mass dominates the motion on large time scales. For smaller times, however, the contribution from internal polymer modes becomes important. The radial Green’s function
$G_{\text{rad}}(r; t)$ for a particle starting at $r_0 = 0$ is obtained by integrating $G(r, 0; t)$ over the surface of a sphere of radius $r$:

$$G_{\text{rad}}(r; t) = \frac{4\pi r^2}{(2\pi V(t))^{3/2}} \exp \left( -\frac{r^2}{2V(t)} \right).$$  

(17)

In Sec. 4.1 we compare the time evolution of this transition probability for the case of the end-monomer ($s = \pm L/2$) to BD simulation results.

### 3.2 Hydrodynamic interactions between a target site and a free particle

In the previous section we were able to describe the long-range hydrodynamic interactions between various points on a polymer coil, and their influence on the internal relaxation of the chain. A key simplifying feature in this analysis is the fact that the spatial relationship between any two points on the contour is constrained: their mean separation as the polymer fluctuates in equilibrium can be taken into account through the pre-averaging approximation. For the case of a free particle and a target site on the polymer coil, estimating hydrodynamic interactions is more difficult: the particle can drift away, and the strength of the interaction will be highly dependent on the initial conditions and the elapsed time. To understand the role of hydrodynamics in this situation, we first consider the simpler case of two freely diffusing spherical particles, before tackling the full problem of polymer-particle hydrodynamics. Though it may seem trivial, even the two particle case presents a challenging problem and can only be dealt with approximately (31, 32).

We consider two non-interacting particles at positions $r_i(t), i = 1, 2,$ described by the Langevin equations:

$$\frac{\partial}{\partial t} r_i(t) = \xi_i(t),$$

$$\langle \xi_i(t) \otimes \xi_j(t') \rangle = 2k_BT \delta(t - t') \left[ \delta_{ij}\mu_i \mathbf{I} + (1 - \delta_{ij}) \langle \mathbf{\mu} (r_{12}) \rangle \right],$$  

(18)

where $\mu_i$ is the self-mobility of particle $i$, and hydrodynamics are expressed through the Rotne-Prager tensor $\langle \mathbf{\mu} (r_{12}) \rangle$, defined in Eq. 3, dependent on the inter-particle separation $r_{12}$. Hydrodynamic interactions are long-ranged ($\propto r_{12}^{-1}$) and therefore negligible only at distances much larger than the sum of the particle radii, $r_{12} \gg a_1 + a_2$. For small separations, the stochastic motion of the particles is highly correlated, leading to a slowing down of their relative mobility. To get a realistic estimate of binding rates, where particles clearly have to approach each other, it is therefore necessary to take these hydrodynamic effects into consideration.

The main quantity of interest is the radial Green’s function for the relative motion of the particles, the probability that two particles starting from a distance $r_0 = |r_{12}(0)|$ reach a distance $r = |r_{12}(t)|$ in time $t$. For comparison, we will consider the situation both with and without hydrodynamic interactions, labeling the respective Green’s function $G_{\text{rad}}^h$ and $G_{\text{rad}}^n$. The second case, where the particles are totally decoupled and only the self-mobilities enter
The second term on the right can be rewritten as the variance $V^h(t)$, which involves both a time and ensemble average over the trajectory $\bar{r}_{12}(t)$, and hence is also dependent on the initial separation $r_0$. Our heuristic approach approximates $\chi$ by an effective coupling function $\bar{\chi}(r_0, t)$, where the time and ensemble averages have been replaced by a single ensemble average involving the Green’s function $G^h_{\text{rad}}$ for the non-hydrodynamic system:

$$\bar{\chi}(r_0, t) = \frac{k_B T}{6\pi \eta} \int_{r_a}^{\infty} dr \frac{1}{r} G^n_{\text{rad}}(r, r_0; t) = \frac{k_B T}{6\pi \eta} \frac{1}{2r_0} \left[ \text{erf} \left( \frac{r_0 - r_a}{\sqrt{2V^n(t)}} \right) + \text{erf} \left( \frac{r_0 + r_a}{\sqrt{2V^n(t)}} \right) \right].$$

As in the pre-averaging approximation of the previous section, hydrodynamic interactions are cut off below the distance $r_a = a_1 + a_2$ where the particles overlap. This effective parameter shows the correct limiting behavior: $\bar{\chi}(r_0, t) \propto r_0^{-1}$ for short times where particles are close to their initial separation, and $\bar{\chi}(r_0, t) \propto \left( (D_1 + D_2)t \right)^{-1/2}$ for long times where the particles have drifted far away from each other. In analogy to the non-hydrodynamic case, we define the variance $V^h(t)$ as 1/3 of the MSD, using the effective parameter $\bar{\chi}(r_0, t)$ instead of $\chi$. Thus the final form for our approximate hydrodynamic Green’s function is:

$$G^h_{\text{rad}}(r, r_0; t) = \frac{r}{r_0 \sqrt{2\pi V^n(t, r_0)}} \left[ e^{-\frac{(r-r_0)^2}{2V^n(t, r_0)}} - e^{-\frac{(r+r_0)^2}{2V^n(t, r_0)}} \right],$$

$$V^h(t, r_0) = 2(D_1 + D_2 - 2\bar{\chi}(r_0, t)t).$$

The role of the effective coupling parameter $\bar{\chi}$ is to reduce the relative mobility of the particles when they are near to each other and thus subject to strong hydrodynamic interactions; in
the long-time limit the hydrodynamic effects become negligible as the particles move to large separations. In Sec. 4.2 we test our approximation by comparing it to BD simulation results and show that it works well.

In principle, the procedure outlined above to estimate \( \chi \) can be iterated to produce higher-order approximations: in deriving \( \bar{\chi}(r_0, t) \) one can use the hydrodynamic Green’s function \( G_{\text{rad}}^h \) of Eq. 23 instead of \( G_{\text{rad}}^a \). This would lead to a better approximation for \( \chi \), and hence a more accurate Green’s function which could be input into the next level of the approximation. This iterative method converges quickly, so for simplicity we restrict ourselves to the first order results shown above.

This approach for two freely diffusing particles can be generalized to the problem of a free particle and a polymer. The non-hydrodynamic case is again simple, with the relative motion of the particle and a point \( s \) on the chain described by a radial Green’s function which has exactly the same form as Eq. 19. The only difference is the variance \( V^n(t) \), which now includes the contribution of the polymer’s internal modes (see Eq. 16):

\[
V^n(t) = 2(D_{\text{par}} + D_{\text{pol}})t + 2k_B T \sum_{n=1}^{N-1} \frac{\Theta_n}{\Lambda_n} (1 - e^{-\Lambda_n t}) \Psi_n(s)^2.
\]

(25)

Here \( D_{\text{par}} = k_B T / 6\pi \eta r_{\text{par}} \) is the diffusion constant of the free particle, and \( r_{\text{par}} \) is the particle radius.

For the hydrodynamic case, we can divide the complicated interactions between the particle and the chain into three parts: (i) the influence of the local region of radius \( a \) around the target site \( s \) on the free particle; (ii) the influence of the rest of the chain on the particle; (iii) the back influence of the particle on the entire polymer. For the specific problem we consider—association rates to a given target site—hydrodynamics plays a significant role only in the close vicinity of the target. Hence contribution (i) will dominate. The back influence in (iii) should be negligible for free particles comparable in size to the monomers in the chain, \( r_{\text{par}} \sim O(a) \), since the motion of the polymer is mainly governed by relaxation of the internal modes. The relative unimportance of (ii) is more subtle: one can take it into account in a more elaborate numerical evaluation of the pre-averaged MFT Langevin equations, but comparison to the simpler approximation discussed below does not show significant improvement with respect to BD simulations (which include all three contributions). Thus we can construct a simple estimate for the hydrodynamic Green’s function by focusing on contribution (i). \( G_{\text{rad}}^h \) has the same form as the two-particle case, Eq. 23 but with a variance given by:

\[
V^h(t, r_0) = V^n(t) - 4 \bar{\chi}(r_0, t) t,
\]

\[
\bar{\chi}(r_0, t) = \frac{k_B T}{6\pi \eta} \left[ \frac{1}{2r_0} \left( \text{erf} \left( \frac{r_0 - r_a}{\sqrt{2V^n(t)}} \right) + \text{erf} \left( \frac{r_0 + r_a}{\sqrt{2V^n(t)}} \right) \right) \right],
\]

(26)

in analogy to Eq. 24. Here \( V^n(t) \) is the non-hydrodynamic polymer-particle variance of Eq. 25. In this way we have accounted for both the internal fluctuations of the target site and, through \( \bar{\chi}(r_0, t) \), the decrease in relative mobility for the approaching particle. Our heuristic treatment of hydrodynamic effects is compared to BD simulation results in Sec. 4.3.
3.3 Diffusion-controlled reaction rates

In general, association rates are calculated by finding the steady-state solution of a diffusion equation with absorbing boundary conditions (33, 34). In our case, we can employ the simpler renewal approach (35), which avoids the necessity of imposing absorbing boundaries: first passage times and binding rates can be directly extracted from the solution of the unbounded problem. This allows us to use the Green’s functions derived in the last section for the relative motion of a target site on the polymer and a freely diffusing particle. The renewal approach is in principle equivalent to the Wilemski-Fixman formalism, and they share the same underlying approximations (36, 37): (i) the Green’s function for the time evolution of the particle-target distance is assumed to be that of a stationary Markov process; (ii) excluded volume between the reactands is ignored. We briefly review the main aspects of the approach below.

For a stochastic process in one dimension, the Green’s function $g(x, x_0; t)$ specifies the probability to find the particle at $x$ at time $t$ given a starting point $x_0$ at time $t = 0$. If we are interested in paths that reach a boundary point $x_a$ in time $t$, the corresponding transition probability can be written as a convolution,

$$g(x_a, x_0; t) = \int_0^t dt' f(t'; x_a, x_0) g(x_a, x_a; t - t'),$$  

where $f(t; x_a, x_0)$ is the first passage time distribution: the probability of reaching $x_a$ in time $t$ starting from $x_0$ at $t = 0$ without passing through $x_a$ along the way. A Laplace transformation $L$ acting on the time variable $t$ leads to

$$\tilde{f}(s; x_a, x_0) = \frac{\tilde{g}(x_a, x_0; s)}{\tilde{g}(x_a, x_a; s)} \leftrightarrow f(t; x_a, x_0) = L^{-1}\left[\frac{\tilde{g}(x_a, x_0; s)}{\tilde{g}(x_a, x_a; s)}\right],$$

where Laplace transforms are denoted by $L[f(t)] = \tilde{f}(s)$. Note that $g(x, x_0; t)$ is the Green’s function in the absence of absorbing boundary conditions; we assume only that the probability vanishes at $x \to \pm \infty$.

For the various systems we consider, the binding process between two reactive particles is effectively one dimensional, depending only on the distance $r$ between them. In the case of perfect absorption, particles bind when they collide for the first time—when the relative distance $r$ reaches the absorption radius $r_a$. As a result, the binding rate can be obtained from the first passage time distribution by integrating over all possible initial separations:

$$k_a(t) = 4\pi \int_{r_a}^{\infty} dr_0 r_0^2 f(t; r_a, r_0).$$  

The steady-state rate $k_a$ reached at long times is extracted from the Laplace transform $\tilde{k}_a(s)$ using the final value theorem:

$$k_a = \lim_{t \to \infty} k_a(t) = \lim_{s \to 0} s \tilde{k}_a(s).$$

For the simple case of two kinds of uncoupled Brownian particles with diffusion constants $D_1$ and $D_2$, the radial Green’s function, Eqs. 19-20, yields:

$$\tilde{f}(s; r_a, r_0) = \frac{r_a}{r_0} \exp\left(-\frac{r_a^2 - r_0^2}{D_s}\right),$$

where $D_s = D_1 D_2$. This result is generalizable to the case of an absorbing boundary by imposing the Laplace transform $\tilde{f}(s; r_a, r_0)$, which in our case is found to be:

$$\tilde{f}(s; r_a, r_0) = \tilde{G}(s) \tilde{f}_a(s)$$

where $\tilde{G}(s)$ is the Green’s function for the unbounded problem and $\tilde{f}_a(s)$ is the first passage time distribution.
with total diffusion constant $D = D_1 + D_2$. Applying Eq. (29) which corresponds to impose uniform initial concentrations at $t = 0$, one obtains the association rate:

$$k_a(t) = 4\pi Dr_a \left( 1 + \frac{r_a}{\sqrt{\pi Dt}} \right), \quad (32)$$

which at long times reduces to the well-known Smoluchowski rate \( k_S = 4\pi Dr_a \) constituting the upper limit for reaction rates governed by Brownian diffusion. For the more complicated polymer-particle case, the renewal method works analogously, but the Laplace transforms must be carried out numerically; the results are presented in section Sec. 4.4.

### 4 Results

In order to validate the various analytical approaches described in Sec. 3, we test them against BD simulations. Since the binding rates depend sensitively on having good estimates for the Green’s functions, we will focus on showing that the MFT approximation for the transition probabilities can reproduce the crucial physical effects: (i) the influence of internal polymer modes on the diffusion of the target site; (ii) the slow-down of relative motion between the free particle and target due to hydrodynamics. For simplicity, we concentrate in our analysis on one particular target site, the end-monomer of the chain. This has special relevance in biological processes, for example in the case of polymerization.

#### 4.1 Polymer motion

We begin by considering just the internal relaxation of the polymer: the radial Green’s function of Eq. (17) for $s = \pm L/2$ describing the diffusive motion of the polymer end-point. In Fig. 1 we compare this analytical MFT expression for $G_{rad}(r, t)$ to histograms extracted from simulations of a chain with $L = 100a$, $l_p = 20a$. The histograms are based on the analysis of 25 independent trajectories, each with $10^8$ steps. The time evolution of the probability distribution is in excellent agreement with $G_{rad}(r, t)$ over time scales spanning four orders of magnitude. Note that the largest time-scale considered ($t = 300 \tau$) is less than the largest relaxation time of the polymer, $\tau_1 \sim 2 \times 10^3 \tau$, meaning that internal fluctuations dominate the polymer motion throughout this entire time range. We illustrate the time evolution more directly in Movie S1 (38), which depicts the motion of polymer end-points (red dots) superimposed from an ensemble of simulation trajectories, each starting at the origin (purple dot). The inset shows the evolving radial probability \( P(r, t) = G_{rad}(r; t)/r^2 \) taken from the simulation histograms (red markers) compared to the MFT results (blue curve). Again we see a remarkable agreement, even in the tails of the distribution (which are visible on the logarithmic scale spanning seven decades of magnitude). Our comparison here is more detailed than in the earlier MFT study of Ref. (22), since we consider the full transition probability and not just the end-point MSD. But the conclusion is the same: the MFT provides a highly accurate picture of internal polymer dynamics.
Figure 1: The probability $G_{\text{rad}}(r, t)$ that the end-point of a polymer with length $L = 100a$ and persistence length $l_p = 20a$ will diffuse a distance $r$ in time $t$. The MFT predictions (lines) are compared to the results from BD simulations (black dots) for three different time regimes. Times are measured in units of $\tau = a^2/(k_B T \mu_0)$. 
Figure 2: The probability $G^\alpha_{\text{rad}}(r, r_0; t)$ that two spherical particles of radius $a$ end up at separation $r$ after time $t$ given an initial separation $r_0 = 3a$. For each time $t$, BD simulation data including hydrodynamics (black dots) are compared to two theoretical results: the non-hydrodynamic Green’s function for decoupled particles labeled by $\alpha = n$ (Eqs. 19 and 20), and the approximate hydrodynamic Green’s function labeled by $\alpha = h$ (Eqs. 23 and 24). Times are measured in units of $\tau = a^2/(k_B T \mu_0)$.

4.2 Relative motion of two spherical particles including hydrodynamics

Since the heuristic estimate for the hydrodynamic Green’s function $G^h_{\text{rad}}(r, r_0; t)$ of two freely diffusing particles (Eqs. 23-24) is the basis of our approach to polymer-particle interactions, we need to check that this estimate is reasonable. For this purpose, we performed BD simulations of two single spheres of radius $a$ and extracted histograms from the variation of the inter-bead distance over time. In total 2400 independent trajectories were calculated, each starting at a distance $r_{\text{init}} = 3a$ and lasting $10^7$ time steps. For given separations $r_0$ and $r$, relevant transition events were identified, i.e. parts of the trajectories starting at a certain distance $r_0 \pm \delta r/2$ and ending at $r \pm \delta r/2$, where $\delta r$ is the histogram binwidth. These were used to estimate the probability distribution corresponding to $G^h_{\text{rad}}(r, r_0; t)$. In Figs. 2 and 3, we show the BD simulation results for two different $r_0$ and various $t$ together with $G^h_{\text{rad}}$ (Eq. 23-24) and the decoupled Green’s function $G^n_{\text{rad}}$ (Eq. 19-20). The inhibition of relative motion due to hydrodynamics is clearly evident at short times: the distributions from the simulations are more narrowly peaked than the decoupled results, which spread
out noticeably faster. The slowing down is correctly reproduced in the $G_{\text{rad}}^h$ curves, though it is slightly underestimated when compared to the simulation data. Despite the simplicity of the underlying approximation, $G_{\text{rad}}^h$ still captures the essential features of the interaction. For longer times, when the inter-particle distance has become large and hydrodynamics plays a smaller role, $G_{\text{rad}}^h$ converges to $G_{\text{rad}}^n$, and both agree with the BD results.

### 4.3 Relative motion of a polymer and a spherical particle including hydrodynamics

The final test for our Green’s function approach concerns the approximate description of polymer-particle relative motion, contained in Eqs. 23 and 26. To extract the corresponding transition probabilities from BD simulations, we take a polymer with $L = 100a$, $l_p = 20a$, allow it to thermalize, and then add a single free particle of radius $a$ that is hydrodynamically coupled to the polymer beads. The particle is positioned at an initial distance $r_{\text{init}} = 3a$ from one of the polymer ends, and data is collected over $10^7$ time steps. This procedure is repeated to obtain 2500 independent trajectories. As in Sec. 4.2, relevant transition events are used to determine the probability distribution for diffusing from a separation $r_0$ to $r$ in time $t$. The results, plotted in Figs. 4 and 5, are qualitatively similar to the case of two particles: compared to the non-hydrodynamic case we see a reduced relative mobility between the target site and the particle for small separations. The hydrodynamic Green’s function is quite close to the simulation results, again slightly underestimating the strength of
Figure 4: The probability $G^{\alpha}_{\text{rad}}(r, r_0; t)$ that the end-monomer of a polymer with $L = 100a$, $l_p = 20a$, and a spherical particle of radius $a$ end up at separation $r$ after time $t$ given an initial separation $r_0 = 3a$. For each time $t$, BD simulation data including hydrodynamics (black dots) are compared to two theoretical results: the non-hydrodynamic Green’s function labeled by $\alpha = n$ (Eqs. [19] and [25]), and the approximate hydrodynamic Green’s function labeled by $\alpha = h$ (Eqs. [23] and [26]). Times are measured in units of $\tau = a^2/(k_B T \mu_0)$. 
Figure 5: Same as in Fig. 4 but with initial separation $r_0 = 5a$ between the end-monomer and the free particle.
Figure 6: Schematic view of a bead-spring polymer with a reactive end and a free particle of radius $r_{\text{par}}$. The particle is absorbed as soon as the separation $r$ reaches the absorption radius $r_a = r_{\text{par}} + a$.

the coupling. However, given the complexity of the correlations between the particle and the entire polymer coil, it is notable that we are able to get good quantitative agreement. Since the association rates, discussed in the next section, are derived directly from this Green’s function, we should be able to obtain realistic estimates for the reaction process.

4.4 Association rates

The diffusion-limited reaction we consider is schematically illustrated in Fig. 6: free particles are absorbed by the reactive end-monomer of a chain as soon as the separation $r$ reaches the absorption radius $r_a = r_{\text{par}} + a$. The association rate is calculated from the renewal approach in Sec. 3.3, with the only input being the radial Green’s functions of Sec. 3.2 for the relative motion of the particle and the chain end.

Since polymer fluctuations and the polymer-particle hydrodynamic coupling have competing effects on the association rate, it will be instructive to start with the simple case where the coupling has been turned off, i.e. we use the non-hydrodynamic Green’s function $G_{\text{rad}}^n$ of Eqs. 19 and 25. The resulting association rate as a function of particle radius $r_{\text{par}}$ for a polymer with $L = 1000a$, $l_p = 50a$ is marked by red dots in Fig. 7. (For DNA, where $a \approx 1$ nm and $l_p \approx 50$ nm, this would correspond to a strand of length 1 $\mu$m.) The Smoluchowski rate,

$$k_S = 4\pi(D_{\text{pol}} + D_{\text{par}})r_a,$$

which involves only the center-of-mass motion of the polymer coil and particle, is shown as a line; the corresponding numerical results of the renewal approach are shown as green triangles. The Smoluchowski value is the standard point of reference when considering DNA-protein interaction [39]. Clearly, internal polymer fluctuations have a significant impact, enhancing the association rates by $50-135\%$ relative to $k_S$ over the range $r_{\text{par}} = 0.5a - 6a$; the minimum at $r_{\text{par}} \approx 2a$ for the rates with internal polymer motion indicates that the effect of larger absorption radius $r_a = r_{\text{par}} + a$ with increasing $r_{\text{par}}$ quickly dominates the one of decreasing diffusion constant $D_{\text{par}} \propto r_{\text{par}}^{-1}$.
Figure 7: Three estimates for the association rate of a free particle to the end-point of a polymer with $L = 1000a$, $l_p = 50a$, as a function of particle radius $r_{par}$. For DNA, where $a \approx 1$ nm and $l_p \approx 50$ nm, the corresponding strand would have a length $L = 1 \mu$m. The rates are measured in units of $k_BT/6\pi\eta$, or $\approx 1.3 \times 10^8$ M$^{-1}$s$^{-1}$ for water at room temperature. Green triangles and solid line: Smoluchowski rate (Eq. 33) considering only the center-of-mass diffusion of the particle and the polymer coil, without hydrodynamic coupling. Red dots: the rates including the internal fluctuations of the polymer, without hydrodynamics (Eqs. 19 and 25). Blue crosses: the total rates including both fluctuations and hydrodynamics (Eqs. 19 and 25). All the data marked by symbols is obtained from the numerical evaluation of the renewal approach (Eqs. 28-30).
In the absence of hydrodynamics, we can use an earlier result of Berg (18) to do a consistency check on the renewal approach derivation of the association rates. For the case of a Gaussian Green’s function, and assuming a Gaussian sink profile $S(r) = \exp (-3r^2/2a^2)$ instead of a perfectly absorbing boundary at $r_a$, Berg derived an expression for the association rate in terms of the relative non-hydrodynamic variance $V_n(t)$:

$$k_Berg = \left(2\pi\right)^{3/2} \left[ \int_0^\infty dt \left(V_n(t) + 2/3 r_a^2 \right)^{-3/2} \right]^{-1}.$$  (34)

Plugging $V_n(t)$ from Eq. 25 into Eq. 34, we recover the non-hydrodynamic rates shown in Fig. 7 within a difference of 5% (comparison not shown).

When hydrodynamic interactions are included together with internal polymer motion ($G_{rad}^h$ of Eqs. 23 and 26 is used instead of $G_{rad}^n$ of Eqs. 19 and 25), the association rates are smaller than the non-hydrodynamic case, as seen in the data marked by blue crosses in Fig. 7. This is due to the inhibited mobility between the particle and the target at short distances. However the rate decrease is only $\sim 15-20\%$, so the overall association rate is still $30-100\%$ larger than the Smoluchowski result for the range of particle sizes considered. The magnitude of the rate decrease is comparable to previous estimates derived for the simpler problem of a reaction between two spherical particles: Friedman obtained a $15\%$ reduction due to hydrodynamics (31), while Deutch and Felderhof saw a $46\%$ drop-off (32).

Since the conformational fluctuations depend on the mechanical properties of the chain, it is natural that the association rates will vary with the parameters $L$ and $l_p$ that characterize the semiflexible polymer. In Fig. 8 we show contour diagrams of the association rate in terms of $L/a$ and $l_p/a$ for two different particle radii: $r_{par} = a$ in the top panel, as would be the case in a polymerization process, and $r_{par} = 4a$ in the bottom panel, which corresponds to an average protein size for the case of DNA-protein interaction (with $a = 1\text{nm}$). Fig. 9 depicts the same data, but in terms of percent rate increase over the Smoluchowski result $k_S$ of Eq. 33. Interestingly, while the absolute rate in Fig. 8 is almost independent of $L$ for $L \gg l_p$, it does show a slight maximum for $l_p \approx 20a$ when $r_{par} = a$ and $l_p \approx 30a$ when $r_{par} = 4a$. This behavior as a function of $l_p$ is an intrinsic property of the polymer, because it appears also in the absence of hydrodynamic coupling (data not shown). The maximum is more prominent in the relative rates of Fig. 9 where the increase compared to $k_S$ rises sharply to $\sim 30\% \ (r_{par} = a)$ and $\sim 100\% \ (r_{par} = 4a)$ for long polymers with $l_p = 20a - 60a$ including double-stranded DNA ($l_p \approx 50a$).

5 Discussion and summary

In this paper, we have studied the association of free particles and a target site on a semiflexible polymer—a class of diffusion-limited reactions of wide biological relevance, whether in polymerization of biomolecules or gene regulation by DNA-binding proteins. We focused on two competing effects that are, with the lone exception of the segmental diffusion considered in Ref. (18), entirely neglected in existing theories for these processes: the bending fluctuations of the polymer in equilibrium, which enhance the association rate, and the hydrodynamics between the polymer and particle, which reduces it. Quantifying the fluctuations required an accurate description of internal polymer motion, available through the
Figure 8: The association rate $k_a$ (Eqs. 28-30 with Eqs. 23 and 26) between a free particle and a polymer end as it varies with the polymer contour length $L$ and persistence length $l_p$. Top panel: for particle radius $r_{par} = a$. Bottom panel: for $r_{par} = 4a$. The rates include the effects of polymer fluctuations and hydrodynamic coupling, and are measured in units of $k_B T / 6 \pi \eta$, or $\approx 1.3 \times 10^8 \text{M}^{-1} \text{s}^{-1}$ in water at room temperature.
Figure 9: Same as in Fig. 8, but showing the percent rate increase over the Smoluchowski result, $k_S$ (Eq. [33]), instead of the absolute rate.
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mean field theory of semiflexible polymer dynamics. For the hydrodynamics, we developed a simple heuristic estimate to model the decrease in mobility when two diffusing objects approach each other. The end result of the competition sensitively depends on the mechanical properties of the polymer and the size of the reactive particle: we see a maximal increase over the Smoluchowski rate for persistence lengths $l_p = 20a - 60a$; this increase is $\sim 30\%$ for the case of small particles, and $\sim 100\%$ for particle sizes typical of regulatory proteins. As a function of particle size, the reaction rate displays a minimum at a particle radius equal to the polymer diameter; for larger proteins the probability of hitting the DNA increases. Since most measured DNA-protein reaction rates are on the order of the Smoluchowski rate (1), the effects described here will be crucial to getting a complete quantitative theory of these reactions. We have neglected the possibility of encounters between the protein and the target site on the DNA that do not immediately lead to a reaction, for example due to orientational constraints. This is clearly an oversimplification, which however can be easily rectified by a reaction factor smaller than unity (40).

Directly testing our theoretical predictions may be possible with existing experimental techniques. In particular, one can study the role of polymer fluctuations on association rates by comparing two different setups involving bimolecular diffusion-limited reactions, shown schematically in Fig. In scenario I both reactands are free in solution, while in scenario II one of the reactands is bound to the end of a semiflexible polymer. The corresponding rates $k_I^a$ and $k_{II}^a$ could be measured through simple kinetic experiments or using fluorescence microscopy. In the latter case, the reactands would be fluorophores and quencher molecules, and the rate of the diffusion-limited quenching reaction can be extracted from the decay of the total fluorescence signal over time. As shown in Table our theory predicts a ratio $k_{II}^a/k_I^a \approx 0.77$ for the two scenarios using $r_{\text{par}} = a$ and a 1 $\mu$m strand of DNA. This is clearly distinguishable from the Smoluchowski prediction, $k_{II}^a/k_I^a = 0.5$, which ignores hydrodynamics and internal fluctuations.
Table 1: Estimates for diffusion-controlled bimolecular association rates in the experimental scenarios shown in Fig. 10. The polymer is assumed to be a 1 µm strand of dsDNA, and the particle radius $r_{\text{par}} = 1$ nm. The rates $k_a$ are given in units of $k_B T / 6\pi\eta$, or $\approx 1.3 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ in water at room temperature.

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