Minireview

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Facilitated Target Location in Biological Systems*

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In 1970 Riggs *et al.* (1) reported that *Escherichia coli lac* repressor binding to λ DNA *in vitro* seemed to find its target (operator) site on the DNA at a rate as much as 1000-fold faster than the upper limit estimated for a diffusion-controlled process involving macromolecules of this size. This observation startled and intrigued many physically oriented molecular biologists and biochemists and initiated a flurry of theoretical and experimental papers seeking to offer an explanation. However, scrutiny of the older literature reveals that scientists, ranging from mathematicians to biologists, had long been concerned with how systems of various sorts might transcend the rate limits set by three-dimensional diffusion control (2).

Such problems are now of interest at many different levels. The pure physical chemist feels that an understanding of such phenomena might provide new insight into what happens when molecules meet and rearrange in the course of forming and passing through the transition state complex. The enzyme mechanician hopes that the secrets of some of the astonishing increases in rates achieved in enzyme-catalyzed reactions may be revealed by a study of these rate accelerations. And the cell biologist who studies macromolecular interactions and assembly processes is intrigued by the possibility that these systems may reveal opportunities for acceleration of intracellular rates beyond the limits set by the relatively slow diffusion of macromolecules in the cytoplasm.

In this minireview we propose to touch on recent progress in all of these areas but will focus primarily on a problem that has engaged our attention over the past few years, *i.e.* how do protein regulators of gene expression at the transcriptional level find their regulatory DNA targets at speeds that appear to be faster than diffusion controlled?

What Limits Reaction Rates?

The rates of biological reactions, just as those of regular chemical processes, are, in principle, limited by the rates at which diffusion can bring the reactants together. Thus the maximum rate of a reaction depends on the encounter probabilities of the components, which for a bimolecular association of two uniformly reactive spherical molecules (A and B) corresponds to the Smoluchowski limit,

$$k_{\text{encounter}} = 4\pi(D_A + D_B)\,(r_A + r_B)N_0/1000 \qquad (1)$$

where D_A and D_B are the diffusion constants (in cm^2/s) and r_A and r_B (in cm) are the hydrodynamic radii of molecules A and B, respectively. N_0 is Avogadro's number, and the factor 1000 normalizes the units of $k_{\text{encounter}}$ to $M^{-1}\,s^{-1}$.

The net rate at which two such spherical molecules diffuse together depends on their sizes, on temperature (T), and on solvent viscosity (η), as defined by the Stokes-Einstein relation.

$$D_A = kT/6\pi\eta r_A; \quad D_B = kT/6\pi\eta r_B \qquad (2)$$

Actual molecular association or reaction (as opposed to encounter) rates may deviate from those predicted by the simple Smoluchowski relation for a number of reasons: (i) the entire surfaces of the molecules are not generally uniformly reactive; (ii) there may be electrostatic attractive or repulsive forces that either increase or decrease the simple diffusion-driven association rate; (iii) the reactive particles may not be spherical (molecular asymmetry generally decreases diffusion rates); and (iv) the interaction distance may differ from the sum of the hydrodynamic radii of the interacting particles. These aspects result in a modified Smoluchowski equation,

$$k_{\text{assoc}} = 4\pi\kappa a f(D_A + D_B)N_0/1000 \qquad (3)$$

where κ is a unitless interaction parameter determined by the fractions of the surfaces of particles A and B that are reactive, a is the interaction distance (in cm), f is a unitless factor that reflects the increase or decrease in the diffusional collision rate due to electrostatic attraction or repulsion of the interacting molecules, and D_A and D_B are the actual diffusion constants of the (generally nonspherical) interacting particles.

We can use Equation 3 to estimate the forward rate constant (k_{assoc}) for the association of (*e.g.*) *lac* repressor with a specific DNA operator site. We set the diffusion constant of repressor (D_A) at 5×10^{-7} cm^2/s (the diffusion constant of the operator within a large piece of DNA (D_B) will be much smaller than D_A and thus can be effectively ignored, since diffusion constants add in Equation 3). The average radius of the repressor is estimated at 40 Å and that of the DNA cylinder at 10 Å; thus we use an interaction distance (a) of 50×10^{-8} cm. The electrostatic factor (f) is set at unity (both DNA and repressor are negatively charged and thus will repel one another, but this may be offset by a close-range attraction, since the repressor binding site is positively charged). Finally, we crudely estimate κ to be 0.05, assuming that approximately one-fifth of the repressor surface represents active site and that approximately one-fourth of the cylindrical surface of the operator DNA sequence actually interacts with repressor.

Using these parameters, k_{assoc} for the interaction of *lac* repressor with its operator target in a large DNA molecule turns out to be approximately 10^8 $M^{-1}\,s^{-1}$. In contrast Riggs *et al.* (1) measured, and others have confirmed (3, 4), that k_{assoc} for the interaction of *lac* repressor with its operator DNA target carried on a λ phage DNA molecule (50,000 base pairs) can range up to 5×10^{10} $M^{-1}\,s^{-1}$.[1] How can these large discrepancies be resolved?

Forward Rate Constants for Macromolecular Associations in Solution

In addition to the modifications in the Smoluchowski equation introduced via Equation 3, macromolecules interacting in solution have special features that can increase the apparent bimolecular association rate. We have recently reviewed this subject in detail (5); here we briefly summarize the relevant features and show how they affect interaction rates.

First, it is important to realize that macromolecular collisions in aqueous solution cannot be considered to be elastic. Rather the fairly small diffusion constants of macromolecules, plus a general (van der Waals?) "stickiness," makes macromolecules that have collided rather slow to drift apart. As a consequence a single classically defined collision can include many reiterated "minicollisions" during which the macromolecules can undergo appreciable relative rotational rearrangements and thus overcome (at least partially) the limitations of interaction geometry as defined in the steric interaction term (κ). These rotational rearrangements can partially or completely overcome the expected steric factors in many known enzyme-substrate and macromolecular interactions, and thus the reactions appear to proceed at essentially diffusion-controlled rates. How might one explain still further rate enhancements, *i.e.* those that go *beyond* the apparent diffusion-controlled limit?

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[1] To get an idea of how astonishingly large this rate really is, we point out that the rate constant for the *facilitated* (see below) effective association of the superoxide anion (O_2^-) with the enzyme superoxide dismutase is only 2×10^9 $M^{-1}\,s^{-1}$ and that the diffusion constant of the superoxide anion is more than 10-fold larger than that of the *lac* repressor.

Electrostatic Rate Enhancements for Macromolecular Reactions

A number of macromolecular reactions display forward rate constants that appear to *exceed* the limits set by the simple Smoluchowski equation. Reactions of this type that have been carefully examined include those of enzymes with highly charged small molecule substrates (*e.g.* the interaction of superoxide dismutase with the superoxygen anion (O_3^-) (6)) and those of charged enzymes with charged macromolecular substrates (*e.g.* the association of cytochrome *c* peroxidase with cytochrome *c* (7)). In both of these (theoretical) studies highly detailed molecular models of the protein structures and their related electrostatic fields have been used together with Brownian dynamic computer simulations of the diffusional approaches of the associating species.

In both instances the macromolecules set up large electrostatic fields about themselves that "guide" the substrate into the active site of the macromolecule. In effect, this increases the magnitude of the steric factor (κ) of Equation 3 as well as (in specified directions) increasing the reaction distance (a). The electrostatic basis of these effects is clear since they can be abolished by increasing the ionic strength of the solution. The result for the cytochrome *c*-cytochrome *c* peroxidase interaction is particularly striking since the net charge of both interacting macromolecules is the same (positive). It appears that the overall electrostatic field set up around the cytochrome *c* peroxidase "funnels" the basic cytochrome *c* into the negatively charged active site of the enzyme.

In summary, it appears that one way to increase reaction rates (at least somewhat) above the expected diffusional limit is to use "shaped" electrostatic fields that extend well beyond the surface of the macromolecule. These fields then serve to guide approaching reactants into the (appropriately charged) active site and thus increase the frequency of successful collisions.

Special Features of DNA-Protein Interactions

DNA-Protein Collisions Are "Inelastic"—The interactions of DNA with genome regulatory molecules have special features that can serve to enhance association rates still further. First, of course, both parties in this reaction are macromolecules, and thus they share the rate-enhancing features of long-lived (inelastic) collisions during which they can engage in relative rotatory diffusion to bring the interacting surfaces into appropriate apposition. Because of the local cylindrical geometry of the DNA double helix, these processes can include short excursions of the protein along the DNA during the reiterated mini-collisions. This phenomenon, which we have previously termed "hopping" (8), can translocate the protein along the DNA by as much as 4–8 base pairs during a collision and thus help in the sampling of nonspecific sites and in the final stages of aligning (docking) the protein with the DNA target sequence. In addition most genome regulatory proteins are characterized by a positively charged active site within a net negatively charged protein; this also can help to establish correct mutual orientation between the colliding macromolecules.

Initial Interactions Are with Nonspecific Sites of DNA Domains—There are other features, however, that can (and do) enhance the rate of protein-DNA interactions still further. These are shown schematically in Fig. 1 and have been described in detail elsewhere (4, 8). As Fig. 1 makes clear, double-stranded DNA molecules exist in solution as extended random coils. In dilute solution these random coils occupy molecular "domains" or volumes of the solution that are generally quite far apart and do not appreciably overlap. A regulatory protein (*e.g.* a repressor) diffusing to such a domain will obviously have little chance of making a direct collision with the specific DNA target site (the operator); rather initial contact will generally be with a segment of nonspecific DNA.

The subsequent course of events, as indicated in Fig. 1, will be that the repressor undergoes association-dissociation reactions *within* the DNA domain, eventually encountering the operator and thus achieving a successful interaction. On the average, we expect the repressor to form N (where N is the number of base pairs in the DNA molecule) incorrect transient complexes with nonspecific DNA sites prior to finding the operator. How will the formation of all these transient nonspecific complexes affect the observed association rate?

Obviously, if these incorrect sites can be viewed as competitive binding targets, the rate of association with the correct site is expected to *decrease* with increasing N. At low salt concentrations (where these nonspecific associations are tighter and dissociation is slower), the rate is expected to decrease further. In fact, the opposite is observed; increasing the number of nonspecific sites around the target operator and decreasing the salt concentration both seem to *increase* the apparent association rate (at least within a wide range of experimental conditions).

Nonspecific Binding Speeds DNA Target Location—Thus it appears that the formation of intermediate complexes between nonspecific sites within the DNA domain and the incoming regulatory protein *speeds* target location. How can this be? Fig. 1 suggests two general ways in which nonspecific complex formation can, in principle, increase the rate of DNA target sequence location. We have termed these two mechanisms "sliding" and "intersegment transfer" (8). Both involve diffusion of the protein while *in* the nonspecifically bound state and thus effectively decrease the volume of solution that needs to be "searched" by the protein in finding its regulatory DNA target.

Sliding was first proposed in general terms as a mechanism to facilitate diffusional target location by Adam and Delbruck (2). The mathematical formulation of the problem was subsequently outlined by Richter and Eigen (9) and developed in full for the DNA-protein interaction case by Berg and co-workers (8, 10–13). Intersegment transfer as a mechanism to speed operator location by *lac* repressor was initially proposed by von Hippel *et al.* (14) and mathematically developed by Berg *et al.* (8) and Berg (15, 16).

Sliding of Proteins on DNA—The sliding process can be viewed as a form of "one-dimensional" diffusion of the protein along the contour length of the DNA.[2] In order for this process to work, it is required that the activation barrier for translocation of the protein *along* the DNA in the nonspecifically bound state be small compared to thermal energies (kT; 0.6 kcal/mol at physiological temperatures). This requires a relatively delocalized type of binding of the proteins to the DNA; charge-charge interactions appear to provide the appropriate binding free energy for this purpose.

Transcription regulatory proteins often appear to be characterized by two conformational states or "binding modes." One is the sequence-specific binding state in which complementary arrays of hydrogen bond donors and acceptors (located respectively in the active site of the protein and in the grooves of the DNA double helix) provide specific recognition interactions between the protein and its DNA target site. These hydrogen bond interactions are disfavored when the protein is located at sites containing several "incorrect" base pairs (*i.e.* at nonspecific sites) and the protein instead switches to the nonspecific (totally electrostatic) binding mode in which it can undergo one-dimensional diffusion.[3]

In this conformation movement along the DNA is thought to occur by the displacement of bound (delocalized) positive counterions from the DNA. Using the polyelectrolyte ion condensation approach to DNA-protein interactions pioneered by Manning (20) and by Record and co-workers (21), we (4, 8, 22) have proposed that the DNA cylinder be viewed as an isopotential surface along which the protein can diffuse in a one-dimensional random walk while bound in a non-sequence-specific binding conformation. Increasing the lifetime of the nonspecifically bound state (*e.g.* by decreasing salt concentration) permits wider ranging diffusional excursions of the protein along the DNA and thus increases the rate of target location for DNA sites that are close along the DNA contour. The existence of sliding as a means of target location for DNA-binding proteins has been demonstrated experimentally in a number of systems including the *lac* repressor-operator interaction (3, 4), *Eco*RI restriction enzyme target location (23, 24), and recently RNA polymerase binding to promoter sites (25, 26).

Facilitated Target Location by Direct Intersegment Transfer—Direct intersegment transfer of proteins between nonspecific DNA sites within the domain (we have also called this process "intradomain transfer"; see Refs. 4 and 8) speeds up specific DNA target location in quite a different way, though again the protein can be viewed as moving about the DNA while *in* the nonspecifically bound state. Here it was proposed that the protein can bind to two DNA sites that are quite far apart along the DNA contour but are brought together transiently by the segmental diffusion of individual loops of the DNA

[2] It is important to distinguish this form of diffusional sliding from the various forms of chemical energy-dependent translocation of proteins along DNA (*e.g.* in helicase function, etc.). Energy-requiring translocation events are generally unidirectional and involve the hydrolysis of ATP or other energy-yielding substrates. Diffusion-driven translocations are random walks and are driven by thermal fluctuations in the solvent.

[3] For recent discussions of protein-DNA recognition and binding conformations see Refs. 17–19.

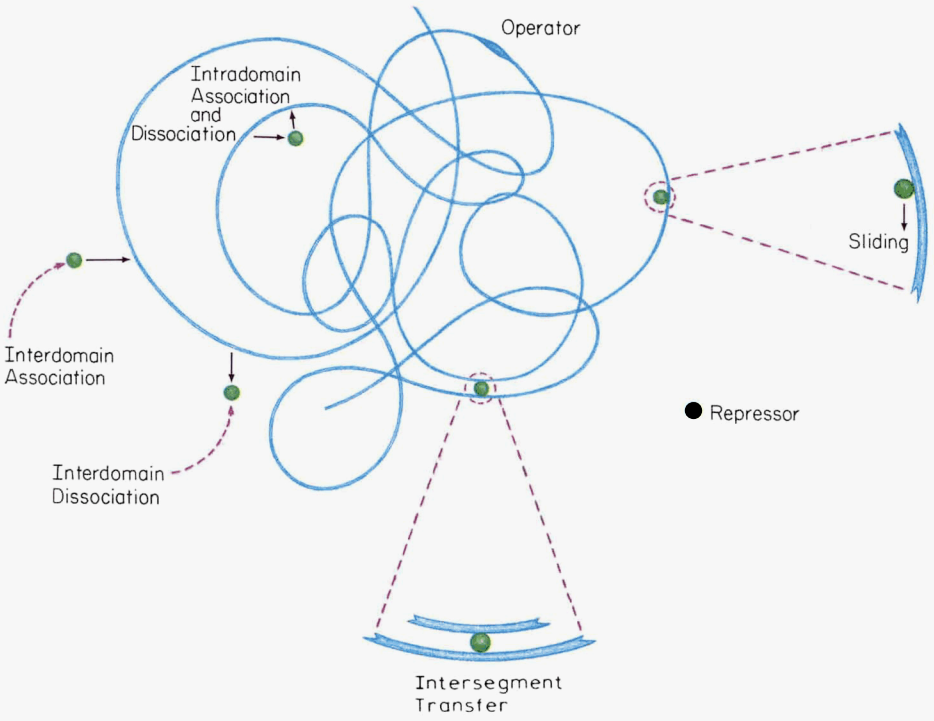

FIG. 1. **Schematic view of *lac* repressor interacting with a large operator-containing DNA molecule in dilute solution.** (The DNA molecules are well separated into "domains" under these conditions.) The (*upper*) expanded view shows repressor bound to a segment of non-operator DNA, on which it can either "slide" or engage in intradomain dissociation-association processes in seeking its specific (operator) target site. The (*lower*) expanded view shows a repressor molecule double bound to two DNA segments; this corresponds to the intermediate state in the intersegment transfer process.

double helix within the domain. This transient double bound state of the protein is disrupted by subsequent diffusion apart from the DNA segments, resulting (50% of the time if both binding interactions are equally strong) in the direct transfer of the protein from one nonspecific binding site to another that is quite remote along the DNA contour, *without* the need for dissociation of the protein from the DNA.

In contrast to sliding, the direct intersegment transfer process does not favor target location for sites located close along the contour of the DNA; in that sense the path of the protein through the DNA domain more closely resembles that expected for three-dimensional diffusion via intradomain dissociation-association events. However, in contrast to intradomain dissociation-association processes, direct intersegment transfer rates will, of course, *increase* with increases in the duration of the nonspecifically bound state.[4]

Direct intersegment transfer of proteins and protein models between DNA sites has been experimentally demonstrated by Bresloff and Crothers (32) and by Icenogle and Elson (33) for ethidium bromide, and by Fried and Crothers (34) for *lac* repressor. The possible role of such intersegment transfer processes in *in vivo* gene regulation is commented upon below.

Diagnostic Methods to Determine Whether Sliding or Other Modes of Facilitated Diffusion Are Involved in DNA Target Location by Regulatory Proteins—Efforts to determine whether some form of facilitated diffusion is involved in DNA target location for a particular DNA-protein interaction system have often led to considerable confusion. This question is generally fairly easy to address experimentally in simple cases where binding to the regulatory target represents the *only* step in the interaction process (*e.g. lac* repressor binding to its target operator site) or where the initial binding event represents the step that is detected by the assay used.[5,6] For such systems studied *in vitro* any or all of the following observations indicate that facilitated diffusion is involved.

(i) The apparent reaction rate is larger than seems reasonable for a simple (three-dimensional) diffusion-controlled macromolecular interaction. As the examples presented in preceding sections show, small increases above expected values might be attributable to facilitated docking processes (within macromolecular collisions) or to enhancements by shaped electrostatic fields. Large enhancements probably must be explained in terms of sliding or intersegment transfer processes.

(ii) The apparent forward rate constant of the process under study is *larger* when the target DNA site is placed on a larger DNA fragment (or the apparent dissociation rate constant of the protein from the DNA is *smaller* when the target site is placed on a smaller DNA fragment; see Ref. 23 for a good example of a case of this sort). This observation implicates sliding (or an equivalent DNA contour-dependent process) directly.

(iii) The apparent forward rate constant of the process *increases* with decreasing salt concentration, *i.e.* with decreasing nonspecific binding dissociation rates.

(iv) The plot of $\log(k_{assoc})$ *versus* log(salt concentration) for target

[4] For further discussion of the intersegment transfer process see Refs. 8, 14–16, and 27. The central feature of the direct intersegment transfer process is, of course, the formation of double bound DNA-protein complexes. O'Gorman *et al.* (28) first experimentally demonstrated the formation of such complexes between *lac* repressor and two *operator*-containing fragments. Subsequently the formation of such stable "looped" structures between two operator sites and a variety of regulatory proteins, both *in vitro* and *in vivo*, has become a central feature of transcriptional regulatory mechanisms in both prokaryotes and eukaryotes (see *e.g.* Refs. 29–31).

[5] To determine whether sliding is involved in a DNA-protein interaction becomes more difficult when the initial binding event is only the first in a sequence of steps and the assay being used to study the interaction detects one of the subsequent steps. For example, in the interaction of RNA polymerase with its target promoter, the first step is the formation of the *closed* promoter complex. However, assay techniques generally detect a subsequent step, such as the formation of the *open* promoter complex, RNA chain initiation, or even total RNA chain synthesis. In order to see whether sliding is involved in a system such as this it is necessary to set things up so that the closed promoter complex formation becomes the rate-limiting step, because subsequent rate-limiting steps will mask the characteristic features of the (*e.g.*) sliding process, if it is present. Even so, the fact that the overall rate for the entire process is excessively fast (apparent rates of open promoter complex formation of 10^8–10^9 M^{-1} s^{-1}) may be used to infer that initial target location must involve some form of facilitated diffusion mechanism so that it will *not* be rate-limiting. For a recent discussion of this problem in the context of the *E. coli* RNA polymerase-promoter interaction see Ricchetti *et al.* (25).

[6] Additional theoretical approaches to the analysis and quantitation of facilitated diffusion mechanisms are also being developed, *e.g.* see Mazur and Record (35, 36).

sites on large DNA molecules has the bell-shaped form characteristic of reactions facilitated by sliding (3, 4, 8, 12). This shape is due to the fact that at low salt concentration (and/or at high DNA concentration) nonspecific binding can *decrease* the rate of target location because the protein spends an inordinate amount of time sliding and searching in regions of the DNA domain that do not contain the target site. The maximal association rate occurs at the salt concentration at which the nonspecific dissociation constant equals the DNA concentration within the domain (8, 37).

The simplest way to perform such association rate assays experimentally is to use quantitative filter binding techniques in which DNA-protein complexes containing radioactive DNA are separated from free DNA because only the protein, and thus the radioactive DNA to which it is bound, will adhere to the filter (1, 3, 4). Advantages of this method include the fact that it requires very little material and that it can be conducted at enormous dilutions of the reactants (*e.g.* at concentrations as low as 10^{-12} M). This means that extremely large rate constants can be detected on an easily accessible time scale of seconds to minutes.

Other DNA-Protein Interaction Processes in Which Sliding May Be Involved—Sliding of the sort described here, in which proteins in a nonspecifically bound state are able to move along the DNA in a random walk driven by the thermal fluctuations, may apply to processes other than regulatory target location on DNA. For example, elsewhere (38) we have proposed that polymerase-directed DNA synthesis may involve alternate specific binding (at the primer-template junction) and nonspecific binding states of the polymerase. The polymerase may then translocate to the next nucleotide insertion site within each nucleotide addition cycle by one-dimensional diffusion. The same mechanism may apply to the movement of RNA polymerase in transcription.

Rate Facilitation of DNA-Protein Interactions in Vivo—To what extent are these rate facilitation mechanisms likely to be important for regulatory protein target site location *in vivo* where the DNA regulatory sites are located on quite "condensed" chromosomes carrying many bound proteins in a "crowded" cytoplasm and at fairly high (physiological) salt concentrations? Under these conditions sliding path lengths are expected to be fairly short, both because proteins bound to the DNA can interfere and because dissociation rates from the nonspecifically bound state may be quite large. This suggests that the rate enhancements that can be achieved by sliding *in vivo* may be quite limited (37). Thus we might expect regulatory protein sliding to be involved primarily in the final stages of protein docking and that intersegment transfer processes may play a more important role in chromosomal target location *in vivo*. This is likely since, as DNA domains become more "compact," close encounters between DNA segments within the DNA domain as a consequence of segmental diffusion will greatly increase in frequency (8, 15, 16).

Rate Facilitation of Other Biological Processes

As originally pointed out by Adam and Delbruck (2), the rates of many biological processes can be enhanced by diffusion within reduced dimensions. Thus sliding of the sort outlined above for DNA polymerase translocation during synthesis may apply to the movement of myosin molecules along actin filaments in muscle contraction.[7] One-dimensional diffusion of the sort discussed here may also be involved in the assembly of microtubules, in chromosome movement, and in other cellular processes where proteins or other organelles may migrate along microfilaments (*e.g.* Refs. 39 and 40).

Finally, the rates of location of receptors on membranes by specific binding ligands or the rates of assembly of proteins into pores, etc., can, in principle, be greatly speeded if these ligands can engage in two-dimensional diffusion in the membrane surface. In common with proteins sliding on DNA, this requires a nonspecific binding mode for the ligand (electrostatic or hydrophobic?) in equilibrium with a specific (target recognition) binding mode. For examples of such two-dimensional processes, as well as solutions to the relevant equations, see Refs. 37 and 41–43.

[7] W. F. Harrington and P. H. von Hippel, manuscript in preparation.

Summary

In this minireview we have attempted to provide some overall perspective on the question of how various forms of diffusion in reduced dimensions, or diffusion within a nonspecifically bound state, can speed biological interactions beyond the limits normally set by three-dimensional diffusion processes. To this end we began by discussing the rates expected for small molecules engaged in classical elastic collisions. We then proceeded to modify this picture by introducing first the features of inelastic macromolecular collisions in solution, then the effects of specific electrostatic fields set up around macromolecules of known structure at low ionic strengths, and finally the special rate enhancements available to DNA-protein interactions because of the particular geometry of the DNA molecule and the multiple conformations that can be assumed by the protein component. We hope that this exposition will help to clarify the subject for others and also will stimulate more focused examination of this type of problem, both in DNA-protein interaction systems and in other biological systems where such rate facilitation might apply.

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