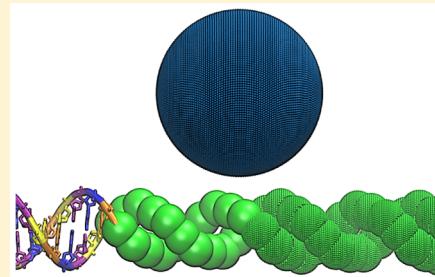


Effects of Hydrodynamic Interactions on the Apparent 1D Mobility of a Nonspecifically Bound Protein Following a Helical Path around DNA

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ABSTRACT: We investigated effects of hydrodynamic interactions on diffusivities of proteins that undergo rotation-coupled sliding along DNA. For that, we applied numerical calculations of mobility and friction tensors to systems consisting of detailed bead-shell models of DNA and proteins of different size. Using tensors that result from these calculations along with an expression for the instantaneous energy dissipation rate due to motions of a nonspecifically bound protein that follows a helical track around DNA, we evaluated apparent one-dimensional friction and mobility coefficients for model proteins. The results that we obtained indicate that hydrodynamic interactions between DNA and proteins may substantially (even several-fold) reduce the apparent one-dimensional diffusivity of proteins, when compared with results of other theoretical analyses of the rotation-coupled sliding of proteins along DNA that neglect hydrodynamic effects. Moreover, accounting for hydrodynamic effects decreases the gap between values of diffusion coefficients of proteins on DNA measured experimentally and those estimated based on theoretical calculations and analyses applied to model systems. Altogether, the current study gives insights into the significance of hydrodynamic interactions in determination of the rate of finding target sites by DNA-binding proteins.



INTRODUCTION

Recent single molecule experiments, theoretical calculations and analyses, and molecular simulations point toward the possibility that some of the DNA-binding proteins undergo a rotation-coupled sliding along the DNA helical pitch.^{1–7} The mechanism according to which a nonspecifically bound protein translates along DNA and at the same time undergoes rotational motion following the helical path around DNA can be, at least partially, responsible for the substantial reduction in apparent mobilities of proteins measured in experiments when compared to their translational mobilities measured in the absence of DNA.^{1–3,8}

Schurr first proposed a theoretical expression that corresponds to such a mechanism and allows one to evaluate apparent mobilities (or diffusion coefficients) of proteins moving on DNA.¹ According to the model proposed by Schurr, the total friction (ξ_{1D}) is in the case of a spherical protein following the helical pitch of DNA a linear combination of translational (ξ_{trans}) and rotational friction (ξ_{rot}) coefficients

$$\xi_{1D} = \xi_{trans} + \left(\frac{2\pi}{10\Delta H} \right)^2 \xi_{rot} \quad (1)$$

where ΔH is the distance between two adjacent base pairs of DNA. Schurr assumed that the center of the protein always remains on the DNA axis and obtained the following expressions for the apparent one-dimensional friction:

$$\xi_{1D}^{Schurr} = 6\pi\eta R + \left(\frac{2\pi}{10\Delta H} \right)^2 8\pi\eta R^3 \quad (2)$$

and mobility (we use mobilities, μ , rather than diffusion coefficients, D , considered by Schurr; a linear relation $\mu = k_B T / D$ holds, where k_B is the Boltzmann constant and T is temperature)

$$\mu_{1D}^{Schurr} = (\xi_{1D}^{Schurr})^{-1} = \frac{1}{6\pi\eta R + \left(\frac{2\pi}{10\Delta H} \right)^2 8\pi\eta R^3} \quad (3)$$

where R is the radius of the protein and η is the viscosity of the solvent (i.e., water). One should note that $6\pi\eta R$ is simply the translational friction drag coefficient for an isolated sphere suspended in a viscous fluid and $8\pi\eta R^3$ is its rotational friction drag coefficient.

The model originally proposed by Schurr was further extended by Bagchi, Blainey, and Xie.² These authors modified expressions for the apparent one-dimensional friction and mobility coefficients to account for the fact that proteins in nonspecific complexes with DNA may be offset from the DNA axis. According to their approach the apparent one-dimensional mobility coefficient of a nonspecifically bound spherical protein undergoing curvilinear motion along DNA can be calculated as the inverse of the friction coefficient²

$$\xi_{1D}^{BBX} = 6\pi\eta R + \left(\frac{2\pi}{10\Delta H} \right)^2 (8\pi\eta R^3 + 6\pi\eta RL^2) \quad (4)$$

as²

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$$\mu_{1D}^{BBX} = (\xi_{1D}^{BBX})^{-1} = \frac{1}{6\pi\eta R + \left(\frac{2\pi}{10\Delta H}\right)^2 (8\pi\eta R^3 + 6\pi\eta RL^2)} \quad (5)$$

with L being the distance between the center of the protein and the axis of the DNA helix. The first term in the denominator of the above expression corresponds to the translational friction in motion along the axis of the DNA helix. The second term in the denominator corresponds to the rotational friction in motion around this axis. One should note that the same terms are present in the expression proposed by Schurr (eq 3). The third term (which is absent in the expression proposed by Schurr) in the denominator accounts for the friction associated with an off-axis circular translational motion around the axis of the DNA helix.

The most important feature of theoretical analyses described by Schurr¹ and by Bagchi et al.² is that according to expressions presented above (eqs 3 and 5), $1/R^3$ size dependence of the apparent one-dimensional mobility of proteins on DNA should be observed, while purely translational diffusion in one dimension is characterized by $1/R$ dependence on the protein size. Indeed, the $1/R^3$ size dependence of measured apparent one-dimensional mobilities of proteins was observed in single molecule experiments.³

However, as described by Bagchi and coauthors, while apparent one-dimensional mobilities predicted with their approach for typical transcription factors are significantly smaller than their mobilities in three dimensions, they are still two to five times larger than the values measured in experiments.² These authors attribute this discrepancy first to the presence of small free energy barriers to sliding of proteins on DNA which can further reduce the diffusivity of proteins from the upper limits calculated using their expression, and second to the fact that hydrodynamic interactions between protein and DNA are neglected in their approach,² as the presence of DNA should increase friction drag on the protein moving in its vicinity.

In the current work we address the second of the issues mentioned by Bagchi and coauthors. Namely, we evaluate apparent one-dimensional mobilities of proteins that follow a helical path around DNA, taking into account hydrodynamic interactions between moving proteins and DNA. We utilize the technique of bead-shell modeling of molecules^{9–12} and numerical calculations of friction and mobility tensors^{12–14} for systems of arbitrarily shaped molecules. We investigate model systems similar to those considered by Bagchi, Blainey, and Xie, i.e., spherical proteins of different size, nonspecifically bound to DNA and offset from the DNA helix axis. We show that accounting for hydrodynamic interactions results in values of apparent one-dimensional mobilities that are substantially (even by a few times) smaller than values resulting from calculations based on the expression derived by Bagchi and coauthors.

This paper is structured as follows. We begin by presenting how mobility and friction tensors for a protein moving in the presence of an unmoving DNA molecule can be derived from the general mobility tensor for the protein–DNA system, and how these tensors, together with an expression for the instantaneous energy dissipation rate due to motions of a protein can be used to calculate the apparent one-dimensional mobility of a protein undergoing a curvilinear motion around DNA. Then we describe hydrodynamic bead-shell models and techniques used in calculations of general mobility tensors. Finally, numerical results regarding apparent one-dimensional friction and mobility coefficients of model proteins on DNA are presented and discussed.

THEORETICAL METHODS

Mobility and Friction for a Protein Moving in the Presence of DNA. In this section the construction of friction and mobility tensors for a protein that moves in the vicinity of unmoving DNA is presented.

As a starting point, we consider a general form of the mobility tensor for a system consisting of two molecules, in our case a protein and a long, straight DNA fragment, both treated as rigid bodies, suspended in an unbounded viscous fluid, μ_{1-2} . Such a tensor that for arbitrarily shaped bodies can be evaluated using standard hydrodynamic modeling techniques,^{9,10,12–15} is represented with a 12×12 matrix

$$\mu_{1-2} = \begin{pmatrix} \mu_{11} & \mu_{12} \\ \mu_{21} & \mu_{22} \end{pmatrix} \quad (6)$$

that consists of four 6×6 blocks, μ_{ij} , of form

$$\mu_{ij} = \begin{pmatrix} \mu_{ij}^{TT} & \mu_{ij}^{TR} \\ \mu_{ij}^{RT} & \mu_{ij}^{RR} \end{pmatrix} \quad (7)$$

where indices $i \in (1,2)$ and $j \in (1,2)$ correspond to molecules. Subtensors $\mu_{ii}^{\alpha\beta}$ ($\alpha \in (T,R)$ and $\beta \in (T,R)$) correspond to translations (TT) and rotations (RR) of the i th molecule, and their couplings (TR/RT). Subtensors $\mu_{ij,\#j}^{\alpha\beta}$ ($\alpha \in (T,R)$ and $\beta \in (T,R)$) describe how motions of one molecule (i) affect motions of the second molecule (j). We thus have coupling between translations of molecules (TT), rotations of molecules (RR), and their translations and rotations (TR/RT). For each molecule, its motions are evaluated in a coordinate system whose origin coincides with the geometry center of that molecule. Axes of these molecule-centered coordinate systems are parallel. Representing translational and rotational velocities of molecules with the generalized vector $\vec{V} = (\vec{V}_1^\dagger, \vec{V}_2^\dagger)$, and forces and torques acting on molecules with the generalized vector $\vec{F} = (\vec{F}_1^\dagger, \vec{F}_2^\dagger)$ (the \dagger symbol denotes the transpose operation) we may write a linear relation applicable at low Reynolds number

$$\vec{V} = \mu_{1-2} \vec{F} \quad (8)$$

or:

$$\vec{V}_1 = \mu_{11} \vec{F}_1 + \mu_{12} \vec{F}_2 \quad (9)$$

$$\vec{V}_2 = \mu_{21} \vec{F}_1 + \mu_{22} \vec{F}_2 \quad (10)$$

Following the reasoning presented in ref 16, we now assume that the protein (lower index 1) can move freely, but external forces and torques are applied to the DNA molecule (lower index 2) so that its position and orientation are fixed in space and \vec{V}_2 vanishes (we consider further a straight long fragment of a DNA molecule and the DNA molecule as a whole is much less mobile than the protein; we also neglect structural fluctuations of DNA). Hence we have

$$\vec{V}_2 = \mu_{21} \vec{F}_1 + \mu_{22} \vec{F}_2 = 0 \quad (11)$$

Using the above equation we may eliminate \vec{F}_2 from eqs 9 and 10 and write

$$\vec{V}_1 = (\mu_{11} - \mu_{12} (\mu_{22})^{-1} \mu_{21}) \vec{F}_1 = \mu_1 \vec{F}_1 \quad (12)$$

where we have introduced the 6×6 mobility matrix, $\mu_1 = \mu_{11} - \mu_{12} (\mu_{22})^{-1} \mu_{21}$, of the protein moving in the presence of the fixed DNA molecule. Corresponding friction tensor is given with

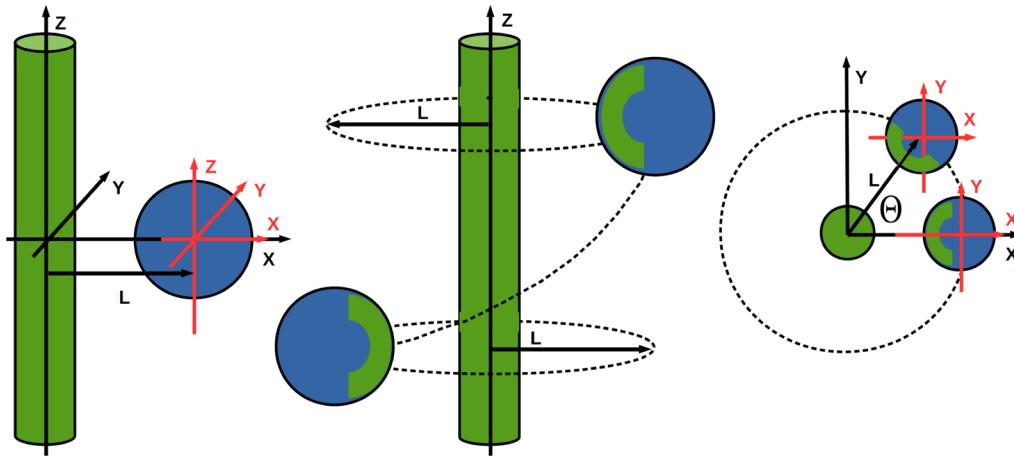


Figure 1. System consisting of DNA (shown as a green cylinder) and a protein (shown as a blue sphere) is considered. In the DNA-fixed coordinate system, denoted in black, the protein follows a helical path around DNA and its motion is described using parameters L and Θ . L is the distance between the center of the protein and the DNA helix long axis (z). Θ is the angle the projection of the protein's position vector onto the xy plane makes with the x axis. Moreover, the protein rotates around an axis that is parallel to the axis of the DNA helix and passes through the center (z axis in protein frame that is denoted in red) of the protein so that its DNA binding site always faces DNA.

$$\xi_1 = (\mu_1)^{-1} = \begin{pmatrix} \xi_1^{TT} & \xi_1^{TR} \\ \xi_1^{RT} & \xi_1^{RR} \end{pmatrix} \quad (13)$$

Subtensors $\xi_1^{\alpha\beta}$ ($\alpha \in (T,R)$ and $\beta \in (T,R)$) are defined as

$$\xi_1^{\alpha\beta} = \begin{pmatrix} \xi_{xx}^{\alpha\beta} & \xi_{xy}^{\alpha\beta} & \xi_{xz}^{\alpha\beta} \\ \xi_{yx}^{\alpha\beta} & \xi_{yy}^{\alpha\beta} & \xi_{yz}^{\alpha\beta} \\ \xi_{zx}^{\alpha\beta} & \xi_{zy}^{\alpha\beta} & \xi_{zz}^{\alpha\beta} \end{pmatrix} \quad (14)$$

where lower indices correspond to axes of the protein-centered coordinate system. One should note that even though proteins considered in the current work are spherical (see below), matrices μ_1 and ξ_1 (which are evaluated at their centers) are not diagonal as the presence of the DNA introduces coupling between translational and rotational motions of a protein. Additionally, diagonal values of the block TT (and similarly RR) of μ_1 and ξ_1 are not equal which results in an anisotropic mobility of a protein and an anisotropic friction.

Apparent 1D Mobility of a Protein Following a Helical Track around DNA. We consider a DNA-fixed coordinate system, which is also a laboratory frame, that is shown in Figure 1. In the DNA frame the center of the protein, with the position vector of components x, y, z , follows a helical path (Figure 1) described with the following parametric equations

$$x = L \cos \Theta \quad (15)$$

$$y = L \sin \Theta \quad (16)$$

$$z = b\Theta = \frac{10\Delta H}{2\pi}\Theta \quad (17)$$

L is the distance between the center of the protein and the long axis of the DNA helix (that coincide with the z axis of the DNA frame). Θ is the angle the projection of the position vector onto the xy plane makes with the x axis. b is the pitch of the helix, ΔH is the distance between two adjacent base pairs of DNA which in the case of B-form DNA is 3.38 Å. At any given time, the translational velocity, \vec{v} , of the protein that follows the helical path around the fixed DNA is defined in the DNA frame as

$$\vec{v} = \begin{pmatrix} v_x \\ v_y \\ v_z \end{pmatrix} = \begin{pmatrix} -L \sin \Theta \cdot \dot{\Theta} \\ L \cos \Theta \cdot \dot{\Theta} \\ b \cdot \dot{\Theta} \end{pmatrix} \quad (18)$$

Moreover, the protein rotates around an axis that is parallel to the long axis of the DNA helix and passes through the center of the protein (Figure 1) so that its DNA binding site always faces DNA, i.e., the protein is nonspecifically bound to DNA. Rotational velocity of the protein is given with the vector $\vec{\omega}$

$$\vec{\omega} = \begin{pmatrix} \omega_x \\ \omega_y \\ \omega_z \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ \dot{\Theta} \end{pmatrix} \quad (19)$$

In the case of the Stokes flow we may write the following expression for the instantaneous energy dissipation rate due to motions of the protein¹⁷

$$\epsilon = (\vec{v}^\dagger, \vec{\omega}^\dagger) \xi (\vec{v}, \vec{\omega}) \quad (20)$$

where the friction tensor

$$\xi = \begin{pmatrix} \xi^{TT} & \xi^{TR} \\ \xi^{RT} & \xi^{RR} \end{pmatrix} \quad (21)$$

corresponds to the situation where the protein moves in the vicinity of the fixed DNA. Friction tensor ξ is evaluated in the DNA-fixed coordinate system (Figure 1). It is convenient to express ξ in terms of the components of the tensor ξ_1 , evaluated in the coordinate system centered on the protein whose axes are, at any give time, parallel to axes of the laboratory (or the DNA-fixed) frame (Figure 1)¹⁸

$$\xi^{TT} = \xi_1^{TT} \quad (22)$$

$$\xi^{RT} = (\xi^{TR})^\dagger = \xi_1^{RT} - \mathbf{U} \xi_1^{TT} \quad (23)$$

$$\xi^{RR} = \xi_1^{RR} - \mathbf{U} \xi_1^{TT} \mathbf{U} + \xi_1^{RT} \mathbf{U} - \mathbf{U} \xi_1^{TR} \quad (24)$$

where the matrix \mathbf{U} is defined using coordinates of the protein in the DNA-fixed frame as¹⁸

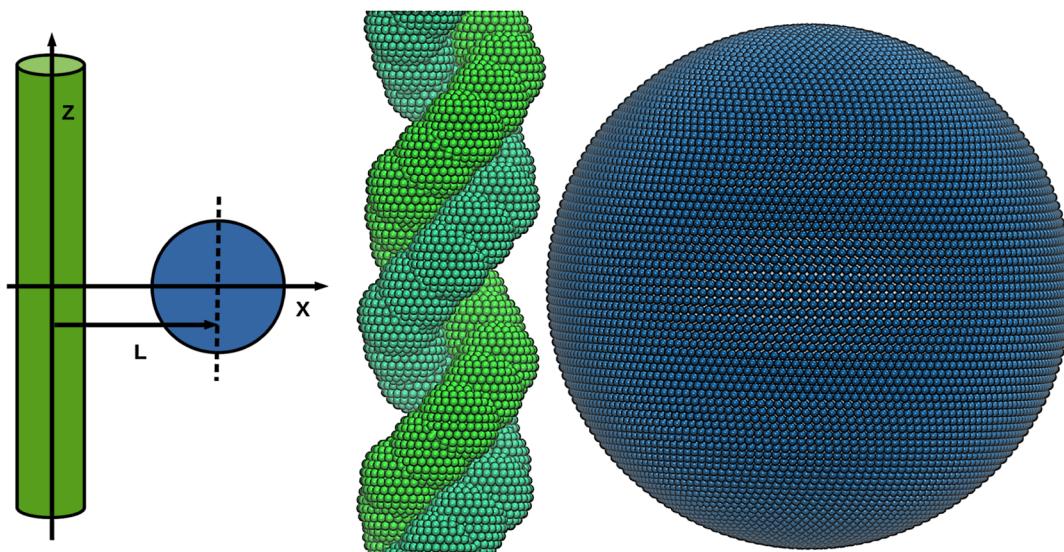


Figure 2. Different protein–DNA systems considered in the current work are generated by translating the center of the protein along the x axis of the DNA-fixed coordinate frame as shown on the left. Bead-shell models of DNA and a spherical protein (with 30 Å radius) in an exemplary configuration are shown on the right; protein faces the major groove of DNA (only a fragment of a bead-shell DNA model is shown for clarity). Drawings on the right were done with the VMD package.¹⁹

$$\mathbf{U} = \begin{pmatrix} 0 & z & -y \\ -z & 0 & x \\ y & -x & 0 \end{pmatrix} = \begin{pmatrix} 0 & b\Theta & -L\sin\Theta \\ -b\Theta & 0 & L\cos\Theta \\ L\sin\Theta & -L\cos\Theta & 0 \end{pmatrix} \quad (25)$$

With protein following a helical path around DNA, the instantaneous energy dissipation rate should be the same, regardless of the position of the protein on the path (that results from the assumption that the DNA is straight and infinite). Thus, we may evaluate ξ_1 and ξ assuming that the angle Θ equals zero so that the x axis of the DNA-fixed coordinate frame is colinear with the x axis of the protein coordinate frame (Figure 1). In this case, the matrix \mathbf{U} has a particularly simple form

$$\mathbf{U} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & L \\ 0 & -L & 0 \end{pmatrix} \quad (26)$$

What follows, is the instantaneous energy dissipation rate expressed in terms of blocks of the ξ_1 tensor

$$\begin{aligned} \epsilon = & \frac{1}{b^2} \left\{ \begin{pmatrix} 0 \\ L \\ b \end{pmatrix}^\dagger \xi_1^{TT} \begin{pmatrix} 0 \\ L \\ b \end{pmatrix} \right. \\ & + 2 \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}^\dagger (\xi_1^{RT} - \mathbf{U} \xi_1^{TT}) \begin{pmatrix} 0 \\ L \\ b \end{pmatrix} \\ & \left. + \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}^\dagger (\xi_1^{RR} - \mathbf{U} \xi_1^{TT} \mathbf{U} + \xi_1^{RT} \mathbf{U} - \mathbf{U} \xi_1^{TR}) \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} \right\} v_z^2 \end{aligned} \quad (27)$$

The above expression can be rewritten in terms of the apparent one-dimensional friction (ξ_{1D}^{HI}) or mobility (μ_{1D}^{HI}) of a nonspecifically bound protein undergoing curvilinear motion around DNA

$$\epsilon = \xi_{1D}^{HI} v_z^2 = (\mu_{1D}^{HI})^{-1} v_z^2 \quad (28)$$

Calculation of Mobility Tensors for Protein–DNA Systems. We consider four molecular systems. Each system consists of a straight fragment of DNA of 50 base-pairs in a model B conformation, and thus contour length of roughly 170 Å, and a spherical protein. Four values are considered for the radius of the protein: 15, 20, 25, and 30 Å. In each system, the origin of the DNA-fixed (or laboratory) coordinate frame coincides with the center of geometry of the DNA fragment and its z axis is colinear with the axis of the DNA helix (Figures 1 and 2). The center of the protein is located on x axis of this coordinate frame. The protein is facing the DNA major groove (Figure 2). The distance L , between the centers of the protein and DNA, in each system is varied. Minimal values of L considered here result in nearly touching protein–DNA configurations while maximal values of L result in protein–DNA separations that are comparable with radii of proteins.

For each system and for each protein–DNA configuration, matrices of mobility tensors μ_{1-2} (eq 6) and friction tensors ξ_1 (eq 13) were evaluated, as described below.

DNA and proteins are represented in hydrodynamic calculations of mobility tensors using bead-shell models. In the case of proteins (which in models considered by Schurr,¹ by Bagchi et al.,² and in the current work, are simply spheres), their surfaces are covered with equidistributed spherical elements with equal radii of 0.43 Å using an algorithm described elsewhere.¹² For each protein the number of spherical elements is maximal while at the same time there are no overlaps between elements. While it is obvious that the smaller the size of spherical elements, the higher the quality of hydrodynamic models and the better the description of hydrodynamic interactions between molecules,¹² the number of spherical subunits increases with their decreasing size. One should keep in mind that hydrodynamic calculations described further involve storage in computer's RAM and operations on matrices whose ranks depend on the number of spherical subunits in considered systems. The bead-shell model of the largest of the proteins considered here is shown in Figure 2.

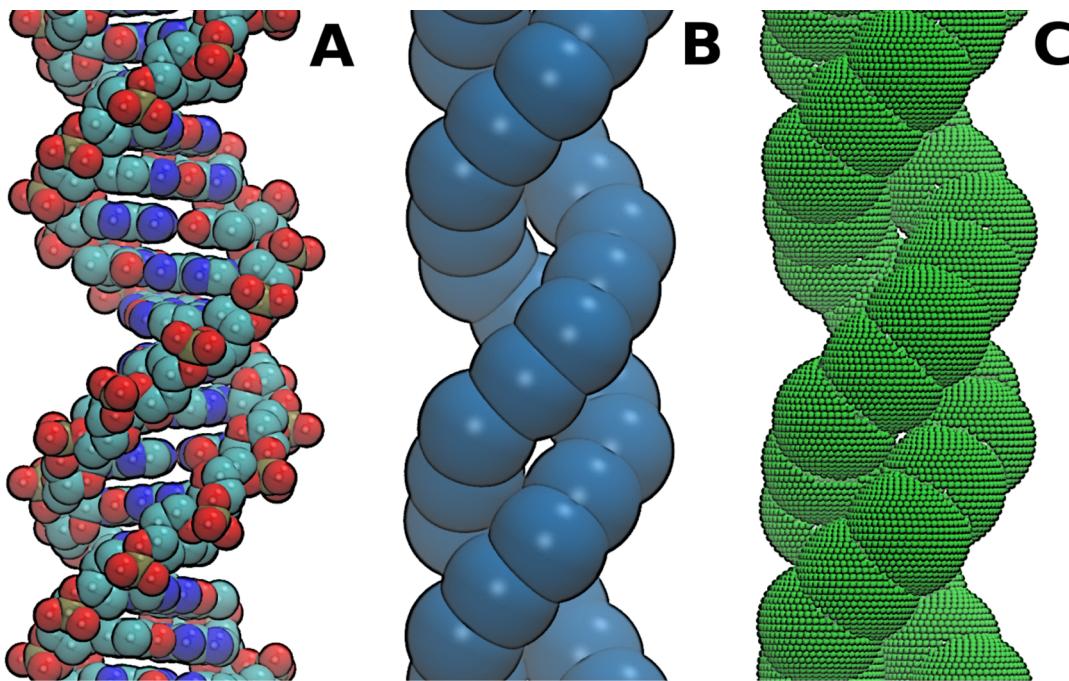


Figure 3. Stages of constructing the hydrodynamic model of DNA: (A) atomistic DNA model; (B) primary bead model in which each DNA residue is replaced with a single pseudoatom; (C) bead-shell model in which surfaces of pseudoatoms are covered with spherical elements. Drawings were done with the VMD package.¹⁹

In the case of the construction of the hydrodynamic bead-shell DNA model a two-step procedure was employed. In the first step of this procedure, a primary bead model of the DNA fragment is created by placing spherical frictional elements at geometric centers of coordinates of the non-hydrogen atoms of nucleotides. Each bead was assigned a radius computed as the mean maximal distance of any atom of a given nucleotide, from the center of its bead, increased by the radius of a water molecule (i.e., 1.4 Å) averaged over four types of nucleotides (A, T, G, C). Resulting primary hydrodynamic model of the DNA molecule consisted of 100 beads with radii of 4.42 Å (Figure 3). This coarse-graining performed in the first step is similar in spirit to the procedure applied previously in the case of protein molecules.^{20,21} Next, surfaces of beads are covered with spherical elements of radii 0.43 Å in a fashion similar to the case of surfaces of proteins. The size of the spherical elements used in modeling DNA and proteins is the same, so both molecules are modeled with similar resolution. We remove overlapping spherical elements belonging to surfaces of neighboring beads. Moreover, spherical elements that are not accessible from the outside of the model are also removed. The resulting DNA bead-shell model is shown in Figures 2 and 3. Numbers of spherical elements used to model proteins and DNA are given in Table 1. Bead-shell models of molecules were

constructed using in-house software. At this point we should mention another approach described and validated by Fernandes and coauthors²² in which the primary bead model of DNA is created by removing hydrogens and replacing each heavy atom with a bead (all beads in the primary model have equal radii). Next, the shell of the primary model is created using smaller beads.

For each protein, deviations of values of isotropic translational and rotational mobility coefficients derived from the 6×6 mobility matrix calculated (using the technique described below) for its bead-shell model in the absence of the DNA, from corresponding values calculated using Stokes–Einstein formulas for translational and rotational mobilities of an isolated sphere of an equal radius are negligible. In the case of the DNA fragment, we may judge the accuracy of the bead-shell model by estimating its hydrodynamic diameter. For that we use formulas for translational²³ and rotational mobility coefficients²⁴ of a rigid cylinder that are applicable in the case of short fragments of double-stranded DNA.²⁵ Substituting translational and rotational mobility coefficients derived from the 6×6 mobility matrix calculated for the bead-shell DNA model in the absence of a protein into formulas proposed by Tirado and de la Torre^{23,24} for a cylinder of length equal to the contour length of the studied DNA fragment, we obtain hydrodynamic diameter of DNA of roughly 19 Å. This value, calculated as an average over values derived separately from expressions for translational and rotational mobility coefficients of a cylinder, is in reasonable agreement with a value of ~20 Å predicted for short DNA fragments by others.^{22,26,27} We note, however, that the performance of our approach to model hydrodynamic properties of rigid DNA fragments can be tuned by modifying values of radii assigned to beads in the primary hydrodynamic model.

Details of the procedure for computing the mobility tensor, μ_{1-2} , for a system consisting of two molecules modeled using bead or bead-shell models are given elsewhere;^{12,14} thus only a

Table 1. Properties of Hydrodynamic Bead-Shell Models of Molecules Considered in This Work^a

molecule	N
DNA	11294
protein, radius 15 Å	2851
protein, radius 20 Å	4856
protein, radius 25 Å	7806
protein, radius 30 Å	10988

^aN denotes the number of spherical subunits constituting the shell of a given molecule.

brief description is given here. First, for a given system in a given configuration (characterized by a particular value of the protein–DNA distance), the general mobility tensor for a system consisting of M spherical subunits is calculated, where M is the sum of the number of spherical subunits in the protein bead-shell model and the number of spherical subunits in the bead-shell model of DNA. While spherical subunits constitute molecules, they are treated at this stage of calculations as independent entities, which results in a general mobility tensor matrix of size $6M \times 6M$ (one should note that for the largest system considered in the current work (Table 1), the general mobility tensor is represented with a matrix of size $133\,692 \times 133\,692$). For the purpose of the current work, $6M \times 6M$ matrices of the general mobility tensor were evaluated at the two-body level, using the analytical Rotne-Prager approach²⁸ described with the whole set of equations given in ref 12 (translational and rotational self-mobilities, and couplings between translations and translations, rotations and rotations, and translations and rotations of different spherical elements are evaluated using expressions in the form of power series of the inverse of interelement distances (r) up to the order of $1/r^3$). It was shown that with the sufficient number of spherical elements in hydrodynamic models of interacting bodies, this level of theory is able to provide a description of hydrodynamic interactions between rigid bodies composed of these frictional elements that is in a reasonable qualitative as well as quantitative agreement with the description resulting from the application of the accurate numerical scheme, the induced forces method,²⁹ even for almost touching bodies.¹² Having calculated the $6M \times 6M$ general mobility tensor, we apply the projection operation^{12,13} (which corresponds to a situation where spherical subunits that build each molecule translate and rotate in concert) to obtain from the general mobility tensor the mobility tensor μ_{1-2} , that is given with a 12×12 matrix (eq 6) which describes a system consisting of two rigid conglomerates of spherical subunits, i.e., molecules.^{12,14} Once μ_{1-2} is known, the ξ_1 tensor (eq 13) for a protein moving in the vicinity of DNA can be derived as described above. All hydrodynamic calculations and matrix operations were performed using in-house software.

RESULTS AND DISCUSSION

In Figure 4 we present values of apparent one-dimensional friction and mobility coefficients that were calculated for four protein–DNA systems considered in this work, for different distances between proteins and DNA, using either expressions derived by Bagchi et al.² or with the approach described above (eqs 27 and 28) that accounts for hydrodynamic interactions between proteins and DNA.

Friction and mobility curves obtained with these two approaches show qualitatively similar behavior, i.e., the apparent one-dimensional friction (mobility) increases (decreases) with the increasing protein–DNA distance. This is true for all sizes of proteins considered in this work. Such behavior of friction and mobility curves is observed due to the term $6\pi\eta RL^2$ that is present in formulas derived by Bagchi and coauthors (eqs 4 and 5) and terms depending on L and L^2 that are present in eq 27. In general, we may consider diffusion of a protein on different helical paths that have the same pitch but different radii (corresponding to different protein–DNA distances). Average square of the displacement of the protein along the helix axis during a fixed time interval decreases with the increasing helix radius and thus the apparent 1D friction (mobility) for the protein increases (decreases) with the increasing protein–DNA distance.

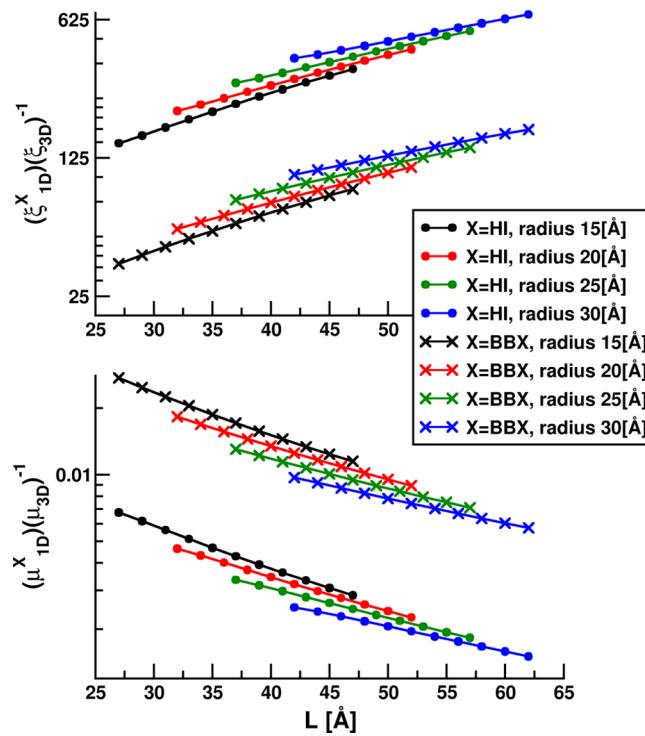


Figure 4. Apparent 1D friction (ξ_{1D} , top) and mobility (μ_{1D} , bottom) coefficients calculated for different protein–DNA systems using the model of Bagchi, Blainey and Xie² (BBX) and with the approach described in the current work (HI), as functions of the protein–DNA distance (L) and the radius of the protein. Values of friction and mobility of proteins are given relative to values obtained for isolated proteins suspended in a viscous fluid, i.e., $\xi_{3D} = (6\pi\eta R)$, and $\mu_{3D} = \frac{1}{\xi_{3D}}$, with η being the viscosity of the solvent and R being the radius of the protein. Base-10 logarithmic scale is used for the y axis in both plots.

As expected, regardless of the approach used to calculate frictions and mobilities, friction increases and mobility decreases with the increasing radius of the protein (Figure 4). However, quantitative differences between values of frictions and mobilities obtained with these two approaches are quite substantial.

For each protein size, we may consider a protein–DNA configuration with the smallest distance between molecules, in which surfaces of molecules almost touch (the surface–surface distance is below 2 Å) as such configurations probably better describe the *real-life* nonspecific protein–DNA complexes. In Table 2 we give values of apparent one-dimensional friction coefficients calculated using the Schurr's expression (eq 2), the approach of Bagchi and coauthors (eq 4), and taking into account hydrodynamic interactions between proteins and DNA (eqs 27 and 28). Overall, smallest friction values result from the Schurr's model and largest from the approach described in the current work. Comparison of apparent mobilities resulting from the current approach and those resulting from the approach of Bagchi and coauthors (such a comparison is also presented in Table 2) reveals that the inclusion of hydrodynamic interactions in calculations of apparent one-dimensional mobilities of proteins leads to values that are on average four times smaller (and roughly ten times smaller when compared with the results of Schurr's model) than those resulting from calculations utilizing the approach of Bagchi and coauthors in which these interactions are omitted.

Table 2. Comparison of Apparent 1D (μ_{1D}) Mobility Coefficients Calculated for Different Protein–DNA Systems in Which Molecules Constitute a Nearly Touching Configuration (i.e., for Each System Hydrodynamic Parameters Obtained for the Smallest L Are Considered) Using the Model of Bagchi, Blainey, and Xie² (BBX) and as Described in the Current Work (HI)^a

protein radius [Å]	$\xi_{1D}^{\text{Schurr}}/\xi_{3D}$	$\xi_{1D}^{\text{BBX}}/\xi_{3D}$	$\xi_{1D}^{\text{HI}}/\xi_{3D}$	$(\mu_{1D}^{\text{HI}}/\mu_{1D}^{\text{BBX}}) \times 100\%$
15	11.6	36.5	148.0	24.6
20	19.6	54.6	215.8	25.3
25	30.0	76.8	299.1	25.7
30	42.6	102.9	398.5	25.8

^aFriction values (ξ_{1D}) resulting from these two approaches and the original approach of Schurr¹ (Schurr) are also given, relative to friction drag coefficients for isolated proteins suspended in a viscous fluid, i.e., $\xi_{3D} = (6\pi\eta R)$.

One could reason that with the increasing size of the protein the influence of DNA on protein diffusivity should be less pronounced (i.e., μ_{1D}^{HI} should converge to μ_{1D}^{BBX} with the increasing radius of the protein) and such a trend can be observed in data presented in Table 2. However, for protein's radius values considered in this work, only slight changes are observed in the $\mu_{1D}^{\text{HI}}/\mu_{1D}^{\text{BBX}}$ ratio with the increasing size of the protein.

Considering expressions for the apparent one-dimensional friction given with eqs 27 and 28 that result from the approach described in the current work, and the expression proposed by Bagchi and coauthors given with eq 4, the latter is simply a linear combination of unmodified, isotropic translational and rotational friction drag coefficients for an isolated sphere suspended in an unbounded viscous fluid. Isolated sphere friction drag coefficients are replaced in eqs 27 and 28 by blocks of the friction tensor ξ_1 (eq 13) that accounts not only for the increased friction drag on the protein resulting from the presence of DNA, but also for the fact that friction is no longer isotropic. Moreover, eqs 27 and 28 account for the hydrodynamic coupling between translations and rotations of the protein, that arises due to the shape of DNA molecule. These effects, i.e., the increased drag, the anisotropic friction, and the translation–rotation coupling result from the fact that the moving protein is affected by the disturbance in the solvent flow field it creates via the nearby DNA fragment, and were considered neither by Schurr¹ nor by Bagchi and coauthors.²

As far as a curvilinear motion of nonspecifically bound proteins around DNA is considered, our calculations show that the magnitude of hydrodynamic effects on apparent one-dimensional mobilities of proteins can be quite substantial (Figure 4, Table 2). We are aware that the mechanism of protein diffusion on DNA is much more complicated than models considered by Schurr and Bagchi and coauthors that we use as a reference. These assume that proteins follow a helical path around DNA and never diffuse away, and that there are no free-energy barriers for this motion. However, the current consensus is that in reality proteins search targets on DNA using a combined mechanism that may involve motions on DNA without dissociation, one-dimensional hopping, and three-dimensional jumps.^{30–33}

Calculations of apparent 1D friction and mobility coefficients were performed in the current work employing a finite DNA fragment. Due to the complexity of the bead-shell DNA model we employ, considering substantially longer DNA fragments would be computationally prohibitive. We believe that

conclusions of our work regarding the significance of hydrodynamic interactions on diffusion of proteins on DNA would remain unchanged if longer DNA fragments were used in calculations, and that our models sufficiently describe effects resulting from the changes in the solvent flow field near fixed DNA arising due to the movement of the protein. We note that longer DNA fragments can be effectively treated in calculations with coarse-grained models.^{7,34} However, it was shown that coarse-grained models are not appropriate to evaluate hydrodynamic interactions between molecules at small separations (i.e., separations that are smaller than approximately two hydrodynamic diameters of beads constituting coarse-grained models), when the Rotne–Prager approximation is employed.¹² Additionally, to account for hydrodynamic effects resulting from the helical shape of DNA, a coarse-grained model consisting of somewhat problematic from the hydrodynamic standpoint overlapping beads would be required.^{35,36} Similarly to Schurr¹ and Bagchi and coauthors² we made an assumption regarding the straight conformation of the DNA and neglected its local structural fluctuations.

According to the current study, hydrodynamic interactions decrease the apparent one-dimensional diffusivity of proteins on DNA. A similar effect, however to a much smaller extent, was described recently in a coarse-grained Brownian dynamics study of model protein–DNA systems by Ando and Skolnick.⁷ These authors used flexible coarse-grained hydrodynamic models of DNA (2 overlapping beads per DNA residue) and proteins (3 beads per protein). They simulated diffusion of proteins on DNA with and without taking into account hydrodynamic interactions between proteins and DNA. From their simulations these authors obtained ~30% reduction in proteins' mobilities on DNA due to hydrodynamic effects. Ando and Skolnick treated hydrodynamic interactions with the Yamakawa's³⁷ variant of the Rotne–Prager approximation for the translational diffusion tensor corrected for overlapping beads as described in ref 36 and, as we have already stated above, such a treatment is likely to fail in describing hydrodynamic effects for short intermolecular distances in the case of coarse-grained hydrodynamic models. On the other hand, Brownian dynamics simulations employed by these authors allowed them to account for DNA flexibility and hopping of proteins.⁷ As we stated above, these factors, which are likely to increase the apparent mobility of proteins on DNA,⁷ are not accounted for in approaches of Schurr,¹ Bagchi, and coauthors² and ours. What is important is that regarding the role of hydrodynamic interactions on diffusion of proteins on DNA (which is not a priori obvious) there is a qualitative agreement between results of numerical calculations described in the current work and results obtained directly from dynamic simulations.

Despite the limitations of models and techniques described above we were able to show clearly that protein–DNA hydrodynamic interactions may play a significant role in the kinetics of proteins' search for their target sites on DNA and that accounting for hydrodynamic effects may decrease the gap between values of diffusion coefficients measured experimentally and estimated theoretically for model systems.^{2,3}

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Notes

The authors declare no competing financial interest.

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