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SHORT NOTE

The one-dimensional diffusion coefficient of proteins absorbed on DNA. Hydrodynamic considerations

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The diffusion-controlled kinetics of association of small globular proteins, such as repressors, with specific sites on long filamentous macromolecules, such as DNA, has been the subject of several recent publications [1–4]. The main effort has been directed at rationalizing the anomalously high association rate observed for the binding of E. coli lac repressor to its specific site on the DNA [5]. The models considered all involve non-specific adsorption (and the reverse process of desorption) of the protein to (or from) the DNA at any location, and the subsequent 1-dimensional diffusion of the protein along the filament until it either desorbs from a non-specific location, or is trapped by binding at the specific site. This 1-dimensional diffusion effectively channels the Brownian motion along a direction that is much more likely to lead to the reactive site in a given time.

An important parameter in the theory is the 1-dimensional diffusion coefficient of the adsorbed repressor on the DNA, which Berg and Blomberg [2,3] have estimated by "fitting" their theoretical formulation to the experimental data [5]. They estimated $D_1 \approx 3 \times 10^{-9}$ cm^2/s, which is very much smaller than the ordinary three-dimensional diffusion coefficient $D_3 = 5 \times 10^{-7}$ cm^2/s. This extremely small value for diffusion along the DNA has been previously presumed to arise from a rather large barrier for diffusive hopping between non-specific sites [4]. It is the purpose of this note to point out that, if the non-specifically adsorbed protein is forced to rotate, as it translates along the DNA, in order to maintain proper register with the two DNA strands, then a very substantial reduction in diffusion coefficient is expected from purely hydrodynamic considerations alone. A rather small upper bound can be placed on D_1 under the present model without introducing additional energy barriers.

The principal conclusion, that translation-induced rotation leads to a much larger rate of energy dissipation than does pure translation alone, is insensitive to specific details of the model, so it suffices to consider the simplest possible case here. It is imagined that the non-specifically adsorbed globular protein straddles the duplex DNA, which then occupies a deep, narrow cleft, or groove, in the former, in such a way that the adsorbed protein is hydrodynamically equivalent (or nearly so) to a ball centered on the axis of the DNA helix. It is further assumed that the adsorbed protein specifically senses the orientation of the two DNA strands at one or more points in the cleft, so that translation along the DNA necessitates rotation of the protein to preserve the correct relative orientation with respect to the DNA. The simple picture, then, is that of a large ball sliding along a pair of narrow gauge parallel, spiralling tracks in such a way that the center of the sphere remains always on the helix axis, while the tracks are closely confined to specific minor grooves in the cleft.

If the center of the ball translates with slow, steady velocity v along the helix axis, then the rate of energy dissipation due to translation alone can be approximated using the Stokes Law force $F = 6\pi\eta a v$, which gives

$$D_{\text{trans}} = 6\pi\eta a v^2 , \tag{1}$$

where a is the radius of the ball, or adsorbed protein. This value actually represents a lower bound, because the stationary DNA present in the fluid flow field acts to introduce additional dissipation. The translating ball must also undergo one full rotation for each turn of the spiralling tracks. Assuming the traditional value of

close to 10 base pairs per turn, and a 3.4 Å rise per base pair [6], one expects the adsorbed protein to undergo one full rotation for every 34 Å of linear translation along the helix axis. The angular velocity of the translating sphere is then $\dot{\theta} = 2\pi v/3.4 \times 10^{-7}$ radians s^{-1}. The rate of energy dissipation can be approximated using the Stokes Law torque $T = 8\pi\eta a^3\dot{\theta}$, which gives

$$D_{rot} = 8\pi\eta a^3\dot{\theta}^2 = 8\pi\eta a^3(2\pi v/3.4 \times 10^{-7})^2 . \qquad (2)$$

As before, this is a lower bound because the presence of the DNA acts to increase the dissipation somewhat. Combining eqs. (1) and (2) gives for the total dissipation $D = 6\pi\eta a\,[1 + (4/3)(2\pi)^2(a/3.4 \times 10^{-7})^2]\,v^2$, from which the effective friction factor for sliding along the DNA can be readily identified as

$$f_{eff} = 6\pi\eta a[1 + \tfrac{4}{3}(2\pi)^2(a/3.4 \times 10^{-7})^2] . \qquad (3)$$

The radius a of the lac repressor can be estimated from its three-dimensional diffusion coefficient using the Stokes-Einstein relation $D_3 = k_B T/6\pi\eta a$ with the result $a = 4.9 \times 10^{-7}$ cm. In this case eq. (3) gives $f_{eff}/6\pi\eta a \approx 110$, which shows that the requirement for rotation has increased the effective hydrodynamic friction factor by 110-fold. The theoretical one-dimensional diffusion coefficient along the DNA is obtained from the Stokes-Einstein relation $D_1 = k_B T/f_{eff}$, or more directly from the ratio $D_1/D_3 = (f_{eff}/6\pi\eta a)^{-1}$. The resulting value $D_1 = 4.5 \times 10^{-9}$ cm^2/s, which represents a *theoretical upper bound*, is not much greater than the value 3×10^{-9} cm^2/s estimated from the experimental data. A proper accounting for the hydrodynamic interaction between the sliding protein and the stationary filament would further decrease D_1, thus improving the agreement with the experimental value. The apparent quantitative success of the present model suggests that translation-induced rotation may actually be a characteristic feature of the 1-dimensional diffusion, or sliding, of the lac repressor along the DNA filament.

In a recent paper Berg and Blomberg [7] estimate that the one-dimensional diffusion coefficient D_1 is an order of magnitude smaller in the absence of Mg^{++} ions than the value cited above [5], which was determined in the presence of 0.01 M Mg^{++} ions. This certainly suggests that the simple hydrodynamic model is not applicable in that case. Without knowing in detail how the equilibrium DNA structure, the geometry of the non-specific DNA: repressor complex, the transient structural inhomogeneities, and the torsional rigidity of the DNA are influenced by Mg^{++} ions it is not worthwhile speculating on the origins of the apparent decrease in D_1 in their absence.

Generalization of the present model to situations in which the center of the absorbed protein lies well off of the helix axis merely increases the purely translational dissipation due to the extra length of the now spiral path travelled by the protein center. Nonetheless the total dissipation in any case is still substantially dominated by the induced rotation, which remains constant at one rotation per 34 Å travelled along the helix axis, regardless of the location of the center, so long as the protein is rigidly constrained to maintain always a fixed orientation with respect to the two strands of the DNA along which it slides. Thus, for any sliding model subject to the constraint of fixed relative orientation the second term in eq. (3) still applies, and for the lac repressor the upper bound for D_1 is still within a percent or so of the value 4.5×10^{-9} computed above.

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