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Protein Diffusion Along Protein and DNA Lattices: Role of Electrostatics and Disordered Regions

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Abstract

Diffusion is a pervasive process present in a broad spectrum of cellular reactions. Its mathematical description has existed for nearly two centuries and permits the construction of simple rules for evaluating the characteristic timescales of diffusive processes and some of their determinants. Although the term diffusion originally referred to random motions in three-dimensional (3D) media, several biological diffusion processes in lower dimensions have been reported. One-dimensional (1D) diffusions have been reported, for example, for translocations of various proteins along DNA or protein (e.g., microtubule) lattices and translation of helical peptides along the coiled-coil interface. Two-dimensional (2D) diffusion has been shown for dynamics of proteins along membranes. The microscopic mechanisms of these 1–3D diffusions may vary significantly depending on the nature of the diffusing molecules, the substrate, and the interactions between them. In this review, we highlight some key examples of 1–3D biomolecular diffusion processes and illustrate the roles that electrostatic interactions and intrinsic disorder may play in modulating these processes.

Contents

1. INTRODUCTION

Diffusion processes are essential for the proper functioning of any living cell (4, 103). This motion is governed by thermal fluctuations that are linked to collisions with the molecules in the surrounding medium, resulting in translocation of biomolecules through that medium. This motion (also called Brownian motion) thus is not controlled by energy consumption but instead by random forces dictated by the microscopic (i.e., molecular features of the solvent) and macroscopic (i.e., viscosity and temperature) properties of the medium. While many important trafficking and functional motions of biological motors and machines are controlled by external energy sources, diffusion processes are also fundamental, particularly when they constitute the rate-limiting step. Diffusion has several forms in biochemical processes. The simplest form of diffusion is in the three-dimensional (3D) environment (such as diffusion of proteins in the cytoplasm). Other forms of diffusion involve diffusion of biomolecules in lower-dimensional spaces, namely, diffusion in one-dimensional (1D) or two-dimensional (2D) spaces (**Figure 1**). 1D diffusion describes the translocation of a biomolecule along a biological polymer (such as a microtubule or DNA), with the diffusion performed along the elongated axis of the polymer. 2D diffusion describes dynamics of a biomolecule on a biomolecular lattice (such as a membrane), with two major axes for dynamics.

The relationship between time and translocation in diffusion processes is given by the Einstein equation $<L^2> \sim D\tau$, where L is the distance the diffusing particle traverses at time τ, and D is a key parameter, called the diffusion coefficient, that is indicative of the diffusion mobility. The value of D is microscopically governed by the velocity of the diffusing molecule and the mean time between collisions. The diffusion coefficient can be obtained from Einstein's relation, $D = k_B T/\xi$, where $k_B T$ is the Boltzmann constant multiplied by the absolute temperature, and ξ is the frictional coefficient for diffusion. For spherical particles, $\xi = 6\pi\eta R$, where η is the viscosity

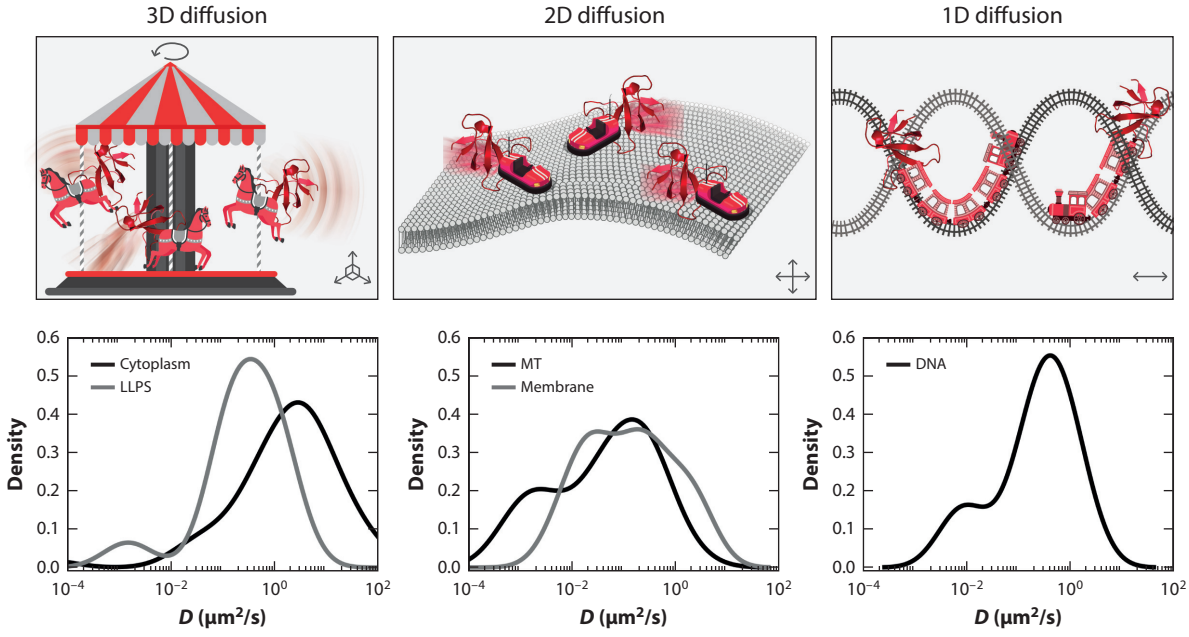

Figure 1

Schematic illustrations of biomolecular diffusion in 1–3 dimensions. The distributions of the experimental values of diffusion coefficients for each type of diffusion are shown at the bottom. Abbreviations: LLPS, liquid–liquid phase separation; MT, microtubule.

of the medium. This produces a Stokes–Einstein relation for translational diffusion of globular proteins of radius R, $D = k_B T/6\pi\eta R$.

Following the Einstein relation, a protein with a diffusion coefficient of 10 $\mu m^2/s$ will cover in a period of a second a distance of approximately 3,000 Å. To appreciate the distance covered by a biomolecule in a diffusion process, one may compare it to the distance covered in another common dynamic process in the cell. For example, in internal dynamics of biomolecules, which are widespread in many biomolecular systems, the distances are much shorter even though the timescales are long. While the timescale of such conformational dynamics spans approximately 16 orders of magnitude (from 10^{-12} to 10^4 s), they cover shorter length scales of 1–100 Å. Accordingly, diffusion processes are often characterized with much smaller energetic barriers than that defined for conformational transitions.

The diffusion processes may be slowed down when interactions with the medium molecules are involved. Such interactions can in principle increase the friction for diffusion and result in a higher barrier for diffusion. In these cases, the diffusion coefficient may be treated as $D = D_0 F(\varepsilon)$, where F is a function that describes the barrier heights depending on the energetic parameter, ε, of the medium. Not all diffusive processes can be described by a single diffusion coefficient, as the diffusing molecules are confined and thus exhibit anomalous diffusion (80). There are various ways to determine the diffusion coefficients. For in vitro determination of D, dynamic light scattering and nuclear magnetic resonance (NMR) are among the techniques that have been used (139). In vivo determination has relied on fluorescence recovery after photobleaching, single-particle tracking, and fluorescence correlation spectroscopy (81). Computationally, D is often probed by measuring the mean squared displacement of the center of mass of the biomolecule that scales linearly with time and satisfies the equation $D = (x(t) - x(0))^2 + (y(t) - y(0))^2 + (z(t) - z(0))^2/6t$. Alternative approaches to estimates of D from molecular simulations are also employed (43).

Both 3D diffusion and 1D and 2D diffusion of a biomolecule on a substrate are linked to a variety of essential functions. The mechanisms of these intrinsic motions are thus linked to cellular activity. Quantifying the molecular and biophysical parameters that regulate diffusion is therefore fundamental to understanding biomolecular interactions. In this review, we discuss key examples of diffusion processes and their determinants. An emerging theme is that electrostatic interactions between the diffusing molecule and the substrate or the existence of disordered regions can facilitate the diffusion.

2. BIOMOLECULAR DIFFUSION IN THREE DIMENSIONS

3D diffusion is often prerequisite for a biomolecular association between two or more reactants. Drug diffusion is an essential mechanism for drug dispersion throughout biological systems. Such a diffusion process is of particularly high importance when it constitutes the rate-limiting step of the interactions. The bimolecular association rate constant for two spherical molecules is $k_a = 4\pi DR \sim 8k_BT/3\eta$, where D and R are the sum of the diffusion coefficients and radii of the two molecules, respectively, which correspond to $k_a \sim 10^9$–10^{10} $M^{-1}s^{-1}$ (106). This maximal diffusion-limited association rate of diffusion-controlled reactions is expected to be slower if the diffusion is affected by steric hindrance, nonspecific binding, and internal modes of motion. In the case of drugs, resistance to diffusion may arise, for example, from the tissue composition, structure, and homogeneity. This rate can increase if the interacting proteins have multiple binding sites or due to electrostatic steering effects, as found for the complex between barnase and barstar (106).

The intracellular environment is not a homogenous medium with a single diffusion coefficient for a given protein. Many factors may retard the diffusion of a protein in a cell, but primary one is the crowding that may provide steric barriers for a diffusing protein. The diffusion coefficient measured for various proteins is, on average, five times slower in solution with crowding conditions that mimic *Escherichia coli* cytoplasm compared to diffusion in water. However, the diffusion coefficients in the *E. coli* cytoplasm itself are 10 times lower than that of diffusion in water. This difference could have various origins (103). Diffusion in the cytoplasm can be slower than in an in vitro crowding solution, for example, due to binding affinities between proteins or weak interactions between different biomolecules and immobile barriers that preclude long-distance movements. The values of diffusion coefficients for various proteins in *E. coli* range between 1 and 10 $\mu m^2/s$, depending on the protein size (103). Variations are also reported when measuring the diffusion of the same protein in the cytoplasm of different bacteria, illustrating the effect of intracellular environment.

Similar to the reduced diffusion of proteins in the cytoplasmatic solution due to nonspecific interactions that can be extensive in crowded cells, slower diffusion has been reported for protein condensates formed via liquid–liquid phase separation. For example, detailed solid-state NMR studies indicated that the ELP3 protein has a diffusion coefficient in the dense phase that is 10–100 times lower than in the bulk, depending on the salt concentration and temperature (96). In addition, the HP1 protein diffuses 10 times more slowly in the phase-separated compartments than in the nucleoplasm (117) (note that the diffusion coefficient may depend on the model used to interpret the experimental data; 123). The high density in the condensate may confine the diffusing particle in some region, which may result in anomalous diffusion due to heterogeneous dynamics (108). Consistent with the experimentally measured D, diffusion coefficients within liquid protein droplets, studied using coarse-grained molecular dynamics (CG-MD) simulations, showed that D is 4–20 times lower than in bulk, depending on the organization of charges in the protein sequences and on temperature. The slower diffusion of polyampholytes in liquid droplets is due to electrostatic, $\pi-\pi$, and cation–π interactions, which are the main driving forces behind the formation of protein condensates. Disordered proteins that also include hydrophobic residues

are found to diffuse more slowly, with their diffusion coefficient being 15–50 times lower than in bulk (39). Polyampholytes (i.e., polymers made up of positively and negatively charged monomers) exhibit greater liquid properties in the droplet phase, and the introduction of hydrophobic residues (that form short-range interactions) results in a significant decrease in the diffusion coefficient. The decrease in D as the degree of hydrophobicity increases suggests that long-range electrostatic interactions play a role in the liquid behavior of the condensate due to the high exchange rate of the intra- and intermolecular interactions that are formed between the charges (40).

3. PROTEIN DIFFUSION IN TWO DIMENSIONS ON MICROTUBULES AND MEMBRANES

Diffusion of proteins also occurs in 2D spaces. The most common case is diffusion of proteins along the surface of a 2D lattice, such as membranes or microtubules (MTs). Another example of 2D diffusion is that of disordered proteins on the surface of a folded protein partner, such as the diffusion of E-cadherin on the surface area of the β-catenin (138). In this section, we focus on diffusion of proteins along MTs and membranes. We note also that integral membrane proteins (102) and lipids (105) often perform 2D diffusion within membranes, but this is not discussed in this review.

3.1. Protein Diffusion on Microtubules

MTs, which are essential components of the eukaryotic cytoskeleton, provide mechanical support to cells, play an important role in cell division, and serve as highways for intracellular trafficking. MTs are composed of repeating units of the α and β tubulin monomers, which associate longitudinally and laterally to form a closed tube (70, 88, 89). The α/β tubulin monomers are composed of a globular body and intrinsically disordered region (IDRs) at the C terminus, known as the tubulin tails. Thus, although they are often viewed as hollow cylinders, MTs are coated with a layer of tails that extrude out of the MT surface and increase the dimensions and influence additional global structural properties of the MT lattice (98).

There are nine isoforms of α/β tubulin in humans, and they share only approximately 50% sequence identity in the C-terminal tails. In addition, the chemical properties of the tubulin tails can be modified via many post-translational modifications, some of which are unique to MTs. These include tyrosination and detyrosination, polyglutamylation, and polyglycylation. The genetic and chemical diversity of tubulin give rise to the so-called tubulin code (50, 98, 137). The functional implications of the tubulin code are being gradually resolved, with recent discoveries related to how information encoded in the sequence and modifications of the tubulin tails regulates trafficking on MTs (15, 32, 73). Several links between misregulation of tubulin modifications and disease were also found (74).

The most well-known translocation mechanism of proteins on MTs is the directed, ATP-driven motility of motor proteins from the kinesin and dynein superfamilies. Nonetheless, there is accumulating evidence that many proteins use diffusional motility to move along and across MTs (often also called longitudinal and lateral diffusion, respectively) to perform diverse biological functions. For example, the depolymerizing kinesin MCAK uses diffusion to target both MT ends more rapidly than direct binding from solution (41). The diffusional motility of MCAK also enables it to cover short distances (<1 μm) faster than would be possible by directed ATPase-driven motion. Interestingly, enzymatic digestion of tubulin tails leads to a significant decrease in the lifetime of MCAK on MTs such that diffusion could not be measured using single-molecule methods (41).

An intriguing case of an intrinsically disordered protein (IDP) that diffuses along MTs is the protein tau. The normal function of tau is to bind and stabilize MTs, but in several

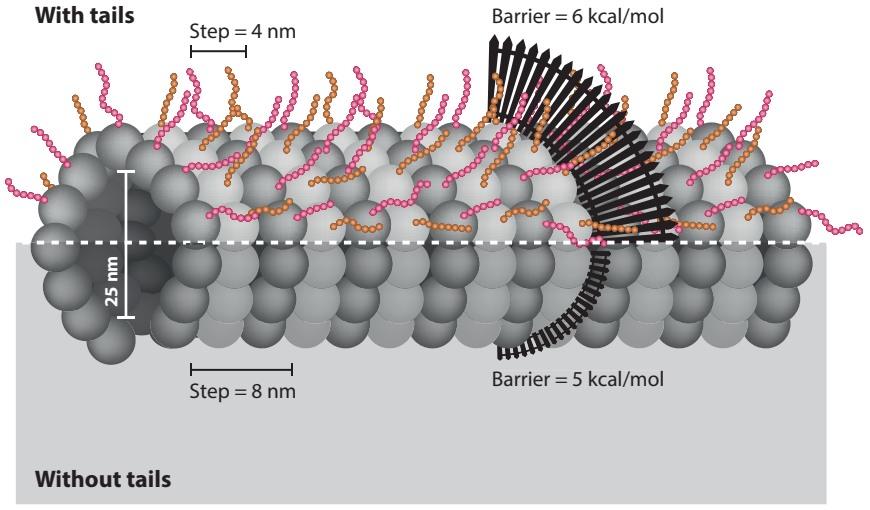

Figure 2

Diffusion of microtubule-binding proteins along microtubules is mediated by the negatively charged C-terminal tails of tubulins. While the tails increase affinity to microtubules by electrostatic attraction, they slow down diffusion by increasing the energetic barrier for diffusion and affecting the diffusion size step (12).

neurodegenerative diseases, the affinity of tau to MTs is decreased, and tau assembles into various forms of pathological filaments (110). Although tau was originally thought to be stationarily bound to MTs, it diffuses bidirectionally along MT protofilaments. The diffusion of tau also depends on the tubulin tails, and diffusion increases with salt concentration (42).

The examples described in this section, together with an increasing list of MT-binding proteins (MBPs) that diffuse on MTs (10, 21), demonstrate the centrality of this type of transport. As described above, several lines of experimental evidence suggest that tubulin tails play an important role in regulating protein diffusion on MTs. However, current single-molecule microscopy experiments provide limited spatial resolution. Thus, from an experimental perspective, it may appear that the diffusion of proteins on MTs is in one dimension, whereas, in fact, a protein can diffuse in two directions, both along and across MT protofilaments. In addition, the contribution of tubulin tails and their modifications to MT-mediated diffusion at the resolution of a single amino acid is not accessible experimentally. Using atomistic molecular dynamics simulations, it was shown that the tails can interact with some specific site on the MT, and that their conformations are sensitive to post-translational modifications (13). Furthermore, using CG-MD, it was shown that, for three different MBPs (EB1, PRC1, and tau), diffusion increases with salt concentration, indicating that the diffusion on MTs is driven by electrostatic interactions (12). The removal of the tubulin tails leads to an increase in the diffusion rate (**Figure 2**), which is in line with the experimental observations reported for tau (42) and MCAK (41). MBP diffusion along and across protofilaments was shown to be dependent on the properties of the disordered tail (12) (e.g., diffusion along MTs that lack tails is predominantly along protofilaments). One may therefore conjecture that the nature of the 2D diffusion along MTs will depend on the tubulin isoforms.

3.2. Protein Diffusion on Membranes

Proteins also diffuse in two dimensions on cell membranes, which often leads to the formation of complexes—a regulatory step in many signaling pathways. For example, the diffusion of two

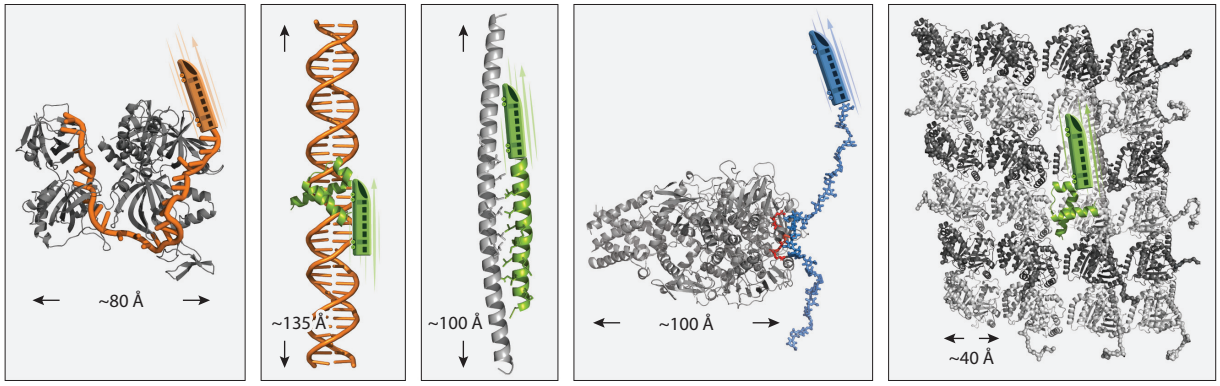

Figure 3

Schematic illustration of one-dimensional (1D) diffusion in several biomolecular systems. From left to right: diffusion of proteins along single-stranded DNA (ssDNA), diffusion of proteins along double-stranded DNA (dsDNA), diffusion at the interface of coiled coils, diffusion of a spike protein along a long polysaccharide, and diffusion of proteins along a microtubule. In this scheme, a diffusing protein is colored green, a substrate protein is colored gray, DNA is colored orange, and polysaccharide is colored blue. A train engine illustrates the direction of the 1D diffusion in each case.

pleckstrin homology domain monomers was measured on a system of supported lipid bilayers. It was found that the diffusion of a complex formed by the two monomers is twofold slower than diffusion of the monomer (from approximately 2.5 to 1.5 $\mu m^2/s$) (145). Similar observations were found for proteins from the synaptotagmin family (125). In addition to decreased diffusion caused by complex formation, protein interactions with lipid membranes can also lead to slower diffusion.

4. ONE-DIMENSIONAL DIFFUSION OF BIOMOLECULAR SYSTEMS

Several cellular functions are governed by linear diffusion in 1D space (**Figure 3**). In these cases, a biomolecule diffuses linearly on the surface of another biomolecule. The substrate often has an elongated, periodic surface that can support continuous diffusion. Diffusion in a periodic potential can be written in terms of Kramers' escape rate theory, which, at the high friction limit, can be written as $D^{\text{Kramers}} = \frac{a^2 \omega_0 \omega_b}{2\pi\gamma} \cdot e^{-\frac{E^{\neq}}{k_B T}}$, where a is the step size between the periodic wells, ω_0 is the curvature of the energy minima, ω_b is the curvature at the top of the energy barrier, γ is the frictional coefficient, $E^{\neq}$ is the energy barrier, k_B is the Boltzmann constant, and T is the temperature. The energy landscape for diffusion might be rugged due to some local energetic traps that originate from transient interactions between the diffusing biomolecule and the substrate. Zwanzig (147) has shown that diffusion in a rugged potential can be described by $D^{\text{Zwanzig}} = D^{\text{Kramers}} e^{-(\frac{\varepsilon}{k_B T})^2}$, where ε is the amplitude of the roughness.

1D diffusion is thus an intrinsic property for molecules diffusing along periodic surfaces, with an underlying energy landscape that is not too rugged, yet its parameters, as discussed below, depend on the molecular characteristics of the diffusing particles and the substrate surface.

4.1. One-Dimensional Diffusion at Protein–Nucleic Acid Interfaces

Linear diffusion at protein–nucleic acid interfaces is found for a variety of proteins and for several types of nucleic acids. 1D diffusion of proteins along double-stranded DNA (dsDNA) has been reported for various systems, which are linked with different functions, yet the molecular mechanism of diffusion may depend on the properties of both the diffusing protein and the dsDNA and the

condition of the environment. Protein diffusion was observed also along double-stranded RNA (58). Linear diffusion of proteins was also reported along single-stranded DNA (ssDNA). The mechanistic characteristics of 1D diffusion of proteins along dsDNA and ssDNA are discussed below.

4.1.1. Diffusion of proteins along double-stranded DNA. Many proteins were reported to diffuse linearly along the elongated axis of dsDNA (14, 45, 46). Linear diffusion by proteins along dsDNA is an important case of diffusion in a lower-dimensional space, and it is crucial for proper cellular DNA processing. dsDNA-binding proteins (DBPs) perform various biological tasks, such as controlling transcription and repairing damaged DNA, all of which involve them scanning the DNA by linear diffusion prior to specific recognition at the functional site. Theoretical and experimental perspectives have attributed the remarkable efficiency and specificity of protein–DNA recognition to the 1D diffusion of proteins on DNA (5, 38, 59, 127). The facilitated diffusion model proposes that DBPs randomly bind to nontarget DNA sites and approach their respective target sites while interchanging between 1D diffusion and 3D diffusion. At physiological salt concentration, both diffusion modes are populated, thus supporting the facilitated diffusion mechanism, yet the optimal salt concentration that corresponds to the most efficient facilitated diffusion may be protein dependent (34). Furthermore, diffusion along DNA has been observed experimentally for various DBPs, such as RNA polymerase (51), the *lac* repressor (3), and the p53 (29, 54, 118) and Egr-1 (141) transcription factors, and for mismatch repair complexes, and its mechanisms have been further quantified by theoretical and computational studies (1, 6, 16, 24, 34, 63, 64, 68, 75, 77, 86, 111, 113, 121, 124, 126, 129, 130, 143).

Linear diffusion may involve the stochastic translocation of the DBP predominantly along the longitudinal dimension of the DNA cylinder while its distance from the DNA axis varies depending on various factors, such as the salt concentration. This diffusion mechanism is often referred to as hopping dynamics. Alternatively, the high nonspecific affinity of the DBP for the major DNA groove sites may allow the DBP to diffuse linearly along DNA while its position is restricted to the major groove. In this scenario, linear diffusion is characterized by coupling between rotation and translation. Such rotational–translational coupling is one of the main features of the 1D diffusion of proteins along DNA and is often referred to as sliding dynamics. When the diffusion includes rotation, the friction for diffusion follows $\xi = 8\pi\eta R^3$ (while for uncoupled rotational–translational diffusion, the friction depends linearly on R). The change in the dependence of D on the protein radius is often used to discriminate between hopping and sliding (2, 107). The diffusion coefficients of various DBPs, which span three orders of magnitude (0.001–1 $\mu m^2/s$) (**Figure 1**), correlate better with $1/R^3$ than with $1/R$ (14), supporting the sliding mechanism. For some other proteins, the diffusion coefficients better correlate with $1/R$ (23). The implication of diffusion coefficient dependence on $1/R^3$ is that sliding is a slower diffusion mode compared with hopping for that protein. Additionally, a weaker dependence of D on salt concentration is often interpreted as an indication that the protein uses the sliding rather than the hopping mechanism (34, 94).

Many proteins are known to be able to diffuse helically along the major groove, which may enable them to probe the DNA sequence and subsequently to bind specifically to their target sites. The ability of globular DBPs to slide along DNA while situated at the major groove is related to both electrostatic and structural complementarities. In addition, a DBP that binds the DNA minor groove can also slide when it is placed at the major grove. Sliding appears to be a mechanism common to diverse DBPs that possess different structural features [e.g., DBPs with different numbers of domains (133, 141), different oligomeric states (52, 56, 57), or IDRs (44, 131, 132)] and perform various functions. However, the detailed biophysical features of sliding

dynamics can be different for different globular DBPs. The diffusion of DBPs along DNA may vary, for example, with respect to the durations of uninterrupted sliding events (before they are interrupted by hopping or dissociation events), the lengths of DNA that are scanned in each sliding event, and the 1D diffusion coefficients (76).

Recently, it was shown that two DNA-repair proteins with similar structures both slide at low salt concentrations, but one of them mostly follows the hopping mechanism at higher salt concentrations (91), which might be linked to its function. The accumulated results to date thus suggest that protein structure, topology, and electrostatic potential, together with the electrostatic potential of the DNA conformations (7), may modulate the balance between the usage of sliding and hopping mechanisms for the linear diffusion of proteins along DNA. A few other DBPs that tend not to follow the sliding diffusion along dsDNA are discussed below in this section.

If one describes 1D diffusion on DNA as diffusion in a rough potential, then sequence-dependent variations in roughness can play a role (75, 78, 113). For many proteins, the energetic ruggedness for sliding along dsDNA is small (approximately 1 k_BT) (14, 79); however, for several proteins, a greater ruggedness of approximately 2 k_BT was reported (53). A pause in 1D diffusion can be achieved upon a conformational transition from the search binding mode, which mostly uses electrostatic interactions between the diffusing protein and the DNA, to a recognition mode that is stabilized by a set of short-range specific interactions.

4.1.2. Diffusion of proteins along single-stranded DNA. Similarly to proteins that interact with dsDNA, proteins that interact with single-stranded DNA (ssDNA) have the ability to diffuse linearly (**Figure 3**). ssDNA-binding proteins (SSBs) are the first responders to the transiently formed ssDNA, which is an intermediate during DNA replication, recombination, and repair processes (109). SSBs bind to ssDNA with high affinity to form very stable SSB–ssDNA complexes whose primary purpose is to secure the information stored in ssDNA. Subsequently, SSBs recycle (i.e., they dissociate from and reassociate with ssDNA) and reposition themselves within the complexes that they form with ssDNA to facilitate metabolic processes. Experimental studies have shed some light on the dynamic activity of different types of SSBs (37, 62, 87, 100, 115) and link the dynamics of SSB–ssDNA complexes to biological function.

The experimentally measured 1D diffusion coefficient of SSBs along ssDNA (87, 100) is approximately 3–4 orders of magnitude lower than that of proteins diffusing along dsDNA (5, 14, 38, 82, 121). The large differences between their 1D diffusion coefficients may arise from the different functionalities of these two classes of proteins. DBPs must locate and bind a specific site, which requires a rapid search and fast diffusion. By contrast, protecting the ssDNA does not require that SSBs bind a specific site, but they should not hinder the functions of other proteins that need to bind the ssDNA—consequently, SSBs are required to stably bind the ssDNA without remaining static at any single site. The binding affinities of SSB proteins are much higher than those of the DBPs in their nonspecific DNA-binding modes. The greater flexibility of ssDNA, the extensive interface that it forms with SSBs, and especially the high affinity of the complex have led to the biophysics of diffusion of proteins along ssDNA being less well understood than that of proteins along dsDNA.

Several mechanisms have been proposed to explain the migration of *E. coli* SSBs along ssDNA (71, 99), among them rolling, sliding, and reptation mechanisms (62, 66). In the rolling mechanism, a segment at one end of the ssDNA is partially released by an SSB tetramer unit that immediately wraps around another portion of the ssDNA strand in its place (100). However, a single-molecule study of the diffusion of SSBs along a stretch of ssDNA ruled out the possibility of rolling being the dominant progression mechanism (37, 120, 144). In the sliding mechanism, breaking of all the interfacial contacts may result in a net motion of the entire ssDNA as it moves together along the

SSB interface. The reptation mechanism is similar to the sliding mechanism with the difference that it does not require a concerted migration of the entire ssDNA but only of smaller stretches, which are stored in bulges. These bulges might be viewed as defects at the interface that, because of thermal fluctuations, accumulate excess ssDNA following breakage of the interfacial contacts at these sites. Following the reptation mechanism (also called sliding-with-bulge), the linear diffusion of the ssDNA is achieved by local formation of transient bulges that assist in fragmenting the large interface and enable sliding in a stepwise manner as the ssDNA progressively moves through the SSB interface. Force-dependent ssDNA diffusion along SSBs provides experimental support for the reptation model (144).

Recently, fast diffusion along a short stretch of ssDNA was observed for heterotrimeric replication protein A (RPA) (20, 87, 146). RPA and *E. coli* SSBs are very different structurally, as the former is a heterotrimer and the latter is a homotetramer, yet they both contain several oligonucleotide- or oligosaccharide-binding domains. The number of nucleotides involved in the RPA–ssDNA interface is known for *Ustilago maydis* RPA, whose crystal structure contains 25 nucleotides (28). The extensive RPA–ssDNA interface defines a high-affinity complex with a K_D in the sub-nM range (87). The estimated 1D diffusion coefficient of RPA on ssDNA is approximately 5,000 nt^2/s, which is approximately 10 times larger than for ssDNA diffusion on *E. coli* SSBs. The high mobility of ssDNA notwithstanding, maintenance of its interface with RPA might be linked to its ability to exchange, while bound to RPA, with a free RPA (33, 65, 146).

The diffusion of the RPA protein along ssDNA was studied using CG-MD, which captured the structures of various ssDNA–SSB complexes (84, 85). The diffusion of RPA along ssDNA is accompanied by the formation of bulges, thus following the reptation mechanism. The bulges are stochastically formed and transient. There are some sites on the protein surface at which the probability of bulge formation is greater than at others, depending on the interface topology and the interfacial residues. Moreover, the lifetime of each bulge and the length of the ssDNA stored at each site vary. For RPA, the bulges store 1–7 nt of ssDNA, consistent with experimental (144) and computational (72) observations for *E. coli* SSBs. Formation of bulges causes the diffusion to be more fragmented, which may serve as an efficient means to diffuse along the extensive and stable interface of RPA–ssDNA. Consequently, the cooperativity of the diffusion of the ssDNA (which can be manifested by a continuous motion of the RPA along ssDNA that fully occupies the RPA-ssDNA interface) throughout the interface that it forms with RPA is affected by the intermittent dynamics introduced by the bulges. Furthermore, the potentially long bulge may mediate the experimentally observed self-exchange of the ssDNA between different RPA molecules (33, 95).

4.2. One-Dimensional Diffusion at Protein–Protein Interfaces

Linear diffusion was also shown experimentally and computationally at protein–protein interfaces (**Figure 3**). This diffusion may occur by microscopic dissociations of the two interacting proteins to allow relative motion along their interface. Two systems that exhibit 1D diffusion at protein–protein interfaces are protein diffusion along MTs and the diffusion of helical peptides in dimeric coiled-coil (CC) complexes (21, 30, 41). Diffusion on MTs is discussed above in terms of 2D diffusion; it can also be categorized as 1D diffusion if one considers the diffusion either along or across MT protofilaments.

1D translational diffusion was observed along the interfaces of dimeric CC protein complexes (35). The CC is a protein motif that comprises two or more α-helices that wrap around each other and can be found in approximately 5% of all proteins (135). CCs widely mediate protein–protein interactions and form rigid structures that are often involved in generating or sensing forces in cells (19, 26, 119). The periodic α-helical structure of CCs and the relative simplicity of their interface

can lead to alternative conformations. One example of conformational plasticity exhibited by CCs is the helix shift, which occurs when the registry of one helix shifts through translation relative to the other, with the length of the translation often being one heptad repeat (22, 61, 140). Despite the high stability and tight hydrophobic cores of CCs, sliding motions and staggered conformations have been reported for some CC systems (22, 114, 116, 140). The resultant staggered helical structures were first proposed when the high-resolution crystal structure of the CC GCN4 leucine zipper domain was obtained (90), yet these alternative conformations have only been observed in a few CCs with special sequence patterns that deviate from the canonical heptad repeat. Such helix sliding has important biological functions, especially for relaying conformational changes to distal domains or across membranes. One prominent example is the antiparallel, two-stranded CC contained in the stalk domain of dynein, which connects its ATPase domain and its MT-binding domain (61, 104).

Sliding at CC interfaces, while demonstrated for several systems, is less well characterized than the sliding of proteins along DNA. Sliding at the interface of homodimeric CCs was explored using coarse-grained and atomistic molecular dynamics simulations, illustrating that sliding is an intrinsic property of these systems and may exhibit similar features in all of them (35). The energy landscapes for registry shifts suggest that sliding of parallel conformations takes place via a metastable state in which a half-heptad repeat is shifted, whereas sliding of an antiparallel CC configuration is achieved via a higher and wider energetic barrier. The energy landscape for sliding is affected by sequence variations, with the sliding of the parallel CC being more sensitive to mutations than that of the antiparallel CC.

In comparison to protein sliding along dsDNA, the energetic barriers to sliding along a CC interface are higher, being approximately 1–1.5 kcal/mol compared to 0.6–1.2 kcal/mol. Sliding along the CC interface is expected to be less widespread and of more limited length scale than sliding along dsDNA both for this reason and because it may involve reduced stability due to losing some interfacial interactions as a result of translocation between helices of the same length. Nevertheless, sliding can be a mechanism for a conformational change in CCs that is manifested in a concerted change in the CC registry and helix packing with a global change of approximately 10 Å in CCs, which corresponds to sliding of one heptad repeat.

5. ROLE OF ELECTROSTATICS IN PROMOTING BIOMOLECULAR DIFFUSION AT PROTEIN–DNA AND PROTEIN–PROTEIN INTERFACES

Diffusion processes in one to three dimensions, as described above, may follow molecular mechanisms with unique characteristics, yet they share common features, such as the role of long-range electrostatic forces in mediating diffusion. Electrostatic interactions play a role in diffusion of proteins along dsDNA and ssDNA, in diffusion of proteins along MTs, and in sliding along the CC interface. Similarly, electrostatic interactions were shown to contribute to the internal dynamics of protein condensates. The electrostatic interactions in all of these systems allow nonspecific binding between partners that are oppositely charged. When at least one of the partners comprises several alternative binding sites (as, for example, in long DNA or MT filaments), this may permit translocation from one binding site to a neighboring one. The long-range nature of electrostatic forces is essential to establishing communication between adjacent sites and thus diffusion. The detailed energetic and geometric properties of such neighboring sites will govern the energy barrier that separates the translocation.

The fundamental role of electrostatics in diffusion is illustrated in the rotational–translational coupled motion along DNA that is performed by a variety of proteins that possess different structural features and perform various functions and is modeled solely by electrostatics interactions.

Reducing the electrostatic strength by increasing the salt concentration may shift diffusion on DNA from sliding to hopping (34). Similarly, DBP mutations that reduce their charge density may result in diffusion via hopping. For example, for a homeodomain protein, it was found that the presence of five positively charged residues in the recognition helix is essential for sliding dynamics, whereas the presence of a smaller number of charged residues may result in hopping (8). The effect of mutations strongly depends on their location (8) (**Figure 4**), suggesting that charge density is not the only parameter that governs the ability of DBPs to slide by rotation-coupled diffusion.

To further elucidate the role of electrostatics in linear diffusion, the diffusion on DNA by proteins that normally interact electrostatically with MTs was explored. A comparison between linear diffusion on DNA and that on MTs would be quite useful given that both DNA and MTs are elongated and periodic cylindrical polymers that share similar electrostatic characteristics. MBPs and DBPs have similar linear diffusion coefficients on their natural substrates (12) (**Figure 1**). MBPs indeed interact with DNA electrostatically, but they do not adopt rotation-coupled translation diffusion, even at a low salt concentration (8, 10). The hopping diffusion of MBPs along DNA is most likely related to their lower positive charge densities compared with DBPs (10), which explains their faster diffusion on DNA. On MTs, the diffusion of MBPs is supported by the negatively charged C-terminal tails of the α and β tubulins.

Several DBPs have been characterized experimentally as diffusing on DNA in a nonhelical fashion (i.e., by hopping). These proteins include the TALE (23) and processivity factor UL42 (60) proteins. Possible reasons for their lack of sliding may include their weak electrostatic affinity, as well as structural and topological features that conflict with the rotation-coupled translation mechanism. Toroidal DBPs serve as interesting cases because, although their symmetric ring shape enables them to rotate around the DNA, it is unclear whether this rotation can be coupled with translation. Several studies show that PCNA diffuses by means of decoupled translation-rotation. The adoption of hopping dynamics is consistent with the weaker electrostatic interface that PCNA forms with nonspecific DNA, in comparison with the interfaces formed by other DBPs. The reported K_D for the PCNA–DNA interface is 0.7 mM, whereas the corresponding values for other proteins are a few micromolars (142). Similarly, mutation of charged residues was found to have much less of an effect on diffusion speed along DNA for PCNA compared with transcription factors, which suggests that electrostatics play a smaller role in the 1D diffusion of the former, again consistent with PCNA using the hopping mechanism (**Figure 4**). A CG-MD study of PCNA showed that, during linear diffusion, the DNA tends to remain close to the central axis of the inner PCNA cavity (25, 36). The PCNA–DNA interface is frustrated by the electrostatic forces between the ring and the cylindrical DNA as a result of the impossibility of satisfying simultaneously all of the potential electrostatic interactions between the inner ring of the homotrimeric PCNA and the DNA. The lowest energy is thus achieved when the DNA is located at the center of the ring (supported by the weak electron density of DNA in the crystal structure; 36).

Electrostatics plays an important role in diffusion of ssDNA, as indicated by the dependence of the size of the interface between SSBs or RPA and ssDNA on salt concentration (87). The interface between proteins and ssDNA, however, can be more heterogeneous compared to that with dsDNA, as hydrophobic interactions can be formed between the DNA bases and aromatic groups on the protein surface (92). Computational mutation of all of the aromatic residues in RPA to positively charged residues results in an energetically smoother landscape for ssDNA diffusion. Long-lived bulges, which mark the onset of the reptation diffusion of ssDNA along wild-type RPA interface, are less common when ssDNA diffuses along such a purely electrostatic RPA interface, presumably because they dissociate more rapidly due to the high exchange rate of electrostatic

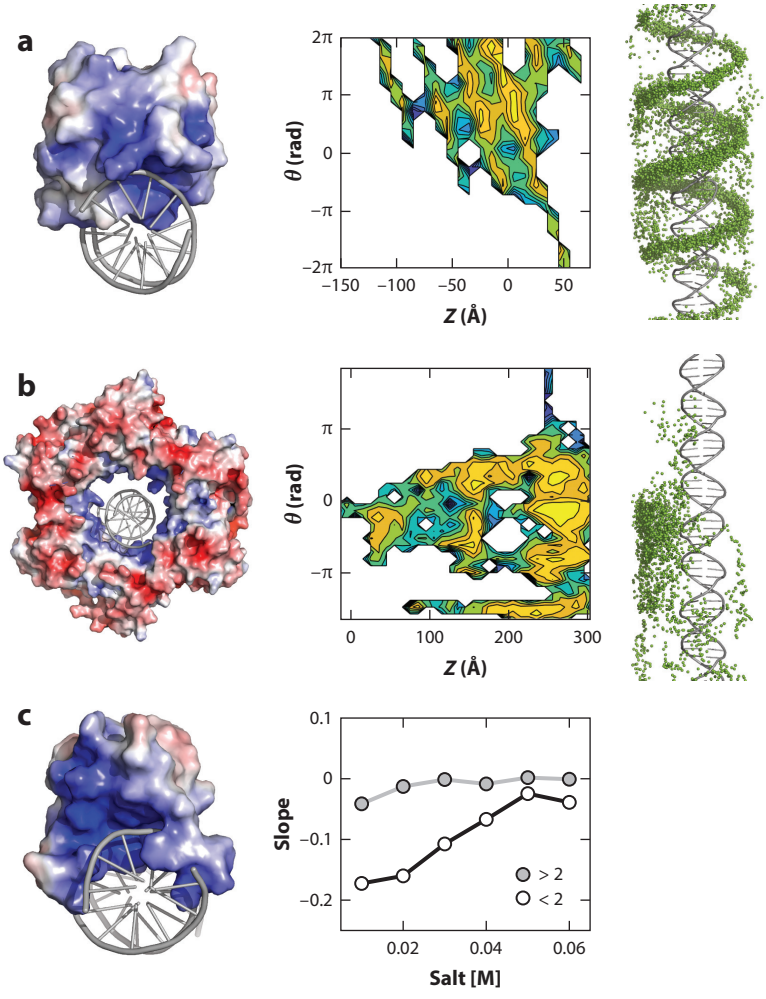

Figure 4

Linear diffusion along double-stranded DNA (dsDNA). (*a*) Diffusion of SAP1 [Protein Data Bank (PDB) ID 1bc8] along dsDNA follows rotation-coupled translation, illustrated in the linear relationship between the rotation angle (θ) and the location on the DNA axis (Z) in coarse-grained molecular dynamics (CG-MD) simulations. A slope of −0.18 between θ and Z is characteristic for sliding along the DNA major groove (8). (*b*) PCNA linearly diffuses along DNA via a translation-decoupled rotation mechanism (i.e., hopping). (*c*) One-dimensional (1D) diffusion of a homeodomain (PDB ID 1hdd) along dsDNA depends on salt concentration and mutations of charged residues. The mean slope between θ and Z is shown at several salt concentrations for two types of variants with either less than or more than two mutations. At low salt concentrations, 1D diffusion follows a sliding mechanism, but as salt increases, it follows a hopping mechanism. When the homeodomains include more than two mutations in the binding site, they diffuse via hopping at all salt concentrations.

interactions between neighboring sites along this periodic interface (83). The long-range nature of electrostatic interactions is essential for this dynamics.

The effect of the interplay between long- and short-range interactions on diffusion has been illustrated also for internal dynamics in biomolecular condensates. Condensates formed by polyampholytes show high internal dynamics that can be affected by the charge pattern of the

sequences. Replacing some charged residues with hydrophobic residues has a more pronounced biophysical effect on the condensate stability and internal mobility than altering the charge pattern along the sequence (39), leading to a decrease in the translational diffusion of each IDP in the dense phase. Changes in the liquid properties of the condensate with increased short-range interactions are linked to a slower breaking of intermolecular contacts with neighboring chains in the droplet, which is coupled with slower configurational chain dynamics.

Finally, linear diffusion along CC interfaces illustrates the role of charge-charge interactions and the consequence of hydrophobic interactions. Charges that form salt bridges with the neighboring helical peptide may stabilize the CC and will disfavor sliding dynamics. Repulsive electrostatic interactions between residues in these positions constitute electrostatic frustration within the CC structure that may facilitate sliding dynamics. In addition to the role of electrostatic frustration, decreasing the stability of the interface by reducing the strength of the hydrophobic core of the CC results in faster diffusion (35).

6. ROLE OF DISORDERED TAILS IN MEDIATING DIFFUSION

6.1. Intrinsically Disordered Regions Assist Diffusion at the Protein–DNA Interface

IDRs are widespread in proteins and are linked to various biological functions. IDRs, particularly those at termini, are involved in several diffusion processes. These IDRs, which are often characterized by a high fraction of charged residues, can be of net positive or negative charge.

IDRs are more common in DBPs than in non-DBPs (130, 133). Such disordered tails of DBPs are longer than those of other proteins (approximately 60% of the tails of DBPs are longer than five residues, while only 30% of non-DBPs have tails longer than five residues). Positively charged IDRs are expected to be functionally important for nucleic acid–binding proteins because they can directly influence protein interactions with nucleic acids via attractive electrostatics.

CG-MD simulations of three homeodomain proteins with different tail lengths and net charges, in which the interactions between proteins and DNA are governed solely by electrostatic forces, demonstrated the role of the disordered tail in facilitating DNA search (129), in agreement with kinetic NMR studies (45, 47). The presence of an N-tail increases the affinity of the protein to the DNA and enhances its sliding propensity at the expense of hopping and 3D diffusion. However, better sliding has its price: The linear diffusion coefficient of the protein moving along the DNA is lower, which results in a slower search (129). Enhanced sliding via the disordered tail has been measured for a DNA glycosylase (97). The tetrameric transcription factor p53 provides another example of the importance of disordered tails in the interactions between proteins and DNA (69, 128). The C-tails of p53 are positively charged and thus strongly interact with DNA and can affect sliding features significantly. Recent single-molecule experiments (29) and a CG-MD study (56) showed that the C-tails of p53 increase its diffusion coefficient for sliding along DNA. Moreover, the disordered C-tails mediate the interactions between the DNA-binding domain and distant DNA regions: Tails from two subunits interact with one DNA region while the other two tails interact with a different DNA.

Most importantly, the N-tail in homeodomains can assist in intersegment transfer, which is known to enhance DNA search when the protein interacts nonspecifically with DNA (27). Direct relocation from one nonspecific DNA sequence to another occurs without accumulation of free protein during the intersegment transfer of transcription factors (47, 129, 130, 133). Tail length can significantly affect the propensity to engage in intersegmental transfer, such that more transfer events are seen for a homeodomain, whose tail is longer and more positively charged. Different homeodomain proteins (129) search DNA quite differently, although they

have very similar globular regions. The presence of an N-tail in these homeodomains modulates the characteristics of the DNA search. A comparison of the tail sequences of the homeodomains reveals that, while the lengths and net charges are different for each, the positive residues are clustered into positive segments in all of them (130, 132).

Intersegmental transfer for proteins that comprise several domains, some of which are IDRs or linked by IDRs, follows the monkey-bar mechanism (129, 132, 142), so named because it resembles the motion of children as they swing along monkey bars in a playground. Similarly to the way a child transfers one hand at a time when swinging from bar to bar, the proteins cross from one DNA molecule or segment to another by transferring first a single domain, followed, after a certain lag time, by the transition of the other domain (or subdomain, e.g., a disordered tail). The monkey-bar mechanism, which can be viewed as searching the DNA in two dimensions, is found for proteins composed of several domains (27, 122), particularly when their binding affinity to DNA is asymmetric, as the existence of a domain with a moderate DNA binding affinity has a greater capture radius for interaction with a distant DNA segment (133). This is exemplified by the ability of proteins with IDRs to jump from one DNA segment to another (46, 131, 132). Introducing mutations that result in more symmetric multidomain DBPs decreases the rate of monkey-bar dynamics. Recently, the monkey bar was observed experimentally in other systems (101). In some cases, the lack of molecular ingredients for fast search is compensated for by higher cellular abundance (93); thus, the protein can achieve fast scanning of the DNA even when the interface between the protein and DNA is extensive and tight.

Although positively charged IDRs are reported to impact DNA search by DBPs, as they affect sliding and monkey-bar dynamics, negatively charged IDRs were found also to be common in DBPs. Such tails are found to be highly negatively charged and are characterized by long D/E repeats (K/R repeats are much shorter in all proteomes). Interestingly, the fraction of proteins with long D/E repeats per organism increases with genome size (9). The highly negatively charged IDR may contribute to the diffusion of proteins along DNA. It was shown that, under some conditions, the negative tails autoinhibit the diffusing protein by screening some positive charges. Such screening may reduce the affinity to DNA and therefore decrease trapping on the DNA. Accordingly, the negative tail served as a molecular mechanism to smooth the energy landscape for sliding and thus led to facilitated diffusion (136). The surprising role of highly negatively charged tails in facilitating search kinetics is another illustration of the importance of IDRs in regulating function and particularly search mechanism. Extraction of the information stored in IDRs that are linked to various functions is far from being complete, especially when the IDRs are long. Indeed, a recent in vivo study showed that long IDRs (>500 aa) in transcription factors contribute to DNA specificity, as the IDRs alone can localize binding to the promotor regions (17, 18). In many transcription factors, IDRs span over hundreds of amino acids and encompass a major fraction of their sequence, and their molecular mechanism of action should be resolved in the future.

6.2. Intrinsically Disordered Regions Assist Diffusion at the Protein–Protein Interface

IDRs also play an essential role in the 2D diffusional motility of proteins on MTs and membranes, as well as in the diffusion of a disordered protein on its folded ligand (138). In addition, manipulating the charge content of the tubulin tails was shown to reshape the energy landscape for protein diffusion by impacting the step size, directionality (i.e., along and across the protofilament), and energy barrier for diffusion (12). Collectively, detailed computational investigations, together with single-molecule experiments, support the central role played by tubulin tails in regulating the diffusion of proteins on MTs.

Since, as discussed above, tubulin tails were found to regulate diffusion of several MBPs on MTs, it is likely that tail modifications will add another layer of regulation to MT-mediated transport. We focus our discussion in this section on polyglutamylation and polyglycylation—the tethering of polyglutamate or polyglycine chains, respectively, to the original tubulin tails via formation of a peptide bond between the N terminus of the constituent moiety and one of the glutamate Cg atoms on the tail. Using chemically modified yeast tubulin, it was shown that the addition of a 10-amino-acid-long polyglutamylate moiety leads to an approximately 50% increase in the processivity and velocity of kinesin 1 and 2, but a similar effect was not found for dynein (112). These findings provide strong support for the impact of the tubulin modifications on the function of MTs as molecular tracks for motor proteins, as was found for nonmotor proteins (12, 13).

To directly test the impact of tubulin modifications on the diffusional motility of proteins on MTs, atomistic and coarse-grained models of MT lattices bearing varying degrees of polyglutamylation or polyglycylation were developed. These models were initially used to quantify the impact of modifications on the biophysical properties on tubulin tails (13) in the context of an MT lattice [unlike previous studies, which focused on tubulin dimers (31, 67, 134) or isolated peptides]. It was found that polyglutamylation leads to an expansion of tubulin tails, while polyglycylation does not affect tail dimensions. The molecular driving force for the expansion of polyglutamylated tubulin was attributed to the electrostatic repulsion between the negatively charged polyglutamate and tubulin tails. By contrast, polyglycine moieties in polyglycylated tubulin were found to hydrophobically collapse on themselves or on the tubulin tails, leading to local screening of the negative charge on the tubulin tails (13).

It was shown that polyglutamylation, but not polyglycylation, leads to a decrease in the diffusion coefficient of proteins along MT protofilaments. Surprisingly, while polyglutamylation also decreases the diffusion coefficient of diffusion across MT protofilaments, polyglycine increases the diffusion coefficient for diffusion across protofilaments (**Figure 5**). In a broader context, since tubulin tails are key regulators of MT interactions, and since modulating the electrostatic properties of the tubulin tails by enzymatic cleavage or by increasing the salt concentration decreases

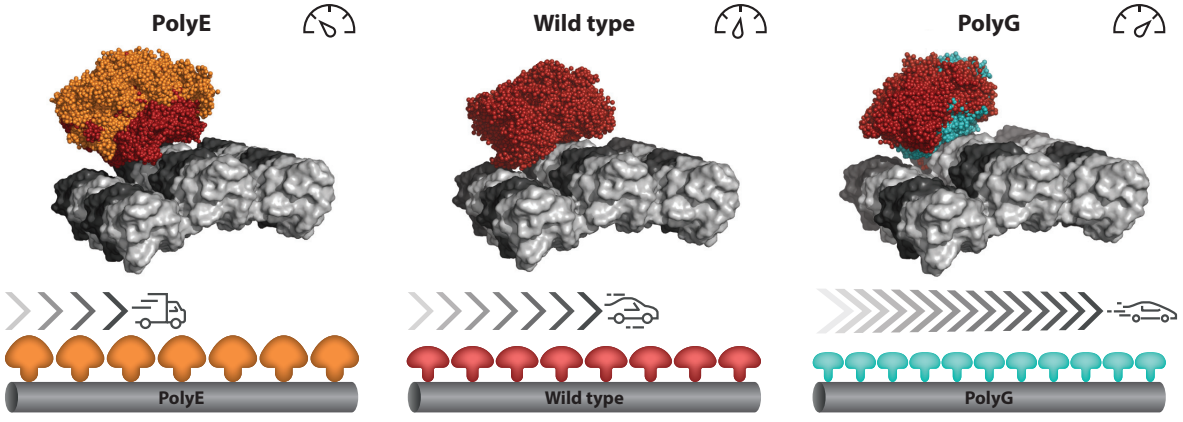

Figure 5

Diffusion along microtubules (MTs) is affected by the post-translational modifications of the C-tails. Polyglutamylation (PolyE) was found to decrease the diffusion rate, while polyglycylation (PolyG) does the opposite. The effect of the modifications on the conformational ensemble of a C-tail is illustrated from atomistic simulations. The modifications affect protein motility along the MT, as illustrated. The dynamics of proteins along the MT surface follows diffusion, which may occur both along and across the MT longitudinal axis.

the affinity of MTs for several MBPs (30, 41, 42, 112), it is likely that polyglycines, in contrast to polyglutamates, reduce MT interactions by locally screening the charged tails (13). Polyglycines and polyglutamates may therefore be viewed as autoinhibitors and enhancers of MT interactions, respectively.

While, for protein diffusion on MTs, there is evidence that tubulin tails, which are part of the 2D MT lattice, regulate diffusion mechanisms, IDRs that are part of the diffusing proteins can also regulate the diffusion of proteins on membranes. For the case of the lipid transfer protein oxysterol-binding protein (OSBP), it was found that a 90-amino-acid-long N terminus facilitates the diffusion of the protein at membrane interfaces (48). Unlike DBPs and MBPs, the N-terminal IDR of OSBP does not have many charged residues; instead, it is rich in Pro, Ala, and Gly. This sequence composition of the IDR may result in a greater hydrodynamic radius than that of folded domains and can facilitate diffusion on crowded membranes.

7. TRADE-OFFS IN PROTEIN DIFFUSION

Various conflicting forces act on proteins and lead to several well-acknowledged trade-offs (11). The speed of protein diffusion trades off with some microscopic properties, indicating that the diffusion should be balanced to optimize function. A major trade-off is between affinity and binding kinetics (93, 141). The formation of tight interactions that must be broken to permit sliding constitutes a barrier to it. High affinity to DNA might be coupled with low diffusion rate and slower monkey-bar dynamics. Proteins with higher asymmetry (e.g., with domains of different affinities or with IDRs) and the existence of two binding modes to DNA (e.g., one of high DNA affinity but a low diffusion coefficient for sliding and the other with low DNA affinity but a higher diffusion coefficient) can balance this trade-off between affinity and diffusion on DNA. In comparison to sliding along dsDNA, the energetic barriers to sliding along CCs are higher (due to the core of the CC being stabilized by hydrophobic interaction), at approximately 1–1.5 kcal/mol compared to 0.6–1.2 kcal/mol. Similarly, the barrier for diffusion can be increased for protein–ssDNA interfaces when hydrophobic interactions are formed between the DNA bases and solvent-exposed hydrophobic residues on the protein surfaces. The balance between the aromatic and electrostatic forces, which is often found in protein–ssDNA interfaces, may confer high affinity on ssDNA–RPA interactions at the interface while ensuring ssDNA mobility at its interface with RPA. Similarly, the negatively charged tails of tubulins increase the energetic ruggedness and therefore slow down diffusion of proteins along MTs.

Another trade-off is between the kinetics of finding and the kinetics of binding the target site (68, 75). Namely, the 1D diffusion is in conflict with the kinetics of the transition from the search mode to the recognition mode (68, 75, 78). Accordingly, DBPs with high diffusion coefficients may have slow rates for binding the target site, and vice versa. This trade-off can be modulated by frustration of interactions between the nonspecific and specific protein–DNA (whose manifestation can be reflected in a conformational difference between the nonspecific and specific binding to DNA) (75, 78). An optimal degree of frustration minimizes the total time for recognition (68). Given the tight and complex interplay between biomolecular diffusion and cellular function, diffusion processes may involve other trade-offs (e.g., between speed and specificity; 49) that still await quantification.

8. CONCLUSIONS

Diffusion is a common transportation mechanism in the cell, even when it takes place in lower-dimensional spaces, such as proteins diffusing along 1D biological polymers. Examples of 1D diffusion include the dynamics of proteins along dsDNA or diffusion of ssDNA along proteins.

Proteins also translationally diffuse on 2D surfaces such as membranes or MTs. 3D diffusion, which is the most widespread form of cellular transportation, involves the translational diffusion of molecules in the cytoplasm or in liquid biomolecular condensates. All of these diffusion processes are essential to proper cellular function. Diffusion in one, two, or three dimensions may depend on various molecular characteristics of the diffusing proteins, as well as those of the medium. 1D diffusion may follow hopping or sliding mechanisms, which differ in the length scale and timescale for translocation. Diffusion of some biopolymers may follow the reptation mechanism. The diffusion is governed also by the energy barrier that separates consecutive steps of the periodic potential for diffusion. Although each diffusion mechanism potentially has unique characteristics, they may share some common features, such as long-range electrostatic forces as major driving forces. Several examples illustrate that IDRs may mediate and modulate diffusion.

The various cases of diffusion in lower-dimensional spaces of biomolecular systems, which are linked to different biological function, reflect its importance in biology. It is not inevitable that it may be essential for other systems yet to be discovered. Indeed, recently, based on a cryo-electron microscopy structure of the spike protein of a Lassa virus with a long matriglycan polysaccharide, it was suggested that a Lassa virion may slide along a matriglycan polymer. One may note that the interactions between the spike protein and the matriglycan are dominated by electrostatic interactions between arginine residues and glucuronic acid (55). It is likely, therefore, that sliding dynamics is more widespread in molecular biology than originally considered and is relevant to other biomolecular systems.

DISCLOSURE STATEMENT

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Errata

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