Effects of isolated nonspecific binders upon the search for specific targets: Absolute rates versus competition between the targets

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Many biological processes involve macromolecules searching for their specific targets that are surrounded by other objects, and binding to these objects affects the target search. Acceleration of the target search by nonspecific binders was observed experimentally and analyzed theoretically, for example, for DNA-binding proteins. According to existing theories this acceleration requires continuous transfer between the nonspecific binders and the specific target. In contrast, our analysis predicts that (i) nonspecific binders could accelerate the search without continuous transfer to the specific target provided that the searching particle is capable of sliding along the binder; (ii) in some cases such binders could decelerate the target search, but provide an advantage in competition with the "binder-free" target; (iii) nonbinding objects decelerate the target search. We also show that although the target search in the presence of binders could be considered as diffusion in inhomogeneous media, in the general case it cannot be described by the effective diffusion coefficient.

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I. INTRODUCTION

Biologically active molecules are often searching for their specific targets that are surrounded by various types of objects with which the searching molecule could somehow interact. One of well-studied examples is sequence-specific DNA binding proteins that are searching for their specific target sequences usually embedded within much longer regions of other (nonspecific) DNA sequences. A fundamental question is whether transient binding to these nonspecific sequences could facilitate the search for the specific target sequence. ("Facilitation" in this case usually means acceleration of the target search, although in the present work we will also discuss facilitation in terms of competition between the targets.) It was realized long ago ([1–3]; for review and additional analysis see [4–11]) that such facilitation could occur in the presence of continuous transfer of the protein between the nonspecific and the specific binding sites. Here by continuous transfer we imply the transfer without disruption of binding with nonspecific sites. This transfer could occur either via sliding from the adjacent DNA regions, or via transient simultaneous binding to nonadjacent DNA segments. (The latter mechanism requires a protein to have several DNA-binding sites, and we do not consider it in this work.)

In terms of conception of sliding in general, it is important to mention that the sliding process implies short-range nonspecific interactions between the protein and the DNA. In many cases, these interactions are electrostatic, so technically they remain nonzero until the distance between the protein and the DNA becomes infinitely long. However, the electrostatic field of DNA is shielded by counterions, so there is a typical distance, an "effective radius" of DNA, beyond which electrostatic interactions could be neglected. Most studies assume that this radius is comparable (though, of course, larger) to the geometrical radius of DNA, and consequently DNA-protein interactions are short-ranged. This is consistent with the experimentally determined electrostatic effective radius of DNA [12]. That being said, it was also hypothesized that the electrostatic interactions between the protein and the DNA could persist over substantially longer distances, and that these long-range interactions rather than continuous transfer are responsible for the facilitated target search [13]. In our consideration, like in most other studies, we assume that the electrostatic and other interactions between the protein and DNA (or other objects) are short-range.

There are multiple experimental observations supporting the sliding mechanism for protein movement (reviewed in [14]), including data in living cells [15]. The search for the specific targets could include both sliding and free diffusion in solution between the binding events [1–11]. Existing theories (e.g., [4,7,16]) predict that the sliding to the specific target from the adjacent DNA region makes the effective size of the target equal to the typical sliding distance, which could be much longer that the actual specific target sequence, and this increase in the effective target size facilitates the target search.

A more difficult question is whether the facilitated target search is possible without continuous transfer between the specific and the nonspecific binding sites, i.e., when binding to the specific target site is always preceded by complete unbinding from the nonspecific site and free diffusion in solution. Intuitively, it seems that such binding-unbinding events (often called "hopping" and "jumping") within the same DNA molecule could facilitate the search for the specific target even in the absence of continuous transfer. However, as was argued in [5,17], if nothing happened to the protein during the nonspecific binding event (i.e., it neither moves relative to DNA, nor binds additional DNA segments), the only effect of the nonspecific binding could be a delay of the searching process.

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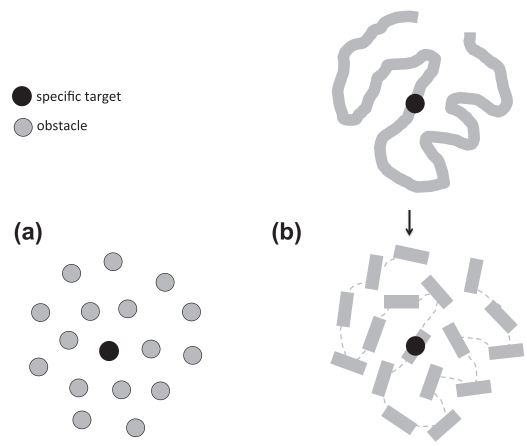

FIG. 1. Specific target surrounded by obstacles. (a) Obstacles are isolated from each other and from the specific target. (b) Both the obstacles and the specific target are actually the parts of the same molecule (e.g., DNA) (top), but can be represented as isolated from each other (bottom).

In general, according to the existing theories (e.g., [4,7,16]), in the absence of continuous transfer to the specific target nonspecific binders cannot facilitate the target search. For example, in the models involving sliding and three-dimensional diffusion, those DNA regions for which the distance (along the DNA contour) from the target is longer than the sliding distance are predicted to work as transient "traps" delaying the search.

However, the target search facilitated by a longer DNA was observed experimentally in the system in which a small DNA circle that contained the specific target was connected to much longer circle of nonspecific DNA via catenation, which excludes continuous transfer between the circles [18].

In the present work we analyze the situation in which the searching particle, although it cannot continuously transfer from the nonspecific binder to the specific target, can slide along the binder. Below, we will switch from the term "binders" to the more general term "obstacles" (in the sense that they are obstacles for the free diffusion in solution), which could be either capable or not capable of binding the searching particle. In these terms, DNA fragments are similar to "slippery obstacles" considered in [19], except that we consider continuous sliding around an obstacle rather than discrete jumps. In addition to DNA, "slippery obstacles" occur in other biological systems including lipids and proteins (reviewed in [19]). In general, some degree of mutual sliding is expected to be ubiquitous during interaction between various particles, because the only requirement for having some sliding before unbinding is that the energy barrier for shifting along the surface is somewhat lower than the energy barrier for complete detachment from the surface, which is likely to be the case for electrostatic and hydrophobic interactions.

In our analysis we consider obstacles as isolated objects [Fig. 1(a)] even if in fact in some cases they could be parts of the same long polymer (e.g., DNA) molecule [Fig. 1(b)]. Such representation of a continuous molecular chain [Fig. 1(b), top] as a "cloud" of isolated fragments [Fig. 1(b), bottom] is often used in theoretical modeling of polymers (reviewed in [20]), and is convenient for analyzing effects of DNA regions localized farther than the sliding distance from the specific target site.

According to our analysis presented in this work, sliding along isolated obstacles could facilitate the specific target search. In application to the target search on DNA, this means that in contrast to expectation based upon existing theories, facilitation of the specific target search could occur without continuous transfer from the nonspecific DNA regions to the specific target.

In addition to the target searching protein, DNA also could be bound to other proteins. Such proteins usually behave as "roadblocks" for sliding, though in some cases the searching proteins are capable of bypassing the roadblock without detachment from DNA [21]. Roadblocks could de-facilitate the target search [22,23], and the degree of de-facilitation depends upon whether the roadblocks are capable of sliding or dissociate from DNA [24]. Interestingly, in some cases roadblocks could also facilitate the target search [22]. In addition to being roadblocks for sliding, DNA-bound proteins would also play the role of obstacles for the three-dimensional component of the target search when the searching particle diffuses through the DNA coil.

In addition to the target search on DNA, our analysis is applicable to phenomena related to diffusion in inhomogeneous media (e.g., [25,26]). Our model provides universal description for obstacles either capable or incapable of binding the searching particle; the former could be either capable or incapable of sliding. For random macroscopically unbiased distribution of nonbinding obstacles (i.e., the average concentration of obstacles is constant on scales substantially larger than the distance between the obstacles), diffusion in inhomogeneous media could be described by the effective diffusion coefficient that can be calculated based upon the Maxwell Garnett approach ([26], reviewed in [27]). This description was extended to reversible binding to immobile obstacles by multiplying the effective diffusion coefficient obtained for the case when the binding was absent, by the probability for the diffusing particle to be in the mobile unbound state [25]. Monte Carlo simulations for randomly distributed immobile obstacles in the presence of binding also produce normal diffusion at sufficiently long timescales, although before a certain critical time diffusion was anomalous [28]. An important question is whether the notion of the effective diffusion coefficient could be extended to the macroscopically biased distribution of obstacles (i.e., when the concentration of obstacles is a function of coordinate). We show that in the presence of binding, such extension could not be done, which is important to take into account upon analysis of diffusion in inhomogeneous media.

II. MODEL ANALYSIS

A. Description of collisions between the searching particle and an obstacle: "Reflection" versus sliding transfer

Figure 1(a) schematically depicts a specific target surrounded by nonspecific targets (that also are referred to as "obstacles"). In our analysis we assume that the mobility of the obstacles is much smaller than the mobility of the

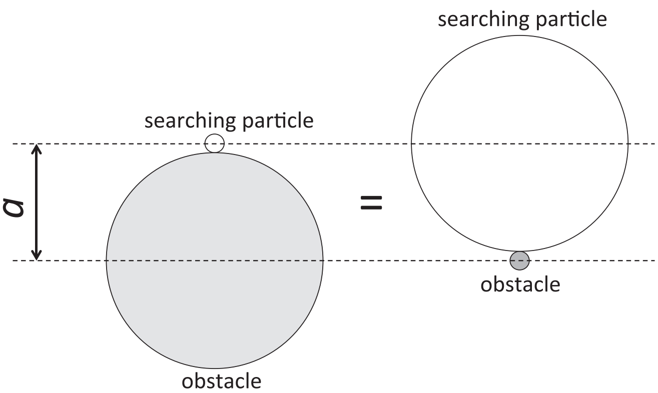

FIG. 2. Alternative representations for the searching particle and an obstacle at the moment of collision. Left: The searching particle is represented as a point object and an obstacle is represented as a sphere of the radius a. Right: An obstacle is represented as a point object and the searching particle is represented as a sphere of the radius a. Note that coordinates of the centers for both objects remain the same for both representations.

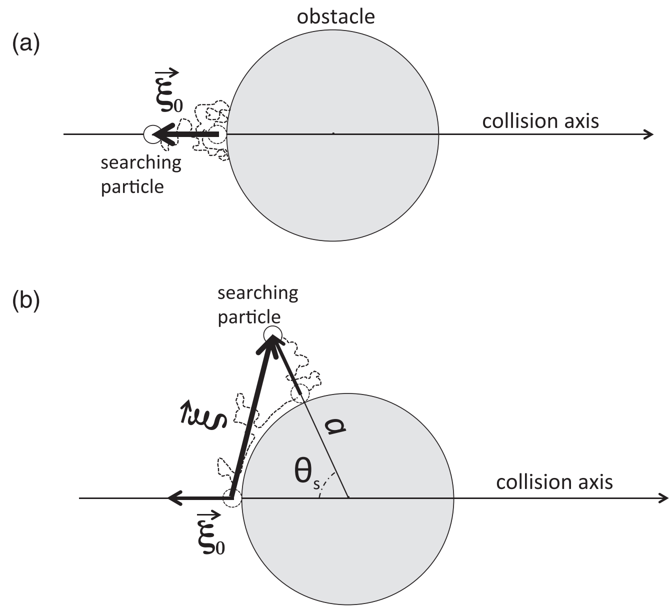

FIG. 3. Transferring of the searching particle as a result of collision. Trajectory of the particle is shown as a dashed line. For designations see the main text. Azimuthal angle is not shown. (a) Collision in the absence of sliding. (b) Collision in the presence of sliding. Sliding regions of the trajectory are shown as the dashed lines stretched parallel to the surface.

searching particle, so the position of an obstacle does not change during the time of collision. In this subsection we consider the simplest case of spherical searching particles and obstacles. The searching particle and an obstacle collide when the distance between their centers becomes equal to the sum of their radiuses designated as a (Fig. 2). For analysis, either a searching particle or an obstacle could be represented as either a point object or a sphere of the radius a (Fig. 2, left and right, respectively), and these representations could be switched in the course of the analysis.

First, we represent the searching particle as a point object, and the obstacle as a sphere of the radius a (Fig. 3). Consider a collision between the searching particle and an obstacle. After the collision, the randomly diffusing searching particle for some time would remain in close vicinity of the obstacle where the probability of repeating collision is very high. We refer to the searching particle localized in such close vicinity as being in a "correlated state." If the searching particle is capable of (reversibly) binding the obstacle, then the correlated state includes a "bound state" in which the searching particle is bound to the obstacle. In the bound state, the searching particle might be capable of sliding along the surface of the obstacle.

Eventually the searching particle would diffuse away far enough from the obstacle, so that the probability of repetitive collision with this obstacle would be low. We refer to such a state of the searching particle as "decorrelated" or "free."

Of course, in reality there is no defined transition between the correlated and decorrelated states. However, in our description we consider the correlated and the free states as discrete states, switching between which occurs at some distance ξ_0 from the surface. We introduce a collision transfer vector $\vec{\xi}$ that connects an initial point of collision and the "decorrelation" position (Fig. 3), and a decorrelation time τ_d that is required for this transfer. The notion of decorrelation time has similarity to the notion of the mean obstacle encounter time described in [25].

Projections of the vector $\vec{\xi}$ upon the axis connecting the centers of the searching particle and the obstacle (further referred as a "collision axis") and upon the perpendicular plane are designated as $\xi_\parallel$ and $\xi_\perp$, respectively. First, consider the situation in which there is no sliding of the searching particle along the surface of an obstacle [Fig. 3(a)]. In this case, postcollision trajectories of the searching particle are symmetrically distributed relative to the point of collision. In addition, on average the shortest (i.e., the fastest) trajectories that reach the decorrelation distance ξ_0 from the surface would be those that end at the normal to the surface emanated from the point of collision. Thus, the collision transfer vector in this case would be perpendicular to the surface of the obstacle at the point of collision, so the particle behaves as if it "reflects" from the obstacle to the distance ξ_0 (e.g., in this case $\xi_\parallel = \xi_0$, $\xi_\perp = 0$), and the time required for this "reflection" is designated as τ_0.

Parameter ξ_0 is proportional to the size of the particle

$$\xi_0 \sim a \tag{1}$$

and parameter

$$\tau_0 \sim a^2/D, \tag{2}$$

where D is the diffusion coefficient in solution. The proportionality coefficient in Eqs. (1) and (2) could be evaluated from the effective diffusion coefficient of the searching particle in the presence of obstacles (see Sec. II E).

Now consider the case when the particle can slide along the surface of an obstacle before it unbinds [Fig. 3(b)]. Behavior of the particle between the binding events would be the same as in the absence of sliding; thus if we "splice" the fragments of the particle trajectories when it is in the unbound state, we would obtain the same ensemble of trajectories as in the absence of sliding. Thus, the effect of sliding could be described as rotation of the vector $\overrightarrow{\xi_0}$ through some angle θ_s relative to the collision axis [Fig. 3(b)]. Consequently

$$\xi_\parallel = -(a + \xi_0)\cos\theta_s + a, \tag{3}$$

$$\xi_\perp = (a + \xi_0)\sin\theta_s. \tag{4}$$

In the system of references connected with the collision axis

$$\vec{\xi} = \xi_\parallel\,\vec{k} \;+\; \xi_\perp \cos\varphi_s\,\vec{i} + \xi_\perp \sin\varphi_s\,\vec{j}, \tag{5}$$

where φ_s is the azimuthal angle, $\vec{k}$ is the unit vector parallel to the collision axis, and $\vec{i}$ and $\vec{j}$ are orthogonal unit vectors perpendicular to the collision axis. (In our case, all azimuthal angles are equal, and the vectors $\vec{i}$ and $\vec{j}$ could be chosen arbitrarily except for the condition of being orthogonal to each other and to the collision axis.)

Equation (5) represents the collision transfer vector in the system of references related to the collision axis. Next, we will represent this vector in the system of references related to the center of the specific target. We will consider a spherically symmetric spatial distribution of obstacles relative to the specific target. In this case the behavior of the searching particle depends only upon one coordinate: the distance r between the centers of the searching particle and the specific target.

Consequently, we are interested in the projection of the collision transfer vector $\vec{\xi}$ upon the line that connects the centers of the searching particle and the specific target. If θ_r and φ_r are the polar and the azimuthal angles for this line relative to the collision line, then this projection

$$\xi_r = \xi_\parallel \cos\theta_r + \xi_\perp \sin\theta_r \cos(\varphi_r - \varphi_s). \tag{6}$$

We also would be using the square of this value

$$\xi_r^2 = [\xi_\parallel \cos\theta_r + \xi_\perp \sin\theta_r \cos(\varphi_r - \varphi_s)]^2. \tag{7}$$

First, we will average Eqs. (6) and (7) over the azimuthal angles φ. Since in this system all azimuthal angles are equal,

$$\langle \cos(\varphi_r - \varphi_s)\rangle = 0, \tag{8}$$

$$\left\langle \cos^2(\varphi_r - \varphi_s)\right\rangle = \tfrac{1}{2}. \tag{9}$$

Thus, by averaging Eqs. (6) and (7) over the azimuthal angles and substituting Eqs. (8) and (9), we obtain

$$\langle \xi_r\rangle_\varphi = \xi_\parallel \cos\theta_r, \tag{10}$$

$$\left\langle \xi_r^2\right\rangle_\varphi = \xi_\parallel^2\cos^2\theta_r + \tfrac{1}{2}\xi_\perp^2\sin^2\theta_r. \tag{11}$$

(Here and below averaging is designated as $\langle\rangle$ and the variable over which the averaging is performed in some cases is shown as a subscript after the brackets.)

Now we will perform averaging over the angles θ_r between the collision axis and the vector $\vec{r}$ that connects the center of the searching particle and the origin that is localized in the center of the specific target. For that, it is convenient to use a representation in which the searching particle is represented by a sphere with the radius a, and the obstacle is represented as a point object (Fig. 4). The probability $\rho(\theta_r)$ that collision occurs at the point that corresponds to the angle θ_r is proportional to the concentration of obstacles $c(\theta_r)$ at that point.

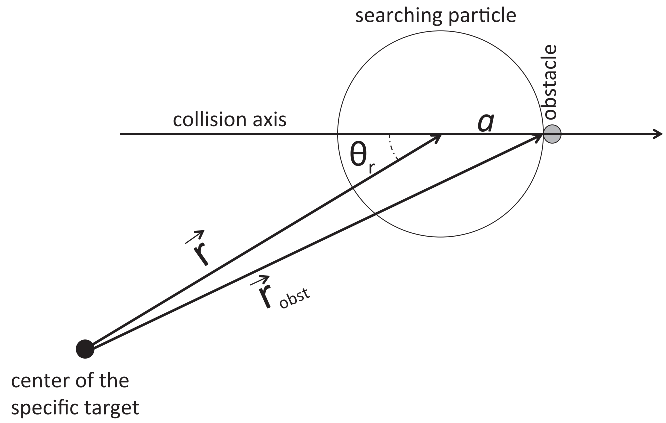

FIG. 4. Positions of colliding obstacle and the searching particles relative to the center of the specific target. For designations see the main text. Azimuthal angle is not shown.

Since we consider a spherically symmetric distribution of obstacles, the concentration depends only upon the distance r_{obst} between this point and the origin (Fig. 4). In further derivations we assume that the distance r between the searching particle and the origin is much larger than a.

From the cosine theorem this distance is

$$r_{\text{obst}} = \sqrt{r^2 + a^2 + 2ra\cos\theta_r} \approx r + a\cos\theta_r. \tag{12}$$

Thus

$$p(\theta_r) \sim c(r_{\text{obst}}) \approx c(r + a\cos\theta_r) \approx c(r) + \frac{dc}{dr}a\cos\theta_r. \tag{13}$$

[The expansion in the right parts of Eqs. (12) and (13) is justified provided that characteristic scale for the distance from the origin and for the change in concentration is substantially larger than the effective radius of interaction a.]

From normalization of Eq. (13) we obtain

$$p(\theta_r) = \frac{\left[c(r) + \frac{dc}{dr}a\cos\theta_r\right]\sin\theta_r}{\int_0^\pi \left[c(r) + \frac{dc}{dr}a\cos\theta_r\right]\sin\theta_r d\theta_r} = \frac{\left(1 + \frac{d\ln c(r)}{dr}a\cos\theta_r\right)\sin\theta_r}{2}. \tag{14}$$

From Eqs. (10), (11), and (14) we obtain the values averaged over the angle θ_r:

$$\langle \xi_r\rangle_{\varphi,\theta_r} = \int_0^\pi \langle \xi_r\rangle_\varphi p(\theta_r)\,d\theta_r = \frac{1}{3}a\,\xi_\parallel\,\frac{d\ln c(r)}{dr}, \tag{15}$$

$$\left\langle \xi_r^2\right\rangle_{\varphi,\theta_r} = \int_0^\pi \left\langle \xi_r^2\right\rangle_\varphi p(\theta_r)\,d\theta_r = \frac{1}{3}({\xi_\parallel}^2 + {\xi_\perp}^2). \tag{16}$$

Finally, we will average the values given by Eqs. (15) and (16) over the polar angle θ_s that describes the sliding of the searching particle over the surface of the obstacle. Since this is the final step of the averaging, we will omit subscripts in the notations, i.e.,

$$\langle\xi_r\rangle_{\varphi,\theta_r,\theta_s} \equiv \langle\xi_r\rangle = \frac{1}{3}a\langle\xi_\parallel\rangle\frac{d\ln c(r)}{dr}, \tag{17}$$

$$\langle\xi_r^2\rangle_{\varphi,\theta_r,\theta_s} \equiv \langle\xi_r^2\rangle = \frac{1}{3}\left(\langle\xi_\parallel^2\rangle + \langle\xi_\perp^2\rangle\right). \tag{18}$$

From Eqs. (3) and (4)

$$\langle\xi_\parallel\rangle = a - (a+\xi_0)\langle\cos\theta_s\rangle, \tag{19}$$

$$\langle\xi_\parallel^2\rangle = a^2 - 2a(a+\xi_0)\langle\cos\theta_s\rangle + (a+\xi_0)^2\langle\cos^2\theta_s\rangle, \tag{20}$$

$$\langle\xi_\perp^2\rangle = (a+\xi_0)^2\langle\sin^2\theta_s\rangle = (a+\xi_0)^2(1-\langle\cos^2\theta_s\rangle), \tag{21}$$

$$\langle\xi_\parallel^2\rangle + \langle\xi_\perp^2\rangle = a^2 - 2a(a+\xi_0)\langle\cos\theta_s\rangle + (a+\xi_0)^2. \tag{22}$$

Substituting Eqs. (19) and (22) into Eqs. (17) and (18) we obtain

$$\langle\xi_r\rangle = \frac{1}{3}a[a-(a+\xi_0)\langle\cos\theta_s\rangle]\frac{d\ln c(r)}{dr}, \tag{23}$$

$$\langle\xi_r^2\rangle = \frac{1}{3}[(a+\xi_0)^2 + a^2 - 2a(a+\xi_0)\langle\cos\theta_s\rangle]. \tag{24}$$

Equation (23) corresponds to the average position shift of the searching particle after collision with an obstacle. Since the diffusion coefficient of the free searching particle is constant, and there are no external forces, the sign of this shift defines the direction of the particle movement. From Eq. (23) it is seen that if the term $[a-(a+\xi_0)\langle\cos\theta_s\rangle]$ is positive, then the sign of this shift coincides with the sign of the concentration gradient, i.e., the particle moves toward the gradient of concentration of obstacles, while if it is negative, it moves against this gradient. This term is the projection of the collision transfer vector upon the collision axis [see Fig. 3(b) and Eq. (3)]. If it is positive, then the sliding transfer effect predominates over "reflection" and the particle moves from the point of collision in the direction of the obstacle (e.g., if at the moment of collision the obstacle was on the right of the particle, then after the collision the particle, on average, would shift to the right). Thus, on average the particle would move in the direction of the position at which the obstacle would occur with a higher probability, i.e., in the direction of increasing concentration. If the term $[a-(a+\xi_0)\langle\cos\theta_s\rangle]$ is negative, then the "reflection" predominates, and the particle moves against the gradient of the obstacles' concentration. The sign of this term is defined by the value of $\langle\cos\theta_s\rangle$. To evaluate $\langle\cos\theta_s\rangle$, consider rotation of the vector connecting the centers of the searching particle and of the obstacle during some small time interval Δt. During this interval, the change in the angle θ_s is $\Delta\theta_s$. The number of such intervals before the particle dissociation is

$$n_b = \frac{\tau_b}{\Delta t}, \tag{25}$$

where τ_b is the time that the particle spends in the bound state during the "lifetime" of the correlated state.

In the case of uniform distribution of azimuthal angles, the average cosine of the polar angle has the property of multiplicativity (reviewed in [20]):

$$\langle\cos\theta_s\rangle = (\langle\cos\Delta\theta_s\rangle)^{n_b} \approx \exp\left(-\frac{\langle(\Delta\theta_s)^2\rangle n_b}{2}\right). \tag{26}$$

The average quadratic change in the polar angle

$$\langle(\Delta\theta_s)^2\rangle = \frac{\langle(\Delta s)^2\rangle}{a^2} = 2\frac{D_s}{a^2}\Delta t, \tag{27}$$

where Δs is the shift of the particle along the surface of the obstacle during the time Δt, and D_s is the apparent diffusion coefficient for sliding.

Substituting Eqs. (25) and (27) into Eq. (26), we obtain

$$\langle\cos\theta_s\rangle = \exp\left(-\frac{D_s\tau_b}{a^2}\right). \tag{28}$$

To evaluate τ_b, we note that from Eq. (1), in the correlated state the searching particle is "confined" in the spatial domain of the size $\sim a$; thus, the apparent concentration of the searching particle in the vicinity of the obstacle is $\sim 1/a^3$. During the lifetime of the correlated state, τ_d, the searching particle spends the time τ_0 in the unbound state and the rest of the time in the bound state. If we assume that within the correlated state the bound and the unbound states are in "quasiequilibrium," then the ratio of times spent in bound and unbound states should be equivalent to the ratio of the concentration and the dissociation constant. Thus, taking into account Eq. (2),

$$\tau_b \sim \frac{\tau_0}{K_d\,a^3} \sim \frac{1}{K_dDa}, \tag{29}$$

where K_d is the equilibrium dissociation constant between the searching particle and the obstacle. This equation could be presented as

$$\tau_b = \frac{\kappa}{K_dDa}, \tag{30}$$

where numerical coefficient κ can be obtained from the effective diffusion coefficient (see Sec. II E).

From Eqs. (29), for the exponent in Eq. (28) we obtain

$$\frac{D_s\tau_b}{a^2} \sim \frac{D_s/D}{K_d\,a^3}. \tag{31}$$

This ratio defines whether "reflection" (at which the searching particle moves against the gradient of the obstacles' concentration) or the sliding transfer (at which the particle moves toward the gradient of the obstacles' concentration) predominates.

If the above ratio is very small, then there is no substantial sliding during the lifetime of the correlated state (i.e., practically pure "reflection" takes place). In this case $\langle\cos\theta_s\rangle \approx 1$, and Eq. (19) and Eq. (23) are converted into

$$\langle\xi_\parallel\rangle \approx -\xi_0 \tag{32}$$

and

$$\langle\xi_r\rangle \approx -\frac{1}{3}a\xi_0\frac{d\ln c(r)}{dr}. \tag{33}$$

In the opposite situation, when this ratio is very large, the particle would slide to the opposite end of the obstacle and back many times before release into the free state, so that the point of release would not depend upon the point of initial collision. We call this regime "saturating sliding." In this case, $\langle\cos\theta_s\rangle \approx 0$, and Eq. (19) and Eq. (23) are converted into

$$\langle\xi_\parallel\rangle \approx a \tag{34}$$

and

$$\langle\xi_r\rangle \approx \frac{1}{3}a^2\frac{d\ln c(r)}{dr}. \tag{35}$$

B. Probability of reaching the specific target: Obstacles localized near the target could either decrease or increase the effective target size

Let the functions $W_f(\vec{r})$ and $W_c(\vec{r})$ be the probabilities that the searching particle that was initially either in the free or in the correlated state, respectively, and localized at the distance r from the specific target, would reach the specific target before it migrates to some distance $R > r$.

Consider behavior of free searching particle during a small time interval Δt. During this time interval it can either convert to the correlated state with the probability $k_{\text{onc}}c(\vec{r})\Delta t$, or remain in the free state with the probability $1 - k_{\text{onc}}c\Delta t$. In the latter case, the searching particle would move from position $\vec{r}$ to some new position $\vec{r} + \overrightarrow{\Delta r}$. Thus

$$W_f(\vec{r}) = k_{\text{onc}}c(\vec{r})\Delta t\ W_c(\vec{r})\ + [1 - k_{\text{onc}}c(\vec{r})\Delta t]W_f(\vec{r} + \overrightarrow{\Delta r}). \tag{36}$$

Here k_{onc} is the diffusion limit for the on-rate reaction constant, which is the value that the on-rate reaction constant would have if every collision with the target would lead to reaction. In this case, we use k_{onc}, rather than k_{on} (which could be substantially smaller), because here we consider "transition" to the "correlated state" rather than to the "true" bound state, so in this case every collision leads to transition.

[Note that, rigorously speaking, Eq. (36) implies that the searching particle and an obstacle could "overlap" in space (i.e., have the same $\vec{r}$), which in reality does not happen. However, since we assume that the collision radius a is much smaller than r, $c(\vec{r})$ could be interpreted as an average concentration in the a vicinity of the point with the radius vector $\vec{r}$.]

For spherical particles, according to the Smoluchowski equation

$$k_{\text{onc}} = 4\pi Da. \tag{37}$$

Expanding $W_f(\vec{r} + \overrightarrow{\Delta r})$ in Eq. (36) up to the term of the second order of Δr, and taking into account that for the constant diffusion coefficient D and in the absence of external fields the average values of all projections of $\overrightarrow{\Delta r}$ is zero, and the averaged squared values of these projections is $2D\Delta t$, we obtain

$$\nabla^2 W_f\ + \frac{k_{\text{onc}}c}{D}(W_c - W_f) = 0. \tag{38}$$

We are considering a spherically symmetric system, where all functions depend only upon r. In this case

$$\nabla^2 W_f = \frac{d^2W_f}{dr^2} + \frac{2}{r}\frac{dW_f}{dr}, \tag{39}$$

and Eq. (38) produces

$$\frac{d^2W_f}{dr^2} + \frac{2}{r}\frac{dW_f}{dr} + \frac{k_{\text{onc}}c}{D}(W_c - W_f) = 0. \tag{40}$$

Next, we consider the searching particle in the correlated state. In this case, the position of the searching particle upon conversion from the correlated to free state is defined by the transfer vector $\vec{\xi}$:

$$W_c(\vec{r}) = W_f(\vec{r} + \vec{\xi}). \tag{41}$$

Expanding the right part of Eq. (41) for a spherically symmetric system, we obtain

$$W_c - W_f \approx \left(\frac{d^2W_f}{dr^2} + \frac{2}{r}\frac{dW_f}{dr}\right)\frac{\langle\xi_r^2\rangle}{2} + \frac{dW_f}{dr}\langle\xi_r\rangle. \tag{42}$$

(The expansion is justified provided that characteristic scale for the distance from the origin and for the change in concentration is substantially larger than $|\xi_r|$ and $\sqrt{\langle\xi_r^2\rangle}$ that are proportional to the effective radius of interaction a.)

Substituting Eq. (42) into Eq. (40), we obtain

$$\left(\frac{d^2W_f}{dr^2} + \frac{2}{r}\frac{dW_f}{dr}\right)\left(1 + \frac{k_{\text{onc}}c}{D}\frac{\langle\xi_r^2\rangle}{2}\right) + \frac{dW_f}{dr}\frac{k_{\text{onc}}c}{D}\langle\xi_r\rangle = 0. \tag{43}$$

Substituting Eqs. (17) and (18) into Eq. (43), we obtain

$$\left(\frac{d^2W_f}{dr^2} + \frac{2}{r}\frac{dW_f}{dr}\right)\left(1 + \frac{k_{\text{onc}}}{D}\frac{(\langle\xi_\parallel^2\rangle + \langle\xi_\perp^2\rangle)}{6}c\right) + \frac{dW_f}{dr}\frac{k_{\text{onc}}}{D}\frac{1}{3}a\ \langle\xi_\parallel\rangle\frac{dc}{dr} = 0. \tag{44}$$

To simplify the above equation, we introduce the volume concentration:

$$\mathcal{C} \equiv \frac{4}{3}\pi a^3 c, \tag{45}$$

and the notations

$$\mu \equiv \frac{\langle\xi_\parallel\rangle}{a} = 1 - \left(1 + \frac{\xi_0}{a}\right)\langle\cos\theta_s\rangle, \tag{46}$$

$$q \equiv \frac{\langle\xi_\parallel^2\rangle + \langle\xi_\perp^2\rangle}{2a^2} = \frac{1}{2} - \left(1 + \frac{\xi_0}{a}\right)\langle\cos\theta_s\rangle + \frac{1}{2}\left(1 + \frac{\xi_0}{a}\right)^2 = \mu + \frac{1}{2}\frac{\xi_0}{a}\left(2 + \frac{\xi_0}{a}\right). \tag{47}$$

[The right-hand parts of Eqs. (46) and (47) are obtained from Eqs. (19) and (22).]

Note that parameter μ could be either positive or negative depending upon $\langle\cos\theta_s\rangle$. Negative values correspond to predominating "reflection" from the obstacle, while positive values correspond to predominating transfer along the obstacle by mean of sliding.

In the absence of sliding, $\langle\cos\theta_s\rangle = 1$, and

$$\mu(\langle\cos\theta_s\rangle = 1) \equiv \mu_0 = -\frac{\xi_0}{a}, \tag{48}$$

$$q(\langle\cos\theta_s\rangle = 1) \equiv q_0 = \frac{1}{2}\left(\frac{\xi_0}{a}\right)^2 = \frac{1}{2}(\mu_0)^2. \tag{49}$$

In the opposite case of "saturating" sliding, the searching particle "equilibrates" along the surface of the obstacle, so that $\langle\cos\theta_s\rangle = 0$, and

$$\mu(\langle\cos\theta_s\rangle = 0) = 1, \quad (50)$$

$$q(\langle\cos\theta_s\rangle = 0) = \frac{1}{2}\left[1 + \left(1 + \frac{\xi_0}{a}\right)^2\right]. \quad (51)$$

Substituting Eqs. (45)–(47) into Eq. (44), we obtain

$$\left(\frac{d^2W_f}{dr^2} + \frac{2}{r}\frac{dW_f}{dr}\right)(1 + q\,\mathcal{C}) + \mu\frac{dW_f}{dr}\frac{d\mathcal{C}}{dr} = 0 \quad (52)$$

or

$$-\frac{d\ln\frac{dW_f}{dr}}{dr} = \frac{2}{r} + \frac{\mu\,\frac{d\mathcal{C}}{dr}}{1 + q\,\mathcal{C}}. \quad (53)$$

This equation has the general solution

$$W_f(r) = -A_0\int_{A_1}^{r}[1 + q\,\mathcal{C}(\mathscr{r})]^{-\frac{\mu}{q}}\frac{d\mathscr{r}}{\mathscr{r}^2}, \quad (54)$$

where A_0 and A_1 are some constants.

Assuming that the searching particle binds the specific target as soon as it collides with it, the boundary conditions for Eq. (52) are

$$W_f(a_t) = 1, \quad (55)$$

$$W_f(R) = 0, \quad (56)$$

where a_t is the effective radius of the target.

For these boundary conditions we obtain

$$W_f(r) = \frac{\int_r^R[1 + q\,\mathcal{C}(\mathscr{r})]^{-\frac{\mu}{q}}\frac{d\mathscr{r}}{\mathscr{r}^2}}{\int_{a_t}^R[1 + q\,\mathcal{C}(\mathscr{r})]^{-\frac{\mu}{q}}\frac{d\mathscr{r}}{\mathscr{r}^2}}. \quad (57)$$

We will analyze this equation for the simple case in which all obstacles are homogeneously distributed within the distance b from the center of the specific target, i.e.,

$$\mathcal{C}(r) = \mathcal{C}_0, \quad (58)$$

for $a_{\rm t} < \mathscr{r} < b$, and

$$\mathcal{C}(\mathscr{r}) = 0, \quad (59)$$

for $r > b$.

Then, for the starting position $r > b$,

$$W_f(r) = \frac{\frac{1}{r} - \frac{1}{R}}{\left(\frac{1}{a_t} - \frac{1}{b}\right)(1 + q\,\mathcal{C}_0)^{-\frac{\mu}{q}} + \frac{1}{b} - \frac{1}{R}}. \quad (60)$$

In the absence of obstacles

$$W_f(r;\ \mathcal{C}_0 = 0) = \frac{\frac{1}{r} - \frac{1}{R}}{\frac{1}{a_t} - \frac{1}{R}}. \quad (61)$$

If $a_t \ll b \ll R$, then Eq. (60) and Eq. (61) could be approximated as

$$W_f(r) \approx \left(\frac{1}{r} - \frac{1}{R}\right)(1 + q\,\mathcal{C}_0)^{\frac{\mu}{q}}a_t \quad (62a)$$

and

$$W_f(r) \approx \left(\frac{1}{r} - \frac{1}{R}\right)a_t. \quad (62b)$$

From comparison of Eq. (62a) and Eq. (62b), the parameter

$$a_{te} = (1 + q\,\mathcal{C}_0)^{\frac{\mu}{q}}a_t \quad (63)$$

could be interpreted as the "effective target size."

It is seen that for positive values of parameter μ (i.e., when the sliding transfer along the obstacle predominates over "reflection") the presence of obstacles increases the effective target size, while at negative μ (when the "reflection" predominates) the presence of obstacles decreases the effective target size.

From Eq. (31) (and the explanation below it) the critical value of dissociation constant above which the parameter μ switches from positive to negative is

$$K_{d(\rm cr)} \sim \frac{D_s/D}{a^3}. \quad (64)$$

The maximal possible increase of the effective target size for a given volume concentration of spherical particles is achieved at "saturating" sliding (i.e., when $a^3K_d \ll D_s/D$, and consequently $\langle\cos\theta_s\rangle = 0$).

In this case, from Eqs. (51) and (63)

$$\left(\frac{a_{te}}{a_t}\right)_{\max} = (1 + q_{\max}\,\mathcal{C}_0)^{\frac{1}{q_{\max}}}, \quad (65)$$

where

$$q_{\max} = \frac{1}{2} + \frac{1}{2}\left(1 + \frac{\xi_0}{a}\right)^2. \quad (66)$$

(In Sec. II E we evaluate that for spherical particles $\frac{\xi_0}{a} = \frac{1}{2}$, so $q_{\max} = \frac{13}{8}$.)

For small volume concentrations Eq. (65) is converted to simply

$$\left(\frac{a_{te}}{a_t}\right)_{\max} \approx 1 + \mathcal{C}_0. \quad (67)$$

If the sliding is negligible (i.e., the diffusion on the surface is very slow, and/or the binding time is too short), then $\langle\cos\theta_s\rangle = 1$, and the effective target size reaches its minimal value

$$\left(\frac{a_{te}}{a_t}\right)_{\min} = \left[1 + \frac{1}{2}\left(\frac{\xi_0}{a}\right)^2\mathcal{C}_0\right]^{-2\frac{a}{\xi_0}} \approx 1 - \frac{\xi_0}{a}\mathcal{C}_0. \quad (68)$$

In Fig. 5, the ratio of dependencies Eqs. (60) and (61) are plotted as functions of $\mathcal{C}_0$ for two opposite cases: the absence of binding, and for the binding with "saturating" sliding (i.e., when the lifetime of the bound state is more than sufficient for the searching particles to diffuse along the whole size of the obstacle several times before detaching from it). Note that this ratio does not depend upon the starting position r. For these graphs, the ratios $a_t/b = b/R = 0.1$. In the absence of binding $\mu = -1/2$, $q = 1/8$; in the case of binding with "saturating" sliding $\mu = 1$, $q = 13/8$.

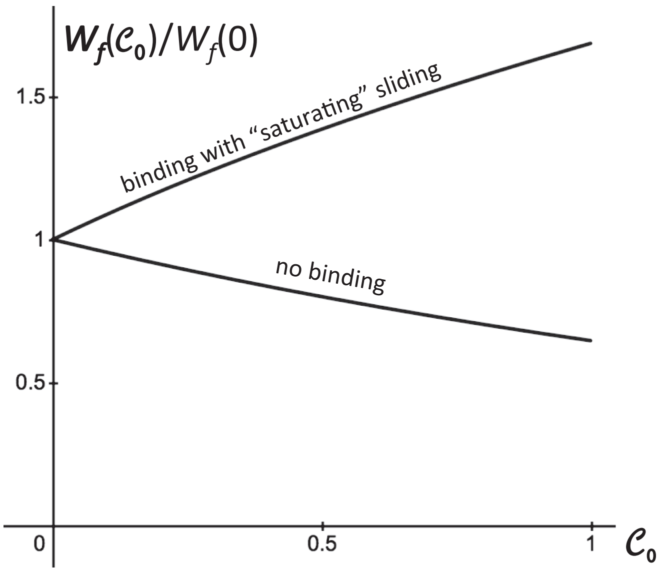

FIG. 5. Dependence of the probability of reaching the target upon the volume concentration of spherical obstacles. The dependencies are normalized upon the probability for zero concentration of obstacles.

C. Competition between targets is defined by their effective sizes

Consider equal numbers of two different types of specific targets, 1 and 2, randomly distributed in solution with the average distance R between the targets. We wish to evaluate probability W_{12} that the searching particle initially localized symmetrically relative to both targets will reach the target 1 before it reaches the target 2. For that, we will use an approximate representation of the system in which the target is localized in the middle of the sphere of the radius R, and each point on the surface of the sphere could be considered as a border (a touching point) between two spheres that surround the targets of the type 1 and the type 2 (Fig. 6).

In other words, if the searching particle starts to move from some distance $r < R$ from the target and reaches the point at the distance R, we assume that this point would be always a touching point of two spheres surrounding the targets of the types 1 and 2. From the position R, the searching particle can move with equal probability over some distance ΔR either

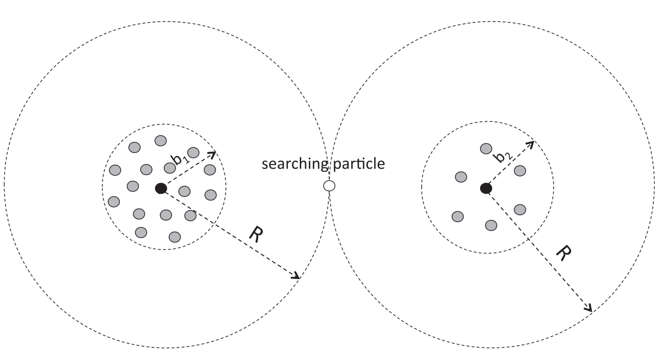

FIG. 6. Distribution of obstacles around two specific targets. These targets could be viewed as representatives of multiple targets distributed in solution with the average distance $2R$ between them.

toward the target 1 or toward the target 2. Then, according to Eq. (60), the probability that the searching particle will hit the respective target before returning to the position R is

$$W_n = \frac{\frac{1}{(R-\Delta R)} - \frac{1}{R}}{\left(\frac{1}{a_{tn}} - \frac{1}{b_n}\right)(1 + q\,\mathcal{C}_{0n})^{-\frac{\mu}{q}} + \frac{1}{b_n} - \frac{1}{R}}, \tag{69}$$

where $n = 1, 2$ is the number of the target.

If the particle did not hit the respective specific target, it returns to the position R, and the whole process starts over again. In general, the particle can make an indefinite number of "loops" (which are travels to one of the areas and returns without hitting the target) in both directions before it hits the target. The probability that the particle makes a total of i loops without hitting either of the targets is

$$[0.5(1 - W_1) + 0.5(1 - W_2)]^i.$$

Thus

$$W_{12} = 0.5 W_1 \sum_{i=0}^{i=\infty} [0.5(1 - W_1) + 0.5(1 - W_2)]^i = \frac{W_1}{W_1 + W_2}. \tag{70}$$

Substituting Eq. (69) into Eq. (70), we obtain

$$W_{12} = \frac{1}{1 + \frac{\left(\frac{1}{a_{t1}} - \frac{1}{b_1}\right)(1+q\,\mathcal{C}_{01})^{-\frac{\mu}{q}} + \frac{1}{b_1} - \frac{1}{R}}{\left(\frac{1}{a_{t2}} - \frac{1}{b_2}\right)(1+q\,\mathcal{C}_{02})^{-\frac{\mu}{q}} + \frac{1}{b_2} - \frac{1}{R}}} \tag{71}$$

or

$$\frac{W_{12}}{W_{21}} = \frac{W_1}{W_2} = \frac{\left(\frac{1}{a_{t2}} - \frac{1}{b_2}\right)(1 + q\,\mathcal{C}_{02})^{-\frac{\mu}{q}} + \frac{1}{b_2} - \frac{1}{R}}{\left(\frac{1}{a_{t1}} - \frac{1}{b_1}\right)(1 + q\,\mathcal{C}_{01})^{-\frac{\mu}{q}} + \frac{1}{b_1} - \frac{1}{R}}. \tag{72}$$

For $a_{t1} = a_{t2} \ll b \ll R$,

$$\frac{W_{12}}{W_{21}} \approx \left(\frac{1 + q\,\mathcal{C}_{01}}{1 + q\,\mathcal{C}_{02}}\right)^{\frac{\mu}{q}}, \tag{73}$$

which is the ratio of the effective target sizes [see Eq. (63)].

Thus, the target with larger effective size has an advantage in competition.

D. Speed of the search for the specific target depends not only upon the effective target size but also upon delay due to binding to the obstacles

The speed of the search for the specific target could be characterized by the average first-passage time $\mathcal{T}(r)$ for the particle to reach the specific target localized at the distance r from it.

The derivation for the first-passage time starting from the unbound state is similar to that for the function $W_f(\vec{r})$ [Eq. (36)]: Again, we consider the behavior of the free searching particle during a small time interval Δt. During this time interval it can either convert to the correlated state with the probability $k_{\text{onc}} c(\vec{r})\Delta t$, or remain in the free state with the probability $1 - k_{\text{onc}} c\,\Delta t$; and in the latter case, the searching particle would move from position $\vec{r}$ to some new position $\vec{r} + \overrightarrow{\Delta r}$. However, since now we are dealing with the time rather than probability, the time interval Δt spent during the described above elementary processes has to be added to the right part of the equation.

Thus, the analogs of Eqs. (36) and (38) for the first-passage time are

$$\mathcal{T}_f(\vec{r}) = k_{\text{onc}}c\,\Delta t\;\mathcal{T}_c(\vec{r})\;+(1-k_{\text{onc}}c\,\Delta t)\mathcal{T}_f(\vec{r}+\overrightarrow{\Delta r})+\Delta t \tag{74}$$

and

$$\frac{d^2\mathcal{T}_f}{dr^2}+\frac{2}{r}\frac{d\mathcal{T}_f}{dr}+\frac{k_{\text{onc}}c}{D}(\mathcal{T}_c-\mathcal{T}_f)+\frac{1}{D}=0, \tag{75}$$

respectively.

To obtain the analog of Eq. (41), we note that in the correlated state the searching particle spent the time

$$\tau_d = \tau_0+\tau_b. \tag{76}$$

Thus, the analog of Eq. (41):

$$\mathcal{T}_b(\vec{r}) = \mathcal{T}_f(\vec{r}+\vec{\xi})+\tau_d. \tag{77}$$

After expansion of $\mathcal{T}_f(\vec{r}+\vec{\xi})$ into the Taylor series like in Eq. (42), and substitutions like in Eqs. (44)–(47), we obtain the analog of Eq. (52):

$$\left(\frac{d^2\mathcal{T}_f}{dr^2}+\frac{2}{r}\frac{d\mathcal{T}_f}{dr}\right)(1+q\,\mathcal{C})+\mu\frac{d\mathcal{T}_f}{dr}\frac{d\mathcal{C}}{dr}+\frac{(1+\varepsilon\mathcal{C})}{D}=0, \tag{78}$$

where we introduce the normalized decorrelation time

$$\varepsilon \equiv \frac{3D}{a^2}\tau_d. \tag{79}$$

Since

$$\tau_d = \tau_0+\tau_b, \tag{80}$$

from Eqs. (79) and (80)

$$\varepsilon = \varepsilon_0+\varepsilon_b, \tag{81}$$

where

$$\varepsilon_0 \equiv \frac{3D}{a^2}\tau_0, \tag{82}$$

$$\varepsilon_b \equiv \frac{3D}{a^2}\tau_b. \tag{83}$$

The general solution of Eq. (78) is

$$\mathcal{T}_f(r) = \frac{1}{D}\int_{A_0}^{r}d\mathscr{r}_1\int_{\mathscr{r}_1}^{A_1}d\mathscr{r}_2\frac{\mathscr{r}_2^2}{\mathscr{r}_1^2}\left(\frac{1+q\,\mathcal{C}(\mathscr{r}_2)}{1+q\,\mathcal{C}(\mathscr{r}_1)}\right)^{\frac{\mu}{q}}\frac{1+\varepsilon\,\mathcal{C}(\mathscr{r}_2)}{1+q\,\mathcal{C}(\mathscr{r}_2)}, \tag{84}$$

where A_0 and A_1 are some constants.

The searching process is over when the searching particle hits the target. Thus

$$\mathcal{T}_f(a_t)=0. \tag{85}$$

In this subsection, we consider a situation in which all targets are equivalent, and the average distance between them is $2R$; and we are interested in the average time that passes before the searching particle hits any of the specific targets. In this case crossing a boundary at the distance R from the target is equivalent to reflection from this boundary. Thus, we use the reflecting boundary condition

$$\frac{d\mathcal{T}_f}{dr}(R)=0. \tag{86}$$

Finally, we consider the initial position equidistant from neighboring specific targets, i.e.,

$$r=R.$$

For conditions (85) and (86), Eq. (84) produces

$$\mathcal{T}_f \equiv \mathcal{T}_f(R) = \frac{1}{D}\int_{a_t}^{R}d\mathscr{r}_1\int_{\mathscr{r}_1}^{R}d\mathscr{r}_2\frac{\mathscr{r}_2^2}{\mathscr{r}_1^2}\left(\frac{1+q\,\mathcal{C}(\mathscr{r}_2)}{1+q\,\mathcal{C}(\mathscr{r}_1)}\right)^{\frac{\mu}{q}} \times\frac{1+\varepsilon\,\mathcal{C}(\mathscr{r}_2)}{1+q\,\mathcal{C}(\mathscr{r}_2)}. \tag{87}$$

In the absence of obstacles Eq. (87) produces

$$\mathcal{T}_f(\mathcal{C}=0) = \frac{R^3}{3Da_t}\left(1-1.5\frac{a_t}{R}+0.5\frac{{a_t}^3}{R^3}\right)\approx\frac{R^3}{3Da_t} = \frac{\frac{4}{3}\pi R^3}{4\pi Da_t}=\frac{1}{k_{\text{onc}\,t}c_t}, \tag{88}$$

were $k_{\text{onc}\,t}=4\pi Da_t$ is the Smoluchowski limit for the on-rate constant, and $c_t = 1/\frac{4}{3}\pi R^3$ is concentration of the specific target.

Next, we will analyze Eq. (87) for the simple situation described by Eqs. (58) and (59), in which all obstacles are homogeneously distributed with the volume concentration $\mathcal{C}_0$ within the distance b from the specific target. In this case, the integral in Eq. (87) could be presented as a sum of three terms,

$$\mathcal{T}_f = I_1+I_2+I_3, \tag{89}$$

where

$$I_1 = \frac{1}{D}\frac{1+\varepsilon\,\mathcal{C}_0}{1+q\,\mathcal{C}_0}\int_{a_t}^{b}d\mathscr{r}_1\int_{\mathscr{r}_1}^{b}d\mathscr{r}_2\frac{\mathscr{r}_2^2}{\mathscr{r}_1^2} = \frac{1}{3D}\frac{1+\varepsilon\,\mathcal{C}_0}{1+q\,\mathcal{C}_0}\frac{b^3}{a_t}\left(1-1.5\frac{a_t}{b}+0.5\frac{a_t^3}{b^3}\right), \tag{90}$$

$$I_2 = \frac{(1+q\,\mathcal{C}_0)^{-\frac{\mu}{q}}}{D}\int_{a_t}^{b}d\mathscr{r}_1\int_{b}^{R}d\mathscr{r}_2\,\frac{\mathscr{r}_2^2}{\mathscr{r}_1^2} = \frac{(1+q\,\mathcal{C}_0)^{-\frac{\mu}{q}}}{3D}\left(\frac{1}{a_t}-\frac{1}{b}\right)(R^3-b^3), \tag{91}$$

$$I_3 = \frac{1}{D}\int_{b}^{R}d\mathscr{r}_1\int_{\mathscr{r}_1}^{R}d\mathscr{r}_2\frac{\mathscr{r}_2^2}{\mathscr{r}_1^2} = \frac{1}{3D}\frac{R^3}{b}\left(1-1.5\frac{b}{R}+0.5\frac{b^3}{R^3}\right), \tag{92}$$

or, leaving only predominating terms in Eqs. (90)–(92),

$$I_1 \approx \frac{1}{3D}\frac{1+\varepsilon\,\mathcal{C}_0}{1+q\,\mathcal{C}_0}\frac{b^3}{a_t}, \tag{93}$$

$$I_2 \approx \frac{(1+q\,\mathcal{C}_0)^{-\frac{\mu}{q}}}{3D}\frac{R^3}{a_t}, \tag{94}$$

$$I_3 \approx \frac{1}{3D}\frac{R^3}{b}. \tag{95}$$

The term I_1 [Eq. (93)] characterizes the search in the volume of the radius b that is filled with obstacles. If the parameter ε is greater than the parameter q, then this term increases with the concentration of obstacles, which corresponds to delay of the search process due to binding to the obstacles.

The second term I_2 [Eq. (94)] corresponds to the search within the volume of the radius R for the target with the effective size defined by Eq. (63).

The third term I_3 [Eq. (95)] corresponds to the search within the volume of the radius R for the target with the effective size b. It is always smaller the second term, and does not depend upon the concentration of obstacles.

Thus, we are primarily interested in interplay between the terms I_1 and I_2, which depend upon concentration of obstacles.

If the term I_2 predominates, the effect of the concentration of obstacles upon the "speed" of the target search (reciprocal to the time of the target search) is similar to the effect upon the probability of reaching the target (Secs. II B and II C): in this case, both the speed of the search and the probability of reaching the target are proportional to the effective target size $(1 + q\,\mathcal{C}_0)^{\frac{\mu}{q}} a_t$ which increases with $\mathcal{C}_0$ if μ is positive, and decreases with $\mathcal{C}_0$ if μ is negative.

However, if the first term is predominating, the search could be delayed in the presence of obstacles even if μ is positive. In this case, the presence of obstacles slow down the searching process, but at the same time the target surrounded by obstacles has better chances of binding the searching particle than the obstacle-free target. In this situation, under the condition of the excess of the targets over the searching particles, the fraction of the searching particles that would bind the target surrounded by obstacles would be greater than the fraction that would bind the obstacle-free target; however, the former fraction would bind slower than the latter due to transient trapping on the obstacles.

In Appendix A we analyze behavior of the first-passage time [Eq. (89)] depending upon various parameters. If the parameter μ is negative, then the first-passage time increases with $\mathcal{C}_0$, while if μ is positive, the outcome depends upon parameter $\gamma = \varepsilon(\frac{b}{R})^3$ [Eq. (A11)]. If this parameter is large, the first-passage time increases with $\mathcal{C}_0$; if it is small, it decreases with $\mathcal{C}_0$; and when it is within a certain interval around unity, the first-passage times goes through the maximum at some value of $\mathcal{C}_0$.

These dependencies defined by Eq. (89) normalized by Eq. (88) are plotted in Fig. 7 for the ratios $a_t/b = b/R = 0.1$. In the absence of binding $\mu = -1/2$, $q = 1/8$; in the case of binding with "saturating" sliding $\mu = 1$, $q = 13/8$. For saturating sliding, the dependencies are shown for three different values of the parameter γ, as indicated in the figure. The dashed line shows the constant level equivalent to unity.

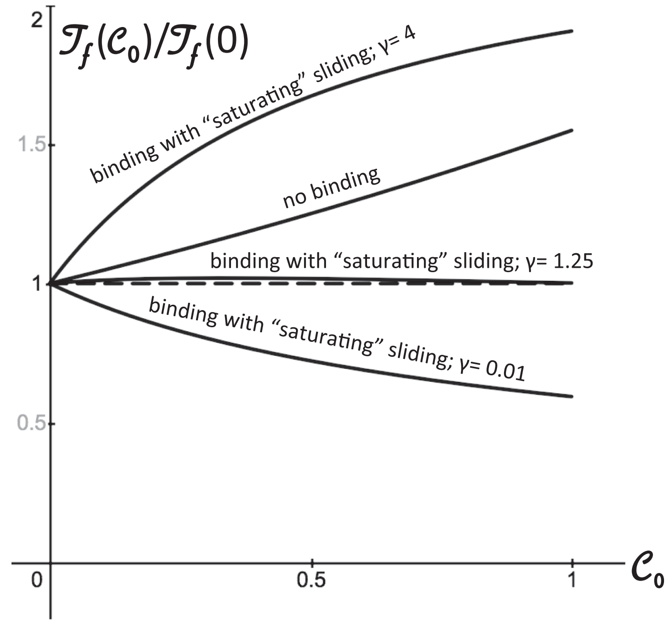

FIG. 7. Dependence of the first-passage time to reach the target upon the volume concentration of spherical obstacles. The dependencies are normalized upon the first-passage time for zero concentration of obstacles.

E. Searching process in the presence of obstacles could be described in terms of the effective diffusion coefficient provided that the spatial distribution of the obstacles is uniform; for nonuniform distribution of obstacles, such a description in the general case is impossible

Migration of the particle in inhomogeneous media is often described by the effective diffusion coefficient. In this subsection, we will analyze whether the searching process in the presence of nonspecific binding could be described in terms of the effective diffusion coefficient.

The expression for the first-passage time in terms of the effective diffusion coefficient D_{eff} in the absence of external forces is

$$\left(\frac{d^2\mathcal{T}_f}{dr^2} + \frac{2}{r}\frac{d\mathcal{T}_f}{dr}\right) + \frac{d\mathcal{T}_f}{dr}\frac{d\ln D_{\text{eff}}}{dr} + \frac{1}{D_{\text{eff}}} = 0. \tag{96}$$

This equation is a special case of Eq. (2.13) in [29]. In Appendix B we present a more direct derivation of this equation.

Equation for the first-passage time in the presence of obstacles [Eq. (78)] can be presented as

$$\left(\frac{d^2\mathcal{T}_f}{dr^2} + \frac{2}{r}\frac{d\mathcal{T}_f}{dr}\right) + \frac{d\mathcal{T}_f}{dr}\frac{d\ln(1+q\,\mathcal{C})^{\frac{\mu}{q}}}{dr} + \frac{1}{D}\frac{1+\varepsilon\,\mathcal{C}}{1+q\,\mathcal{C}} = 0. \tag{97}$$

If the searching process is to be approximated (at least at small volume concentrations of obstacles) by diffusion in homogeneous media with some effective diffusion coefficient, then the respective terms in Eqs. (96) and (97) must coincide (at least up to linear terms on concentration).

To make the second from the end terms in Eqs. (96) and (97) coincide, it is required that

$$\frac{d\ln D_{\text{eff}}}{dr} = \frac{d\ln(1+q\,\mathcal{C})^{\frac{\mu}{q}}}{dr}. \tag{98a}$$

Taking into account that if $\mathcal{C} = 0$, then $D_{\text{eff}} = D$, Eq. (98a) produces

$$\frac{D_{\text{eff}}}{D} = (1+q\,\mathcal{C})^{\frac{\mu}{q}} \approx 1 + \mu\,\mathcal{C}. \tag{98b}$$

To make the last terms in Eqs. (96) and (97) coincide, it is required that

$$\frac{D_{\rm eff}}{D}=\frac{1+q\,\mathcal{C}}{1+\varepsilon\,\mathcal{C}}\approx 1-(\varepsilon-q)\mathcal{C}. \tag{99}$$

To make description in terms of effective diffusion coefficient possible, Eqs. (98b) and (99) must be satisfied simultaneously (at least at small concentrations). Thus

$$\mu=-(\varepsilon-q) \tag{100}$$

or

$$\varepsilon=q-\mu. \tag{101}$$

First, we consider the situation in the absence of binding between the searching particle and the obstacle, in which case $\mu=\mu_0$, $q=q_0$, $\varepsilon=\varepsilon_0$. In the absence of binding diffusivity in the presence of obstacles could be approximated by the effective diffusion coefficient. To substantiate this statement, consider for a moment a situation in which, in contrast to our usual formulation, numerous searching particles are involved in the diffusion process in the presence of obstacles. Since all searching particle are unbound and capable for translational thermal motion, a flux of the particles through a given cross section would be proportional to the gradient of the particles' concentration perpendicular to this cross section, and the coefficient of proportionality could be interpreted as the effective diffusion coefficient. From this consideration, we can calculate parameters of our model, which so far were known up to a numerical coefficient: In [26], the effective diffusion coefficient in the presence of spherical obstacles as a function of their volume concentration was obtained using the modified Maxwell Garnett approach:

$$\frac{D_{\rm eff}}{D}\approx 1-\frac{\mathcal{C}}{2}. \tag{102}$$

Thus, from comparing Eqs. (98b) and (102) (for $\mu=\mu_0$),

$$\mu_0=-\tfrac{1}{2}. \tag{103}$$

Substituting this result into Eq. (49), we obtain

$$q_0=\tfrac{1}{8}. \tag{104}$$

From Eq. (101)

$$\varepsilon_0=q_0-\mu_0=\tfrac{5}{8}. \tag{105}$$

From that, using Eqs. (48), (82), and (104), we obtain the values of collision transfer vector and decorrelation time for spherical obstacles in the absence of binding,

$$\xi_0=\frac{a}{2}, \tag{106}$$

$$\tau_0=\frac{5}{24}\frac{a^2}{D}. \tag{107}$$

Thus, for nonbinding obstacles we could obtain consistent description in term of the effective diffusion coefficient for any distribution of obstacles.

Could this description be generalized for reversible binding of the searching particle to the obstacles? First, consider the case when the concentration of the obstacles and, consequently, the effective diffusion coefficient are constant. In this case then Eqs. (96) and (97) are converted to

$$\left(\frac{d^2\mathfrak{T}_f}{dr^2}+\frac{2}{r}\frac{d\mathfrak{T}_f}{dr}\right)+\frac{1}{D_{\rm eff}}=0 \tag{108}$$

and

$$\left(\frac{d^2\mathfrak{T}_f}{dr^2}+\frac{2}{r}\frac{d\mathfrak{T}_f}{dr}\right)+\frac{1}{D}\frac{1+\varepsilon\,\mathcal{C}}{1+q\,\mathcal{C}}=0, \tag{109}$$

respectively.

In this case we can ignore Eqs. (98a) and (98b) [and, consequently, Eq. (101)], and the effective diffusion coefficient can be defined solely by Eq. (99). We can use this definition to estimate the numerical proportionality coefficient in Eq. (30) for the binding time:

Consider binding in the absence of sliding. In this case, parameters μ and q are the same as in the absence of binding (i.e., $\mu=\mu_0$ and $q=q_0$) Thus, in this case, taking into account Eqs. (81) and (102), Eq. (99) produces

$$\frac{D_{\rm eff}}{D}\approx 1-(\varepsilon-q)\mathcal{C}=1-(\varepsilon_0-q_0)\mathcal{C}-\varepsilon_b\mathcal{C}$$
$$=1-\frac{1}{2}\mathcal{C}-\varepsilon_b\mathcal{C}. \tag{110}$$

From Eqs. (30) and (83)

$$\varepsilon_b\mathcal{C}=\frac{3D}{a^2}\tau_b\mathcal{C}=3\kappa\frac{\mathcal{C}}{K_d\,a^3}=4\pi\kappa\frac{c}{K_d}. \tag{111}$$

Substituting Eq. (111) into Eq. (110) we obtain

$$\frac{D_{\rm eff}}{D}\approx 1-\frac{1}{2}\mathcal{C}-4\pi\kappa\frac{c}{K_d}, \tag{112}$$

where κ is a numerical coefficient.

The result obtained in [25] for reversible binding to the obstacle without sliding in our designations is

$$\frac{D_{\rm eff}}{D}=\frac{1-\frac{1}{2}\mathcal{C}}{1+\frac{c}{K_d}}\approx 1-\frac{1}{2}\mathcal{C}-\frac{c}{K_d}. \tag{113}$$

From comparison of Eqs. (112) and (113), we obtain the value of numerical coefficient in Eq. (30),

$$\kappa=\frac{1}{4\pi}, \tag{114}$$

so that the binding time

$$\tau_b=\frac{1}{4\pi K_d Da}=\frac{1}{K_d k_{\rm onc}}. \tag{115}$$

Could the result for the effective diffusion coefficient in the presence of binding at constant concentration of obstacles be extended to coordinate-dependent concentration of obstacles?

If concentration of obstacles is not constant, the Eqs. (98a) and (98b) cannot be ignored, and, consequently, Eq. (101) must be satisfied. However, this equation cannot be satisfied in the case of binding. That is easier to demonstrate if the sliding is absent. In this case, $\mu=\mu_0$ and $q=q_0$. Equation (101) is satisfied for $\mu=\mu_0$, $q=q_0$, $\varepsilon=\varepsilon_0$; thus, it cannot be satisfied for $\mu=\mu_0$, $q=q_0$, $\varepsilon=\varepsilon_0+\varepsilon_b$, if ε_b is not zero. Consequently, for the cases in which concentration of obstacles is not constant within the whole volume, it is impossible to generalize the notion of the effective diffusion coefficient for the presence of binding. A more formal illustration for why diffusion in the presence of binding cannot be described by the effective diffusion coefficient unless the concentration of binders is constant is presented in Appendix B for the exactly solvable case of diffusion with switching between the mobile and the immobile states.

F. Rod-shaped obstacles could produce stronger effects upon the effective target size comparing to spherical obstacles with the same volume concentration

In the previous subsection we have shown that transferring of the searching particle via sliding along the obstacle could facilitate the target search. The magnitude of this transfer is defined by the typical size of an obstacle, and the total effect is limited by the volume concentration of the obstacles. The largest typical size of a thin cylindrical (or "rod-shaped") obstacle is much larger than the typical size of a compact (e.g., spherical) particle of the same volume. Thus, one can expect that for a given volume concentration of obstacles, the effects of thin rod-shaped obstacles upon the target search would be much greater than for spherical particles analyzed in previous subsections. Also, thin rod-shaped particles are especially interesting because they could model DNA segments.

Consider a cylindrical obstacle with the length along the axis $2a_l$, and the radius $a_s \ll a_l$. In addition, we assume that the radius of the searching particle a_p is also much smaller than a_l. Thus, the effective length of the rod $a_{le} = a_l + a_p \approx a_l$, and the effective radius of the rod $a_{se} = a_l + a_p \ll a_l$.

In this subsection we will consider only the "saturating" sliding regime, in which the lifetime of the bound state is long enough for the searching particle to "equilibrate" on the surface of the obstacle, so its release from the obstacle could occur at any point on the surface with equal probability regardless of where on the surface the initial collision took place. Also, since the axis length a_l is much larger than other typical sizes, the sliding along this axis provides the predominant contribution to the particle transfer upon collision. Because of that, we consider only transferring along this axis and neglect the transfer in the perpendicular direction.

Also, as previously, we assume that mobility of an obstacle is much lower than that of the searching particle, so during the time of collision the obstacle is considered to be immobile. Consider the searching particle that became bound to the obstacle at the distance χ from its center, as shown in Fig. 8. Here the obstacle is shown in gray, and the searching particle is shown in white.

To evaluate the average transfer of the particle upon the collision, we first consider the obstacle with the axis parallel to the radius vector $\vec{r}$. If the searching particle became bound to the obstacle at the moment when the particle coordinate was r, and its distance from the center of the obstacle at that moment was χ, then the position of the center of the obstacle at the moment of collision was $r+\chi$. The probability that the binding occurs at this position would be proportional to the concentration of obstacles at this position $c(r+\chi)$.

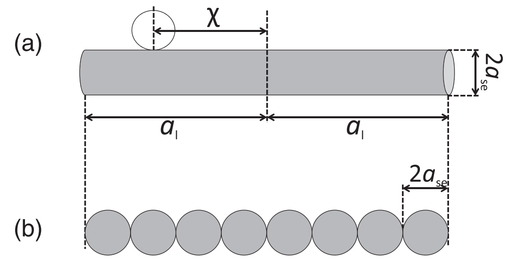

FIG. 8. Rod-shaped obstacles. (a) Cylindrical representation. (b) Representation as a string of beads.

Since we consider equilibration of the searching particle on the surface of the obstacle, the average point of release of the searching particle would be at the middle of the obstacle, i.e., at position $r+\chi$. Thus, the transfer of the searching particle upon release from the obstacle would be equivalent to χ.

Thus the probability for the transfer χ

$$p(\chi) = \frac{c(r+\chi)}{\int_{-a_l}^{a_l} c(r+\chi)d\chi} \approx \frac{c(r)+\frac{dc}{dr}\chi}{\int_{-a_l}^{a_l}\left[c(r)+\frac{dc}{dr}\chi\right]d\chi} = \frac{1+\chi\frac{d\ln c(r)}{dr}}{2a_l}. \tag{116}$$

From that, using the approximation for $p(\chi)$ at the very right part of the above equation,

$$\langle\chi\rangle = \int_{-a_l}^{a_l}\chi\, p(\chi)d\chi = \frac{1}{3}(a_l)^2\frac{d\ln c(r)}{dr}, \tag{117}$$

$$\langle\chi^2\rangle = \int_{-a_l}^{a_l}\chi^2\, p(\chi)d\chi = \frac{1}{3}(a_l)^2. \tag{118}$$

Equation (118) is obtained for the obstacles with the longer axis oriented along the radial direction. To obtain the average transfer in the radial direction for randomly oriented obstacles, the squared length in Eqs. (117) and (118) should be replaced by its squared projection upon the radial direction, which for random orientation in three-dimensional space is equivalent to one-third of the squared length.

Thus, for the transfer in the radial direction ξ_r we obtain

$$\langle\xi_r\rangle = \frac{1}{9}(a_l)^2\frac{d\ln c(r)}{dr}, \tag{119}$$

$$\langle\xi_r^2\rangle = \frac{1}{9}(a_l)^2. \tag{120}$$

In Appendix C we show that the diffusion limit for the on-rate constant for the rodlike obstacles is

$$k_{\text{onc}} \sim D\frac{a_l}{\ln\frac{a_l}{a_{se}}}. \tag{121}$$

The volume of one rodlike obstacle is $2\pi(a_{se})^2 a_l$, so for the rod-shaped obstacles the volume concentration

$$\mathcal{C} = 2\pi(a_{se})^2 a_l c. \tag{122}$$

Substituting Eqs. (119)–(122) into Eq. (43), we obtain for the rod-shaped obstacles

$$\left(\frac{d^2W_f}{dr^2}+\frac{2}{r}\frac{dW_f}{dr}\right)(1+\lambda\mathcal{C}) + 2\lambda\frac{dW_f}{dr}\frac{d\mathcal{C}}{dr} = 0, \tag{123}$$

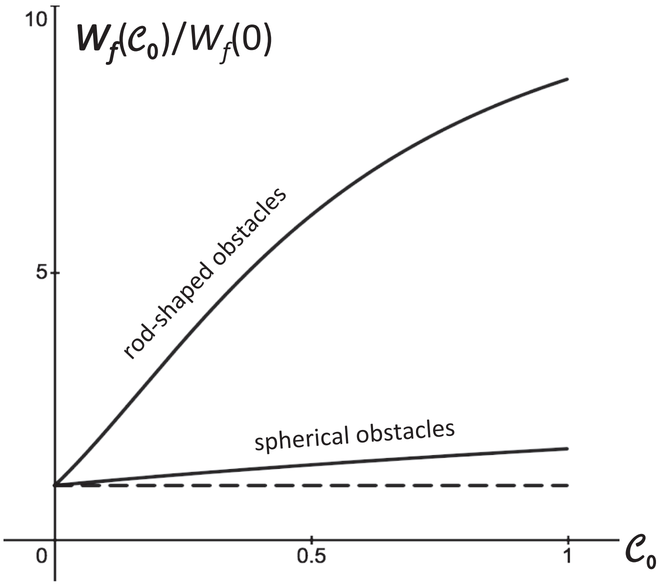

FIG. 9. Dependence of the probability of reaching the target upon the volume concentration of spherical and rod-shaped obstacles. The dependencies are normalized upon the probability for zero concentration of obstacles.

where the parameter

$$\lambda \sim \frac{\left(\frac{a_l}{a_{se}}\right)^2}{\ln\frac{a_l}{a_{se}}}. \tag{124}$$

(If we assume that Eq. (C12) (Appendix C) is exact [i.e., coefficient proportionality in Eq. (121) is 4π], then the coefficient of proportionality in Eq. (124) is 1/9.)

In terms of designations used in previous subsections, from comparison of Eqs. (123) and (52), for the rod-shaped obstacles $\mu = 2\lambda$, $q = \lambda$. For the distribution of obstacles described by Eqs. (58) and (59) the solution is given by Eq. (60). Consequently, from the analogy with Eq. (63), the effective target size in the case of the rod-shaped obstacles

$$a_{te} = (1 + \lambda\mathcal{C}_0)^2 a_t. \tag{125}$$

Since for very thin rodlike obstacles parameter λ could be large, these obstacles could produce substantially larger increase in the effective target size than spherical obstacles at the same volume concentration. To illustrate that, in Fig. 9 we plot dependence $W_f(\mathcal{C}_0)/W_f(0)$ for the spherical particles and for the rod-shaped particles for $\lambda = 5$. This value of λ corresponds to the ratio $a_l/a_{se} \approx 10$, provided that the coefficient of proportionality in Eq. (124) is 1/9 [see comment below Eq. (124)]. The dependence is described by Eq. (60) and normalized upon the probability for zero concentration of obstacles [Eq. (61)]. Note that for the distribution of obstacles given by Eqs. (58) and (59) the ratio $W_f(\mathcal{C}_0)/W_f(0)$ does not depend upon the starting position r, provided that $r > b$. The ratios $a_t/b = b/R = 0.1$. Dependencies are obtained for the case of the "saturating" sliding. For spherical particles $\mu = 1$, $q = 13/8$; and for rod-shaped particles $\mu = 10$, $q = 5$. The dashed line shows the constant level equivalent to unity.

III. DISCUSSION

We analyze the effects of various types of isolated obstacles upon the probability and the speed of the search for the specific target. We conclude that the obstacles surrounding the target could either increase or decrease the effective target size depending upon the ability of the searching particle to bind and to diffuse (slide) along the surface of the obstacle while in the bound state.

If sliding is too slow, and/or the binding time is too short, the searching particle in effect "reflects" from the obstacle. In this case, the obstacles shield the target from the searching particle, which leads to decrease of the apparent target size.

In the opposite case, sliding along the obstacle facilitates transferring to the target thus increasing the effective target size. Which of these two effects predominates depend upon the dissociation constant of the complex between the searching particle and the obstacle, their sizes, and the diffusion coefficients on the surface of the obstacle and in solution.

The effect of nonspecific binding is especially interesting it terms of facilitating the specific target search. This facilitation could be manifested either in absolute acceleration of the search (i.e., decreasing the typical time required to reach the specific target), or in increasing the probability of binding the target surrounded by obstacles in comparison with the obstacle-free target competing for the same searching particle.

We show that the competition between the targets is defined by the effective target size: the larger the effective size of the target, the more advantage it has. However, in the case of the typical search time the situation is more complex: if the time during which the searching particles is bound to an obstacle is too long, obstacles could slow down the search for the specific target even if they increase the effective target size. In this situation, if the targets are in excess and compete with each other for the searching particles, then the specific target surrounded by obstacles would eventually bind the searching particle with higher probability than the competing obstacle-free target. However, there would be a substantial "lag phase" due to nonspecific binding, and consequently, the smaller fraction of the searching particles that binds the obstacle-free target would find their targets faster than the larger fraction of the searching particles that would eventually bind the target surrounded by obstacles.

Although our model is dealing with isolated obstacles, it also could be applicable to long coiled polymer molecules (e.g., DNA), that could be approximated as a "cloud" of independent segments distributed within the volume of the coil. Thus, we consider implications of our results for the specific target search by DNA-binding proteins. For many proteins, this search consists of nonspecific binding events followed by sliding along DNA, and eventual unbinding followed by free diffusion in solution, after which the protein could rebind the DNA, and so these cycles of sliding and free diffusion in solution continue until the protein binds the specific target (reviewed in [4,7]). (Also, some proteins are capable of continuously transferring between two DNA segments due to presence of several DNA binding sites, but we are not considering them here.) The most difficult part for theoretical analysis of the searching process is spatial and temporal correlation between the binding events; thus, various approximations are used to simplify this analysis:

In some approaches (e.g., [4,7]), these correlations are simply omitted; i.e., after dissociation into solution protein is assumed to rebind DNA at random position. Within this approximation, DNA regions localized on DNA much farther from the specific target site than the typical sliding distance would behave as temporal "traps" randomly distributed over the whole volume (e.g., see analysis in [24]). Thus, according to these approaches, facilitation of the target search could be only due to DNA regions within the sliding distance from the target; the rest of the DNA could only delay the search. Thus, the approaches that do not take into account spatial correlation between the binding events cannot reveal facilitation of the search by the fragments localized substantially beyond the sliding distance.

In approaches used in [16] and further advanced in [30,31], correlations between binding events were addressed by solving the diffusion equation for cylindrical volumes surrounding straight DNA fragments, with additional modifications to extend these approaches to the coiled DNA. Although these approaches do take into account correlations between the binding events within their approximation for the DNA spatial arrangement, they still predict that remote DNA regions (i.e., localized much farther than the sliding distance from the target) could only delay the search, although in [30,31] it was shown that this delay could be substantially alleviated in the coiled DNA in comparison with the stretched DNA due to reduced oversampling of nonspecific binding sites.

In contrast, our approach, in which correlations between the binding events are described as diffusion between DNA fragments distributed in space with a certain concentration, predicts that isolated DNA fragments at certain conditions are capable of accelerating the search for the target by increasing the effective target size. In contrast to continuous transfer (which in principle could provide unlimited increase of the effective target size), the effects of isolated obstacles are limited by the volume concentration of the obstacles, which is typically small. However, for thin rodlike obstacles (e.g., DNA segments) the effects might be nonsmall even at small volume concentrations. Thus, it is feasible that effects of isolated obstacles upon the target search could be substantial, especially in crowded environments.

The contribution of these effect to the target search might be important in the cases when continuous transfer between nonspecific sequences and the specific target is either restricted or impossible, for example if the target and most of the nonspecific DNA are localized in different DNA circles connected via catenation (e.g., [18]), or if short DNA fragments are connected by flexible nonbinding linkers, like in dendrimers (e.g., [32]).

In additional to biological systems, the model for the specific target search in the presence of obstacles could be applicable to interactions in composite artificial media, for example in gels (e.g., [33–35]). In this case, the obstacles could be either the components of the gel (e.g., agarose or polyacrylamide polymer chains) or the nonspecific targets (e.g., DNA sequences without recognition sites) that co-localize in gel with the specific target.

An important question is whether the processes analyzed here could be described in term of the efficient diffusion coefficient. For diffusion with the coordinate-dependent diffusion coefficient the average shift of the particle position during infinitesimal time interval is proportional to the derivative of the diffusion coefficient upon coordinate, while the average squared shift is proportional to the diffusion coefficient itself. Thus, for the motion of the particle to be represented as diffusion with some effective coordinate-dependent diffusion coefficient, its average shift during infinitesimal time interval should be equivalent to the derivative of its average squared shift during this interval. We show that in the presence of binding this relationship between shifts holds only if the concentration of obstacles is constant; consequently, for nonconstant concentration of obstacles in the presence of binding the process cannot be represented as diffusion with some effective coefficient. This result is important for description of diffusion in inhomogeneous media.

APPENDIX A: ANALYSIS OF DEPENDENCE OF THE FIRST-PASSAGE TIME TO REACH THE TARGET UPON CONCENTRATION OF THE OBSTACLES

Since only terms I_1 [Eq. (90)] and I_2 [Eq. (91)] contain concentration of obstacles, for analysis concentration dependence we will consider only the sum of these terms:

$$I_1 + I_2 \sim \frac{1+\varepsilon\,\mathcal{C}_0}{1+q\,\mathcal{C}_0}\beta + (1+q\,\mathcal{C}_0)^{-\frac{\mu}{q}}. \tag{A1}$$

Here proportionality "∼" means that a positive multiplier that does not depend upon concentration $\mathcal{C}_0$ is omitted, and the parameter

$$\beta = \frac{\frac{b^3}{a_t}\left(1 - 1.5\frac{a_t}{b} + 0.5\frac{a_t{}^3}{b^3}\right)}{\left(\frac{1}{a_t}-\frac{1}{b}\right)(R^3-b^3)} \approx \frac{b^3}{R^3} \tag{A2}$$

is practically equivalent to the ratio of the volume of the domain that contains the obstacles to the whole volume.

From Eq. (A1)

$$\frac{d(I_1+I_2)}{d\mathcal{C}_0} \sim \frac{\mu}{(1+q\,\mathcal{C}_0)^2}\left[\frac{\varepsilon-q}{\mu}\beta - (1+q\,\mathcal{C}_0)^{1-\frac{\mu}{q}}\right]. \tag{A3}$$

[Here "∼" has the same meaning as in Eq. (A1).]

Let us analyze Eq. (A3) for various values of parameters μ, q, and ε. First, we note that in Eq. (A1), the first term contains the parameter β [Eq. (A2)], which is less than unity, while the second term is always greater than unity. Thus, the first term could have substantial contribution only if $\varepsilon > q$. Because of that, we will consider only the situation in which $\varepsilon > q$; i.e., $\varepsilon - q$ is positive.

In this case, for negative μ (i.e., when "reflection" upon collision predominates over sliding-mediated transfer) the Eq. (A3) is positive for all possible concentrations of obstacles; thus, the first-passage time to reach the target increases with the concentration.

For positive μ (i.e., when sliding-mediated transfer predominates over "reflection"), Eq. (A3) is positive, if

$$\frac{\varepsilon-q}{\mu}\beta - (1+q\,\mathcal{C}_0)^{1-\frac{\mu}{q}} > 0 \tag{A4}$$

and negative if

$$\frac{\varepsilon - q}{\mu}\beta - (1 + q\,\mathcal{C}_0)^{1-\frac{\mu}{q}} < 0. \tag{A5}$$

Since by definition $0 < \mathcal{C}_0 < 1$, and from Eq. (47) it follows that $\mu/q < 1$, then

$$1 < (1 + q\,\mathcal{C}_0)^{1-\frac{\mu}{q}} < (1 + q\,)^{1-\frac{\mu}{q}}. \tag{A6}$$

Consequently, from Eqs. (A4)–(A6) it follows that if

$$\frac{\varepsilon - q}{\mu}\beta < 1, \tag{A7}$$

then the first-passage time to reach the target decreases with concentration of the obstacles for all possible concentrations; if

$$\frac{\varepsilon - q}{\mu}\beta > (1 + q\,)^{1-\frac{\mu}{q}}, \tag{A8}$$

then the first-passage time to reach the target increases with concentration of the obstacles for all possible concentrations; and if

$$1 < \frac{\varepsilon - q}{\mu}\beta < (1 + q\,)^{1-\frac{\mu}{q}}, \tag{A9}$$

then the first-passage time has a maximum at the concentration

$$\mathcal{C}_{0(\max)} = \frac{1}{q}\left[\left(\frac{\varepsilon - q}{\mu}\beta\right)^{\frac{1}{1-\frac{\mu}{q}}} - 1\right]. \tag{A10}$$

Let us consider in more detail the case of "saturating" sliding, when the time τ_b during which the searching particle remained bound to the surface on an obstacle is long enough to "explore" the whole surface of the obstacle by means of sliding, so in the moment of dissociation the particle could be localized anywhere on the surface of the obstacle with equal probabilities. In this case, τ_b should be larger than the typical time a^2/D_s that is required to slide over the distance equivalent to the size of the obstacle. The diffusion coefficient on the surface of the obstacle (D_s) could be much smaller than the diffusion coefficient is solution (D) because of uneven energy landscape on the surface of the obstacle, and the superior hydrodynamic resistance for moving along the curved surfaces (e.g., see [36] and references therein). Thus, in this regime $\tau_b > a^2/D_s$ would be much greater than $\tau_0 \sim a^2/D$, and would have predominant contribution to the total time of delay τ_d.

This means that in this regime parameter $\varepsilon \sim \tau_d D/a^2$ is about or larger than the ratio D_s/D, which could be several orders of magnitude. Thus, parameter ε in the regime of saturating sliding is likely to be large. Since the parameter $\beta \approx (b/R)^3$ is small, and parameters μ and q in this regime are of the order of unity [see Eqs. (50) and (51)], in the regime of saturating sliding the conditions Eqs. (A7) and (A8) that define behavior of the system are primarily defined by the parameter

$$\gamma = \varepsilon\left(\frac{b}{R}\right)^3. \tag{A11}$$

If this parameter is small, then the first-passage time is decreased upon the increase of the concentration of obstacles, while when it is large, the first-passage time increases with the increase of the concentration of obstacles.

APPENDIX B: THE FIRST-PASSAGE TIME IN HOMOGENEOUS MEDIA WITH COORDINATE-DEPENDENT DIFFUSION COEFFICIENT VERSUS COORDINATE-INDEPENDENT DIFFUSION COEFFICIENT WITH SWITCHING BETWEEN MOBILE AND IMMOBILE STATES

First we the consider one-dimensional case. Consider a diffusing particle that starts movement from position x. After some time interval Δt the particle would move to a new position $x + \Delta x$. Then, the average time $\mathcal{T}_f$ that is required for the particle to reach a certain destination (usually referred to as the first-passage time) satisfies the equation

$$\mathcal{T}_f(x) = \langle \mathcal{T}_f(x + \Delta x)\rangle + \Delta t. \tag{B1}$$

Here $\langle\rangle$ designates the averaging over all possible values of Δx.

Upon expanding $\mathcal{T}_f(x + \Delta x)$ into Taylor series up to the terms of the second order of Δx (the terms of higher order of Δx could be ignored because they would produce infinitesimals of the higher order than Δt), Eq. (B1) produces a differential equation

$$\frac{\sigma^2}{2}\frac{d^2\mathcal{T}_f}{dx^2} + \upsilon\frac{d\mathcal{T}_f}{dx} + 1 = 0, \tag{B2}$$

where

$$\sigma^2 = \lim_{\Delta t \to 0}\frac{\langle(\Delta x)^2\rangle}{\Delta t}, \tag{B3}$$

$$\upsilon = \lim_{\Delta t \to 0}\frac{\langle\Delta x\rangle}{\Delta t}. \tag{B4}$$

To calculate σ^2 and υ, we consider the probability $\rho(\Delta x,\ \Delta t)$ that the particle at the time Δt is localized at the point $x + \Delta x$, provided that at the time $\Delta t = 0$, it was localized at the point x. This probability is described by the Smoluchowski equation, which for the one-dimensional case in the absence of external forces is

$$\frac{\partial\rho}{\partial(\Delta t)} = \frac{\partial}{\partial(\Delta x)}\left(\mathcal{D}\frac{\partial\rho}{\partial(\Delta x)}\right), \tag{B5}$$

with initial conditions

$$\rho(\Delta x,\ 0) = \delta(\Delta x), \tag{B6}$$

where $\mathcal{D}$ is the coordinate-dependent diffusion coefficient.

The average value of Δx

$$\langle\Delta x\rangle = \int_{-\infty}^{\infty}\rho\,\Delta x\,d(\Delta x). \tag{B7}$$

From Eqs. (B5) and (B7),

$$\frac{\partial\langle\Delta x\rangle}{\partial(\Delta t)} = \int_{-\infty}^{\infty}\frac{\partial\rho}{\partial(\Delta t)}\Delta x\,d(\Delta x)$$
$$= \int_{-\infty}^{\infty}\frac{\partial}{\partial(\Delta x)}\left(\mathcal{D}\frac{\partial\rho}{\partial(\Delta x)}\right)\Delta x\,d(\Delta x). \tag{B8}$$

Applying integration by parts, and taking into account that at infinitely large Δx the function ρ and all its derivatives approach zero, we obtain

$$\int_{-\infty}^{\infty} \frac{\partial}{\partial(\Delta x)}\left(\mathcal{D}\frac{\partial \rho}{\partial(\Delta x)}\right)\Delta x\, d(\Delta x) = -\int_{-\infty}^{\infty} \mathcal{D}\frac{\partial \rho}{\partial(\Delta x)} d(\Delta x) = \int_{-\infty}^{\infty} \frac{\partial \mathcal{D}}{\partial(\Delta x)}\rho\, d(\Delta x). \tag{B9}$$

Taking into account Eq. (B6),

$$\lim_{\Delta t\to 0}\int_{-\infty}^{\infty} \frac{\partial \mathcal{D}}{\partial(\Delta x)}\,\rho\, d(\Delta x) = \int_{-\infty}^{\infty} \frac{\partial \mathcal{D}}{\partial(\Delta x)}\delta(\Delta x) d(\Delta x) = \frac{\partial \mathcal{D}}{\partial(\Delta x)}(\Delta x = 0) = \frac{\partial \mathcal{D}}{\partial x}. \tag{B10}$$

Thus

$$\upsilon = \lim_{\Delta t\to 0}\frac{\langle \Delta x\rangle}{\Delta t} = \lim_{\Delta t\to 0}\frac{\partial\langle \Delta x\rangle}{\partial(\Delta t)} = \frac{\partial \mathcal{D}}{\partial x} = \frac{d\mathcal{D}}{dx}. \tag{B11}$$

(In the right part of the equation, we took into account that the diffusion coefficient depends only upon coordinate, so we replace the partial derivative with the usual one.) Similarly,

$$\frac{\partial\langle(\Delta x)^2\rangle}{\partial(\Delta t)} = \int_{-\infty}^{\infty}\frac{\partial\rho}{\partial(\Delta t)}(\Delta x)^2 d(\Delta x) = 2\int_{-\infty}^{\infty}\left(\mathcal{D} + \frac{\partial\mathcal{D}}{\partial(\Delta x)}\Delta x\right)\rho\, d(\Delta x) \tag{B12}$$

and

$$\sigma^2 = \lim_{\Delta t\to 0}\frac{\partial\langle(\Delta x)^2\rangle}{\partial(\Delta t)} = 2\int_{-\infty}^{\infty}\left(\mathcal{D} + \frac{\partial\mathcal{D}}{\partial(\Delta x)}\Delta x\right)\delta(\Delta x) d(\Delta x) = 2\mathcal{D}. \tag{B13}$$

Substituting Eqs. (B11) and (B13) in Eq. (B2), we obtain

$$\mathcal{D}\frac{d^2\mathcal{T}_f}{dx^2} + \frac{d\mathcal{D}}{dx}\frac{d\mathcal{T}_f}{dx} + 1 = 0 \tag{B14}$$

or, dividing by $\mathcal{D}$,

$$\frac{d^2\mathcal{T}_f}{dx^2} + \frac{d\ln\mathcal{D}}{dx}\frac{d\mathcal{T}_f}{dx} + \frac{1}{\mathcal{D}} = 0. \tag{B15}$$

(Here we substituted $\frac{1}{\mathcal{D}}\frac{d\mathcal{D}}{dx} = \frac{d\ln\mathcal{D}}{dx}$, which implies that the diffusion coefficient under the logarithm is defined up to some coordinate-independent multiplier to render the value under logarithm dimensionless.) In the special case of constant diffusion coefficient this equation produces

$$\frac{d^2\mathcal{T}_f}{dx^2} + \frac{1}{\mathcal{D}} = 0. \tag{B16}$$

Let us compare these results [Eqs. (B15) and (B16)] with behavior of the searching particle that could switch from a mobile state (designated by subscript f), to an immobile state (designated by subscript b) and back with rate constants k_+ and k_-, respectively. In the mobile state the diffusion coefficient is D, and in the immobile state the diffusion coefficient is zero. Importantly, in this case diffusion coefficient D is assumed to be independent of coordinate x, while k_+ and k_-, in the general case, could depend upon x. This system is formally equivalent to the case of very small searching particles and binders, in which coordinate shift of the searching particle during interaction with the binder is neglected, and, consequently, the only effect of the binding is the "lost time." Note that for this interpretation the switching rate constant k_+ is the product of the on-rate binding constant and the local concentration of the binders.

Again, we consider the searching particle starting in the unbound state at position x. During a small time interval Δt, the particle with probability $1 - k_+\Delta t$ remains in the unbound state and moves to the position $x + \Delta x$, or with probability $k_+\Delta t$ converts to the bound state at some position $x + \Delta x'$. Then

$$\mathcal{T}_f(x) = (1 - k_+\Delta t)\langle\mathcal{T}_f(x+\Delta x)\rangle + k_+\Delta t\langle\mathcal{T}_b(x+\Delta x')\rangle + \Delta t. \tag{B17}$$

Here the averaging is performed for all values Δx and $\Delta x'$, although the value $\Delta x'$ does not contribute to the final result (since it gets multiplied by Δt, thus producing a term of higher order relative to Δt), and could be ignored.

Expanding terms Eq. (B17) similarly to what was done for Eq. (B1), and taking into account that the diffusion coefficient does not depend upon coordinates in this case, we obtain

$$D\frac{d^2\mathcal{T}_f}{dx^2} + k_+(\mathcal{T}_b - \mathcal{T}_f) + 1 = 0. \tag{B18}$$

Once the particle is bound, it eventually converts back to the unbound state after the average "lost" time $1/k_-$. Thus

$$\mathcal{T}_b = \mathcal{T}_f + \frac{1}{k_-}. \tag{B19}$$

Substituting Eq. (B19) into Eq. (B18), we obtain

$$\frac{d^2\mathcal{T}_f}{dx^2} + \frac{K+1}{D} = 0, \tag{B20}$$

where $K \equiv k_+/k_-$. Note that in the general case K depends upon coordinate x.

From comparing Eqs. (B16) and (B20), it is seen that for the special case when K does not depend upon x, the diffusion accompanied by switching between the mobile and immobile stated could be described as diffusion without state switching with the effective diffusion coefficient

$$D_{\text{eff}} = \frac{D}{K+1}. \tag{B21}$$

However, if the above definition of the effective diffusion coefficient were applicable to the state-switching system in the case when K depends upon x, then, according to Eq. (B15), the state-switching system should be described by the equation

$$\frac{d^2\mathcal{T}_f}{dx^2} + \frac{d\ln\frac{D}{K+1}}{dx}\frac{d\mathcal{T}_f}{dx} + \frac{K+1}{D} = 0, \tag{B22}$$

while in fact it is described by Eq. (B20).

Thus, we conclude that in the general case behavior of the state-switching system is impossible to describe as diffusion with some effective diffusion coefficient. In general, if the first-passage time for a given process is described by the equation of the form

$$A\frac{d^2\mathcal{T}_f}{dx^2}+B\frac{d\mathcal{T}_f}{dx}+1=0 \qquad \text{(B23)}$$

(where A and B are some functions of x) this process could be described as diffusion with a certain effective diffusion coefficient only if A and B satisfy the equation

$$\frac{dA}{dx}=B. \qquad \text{(B24)}$$

The first-passage time for diffusion in the presence of binders is described by an equation of the type Eq. (B23), for which condition Eq. (B24) is not satisfied except for the special when A does not depend upon x, and B is zero.

For diffusion in the presence of external forces the function B in Eq. (B23) depends upon both the spatial derivative of diffusion coefficient and the external force field. Thus, if we would try to describe diffusion in the presence of binding by the effective diffusion coefficient, we also would need to add some "fictional" external field to compensate for the differences between $\frac{dA}{dx}$ and B.

Equations (B14) and (B15) can be generalized for three-dimensional movement. In this case

$$\frac{{\sigma_x}^2}{2}\frac{\partial^2\mathcal{T}_f}{\partial x^2}+\frac{{\sigma_y}^2}{2}\frac{\partial^2\mathcal{T}_f}{\partial y^2}+\frac{{\sigma_z}^2}{2}\frac{\partial^2\mathcal{T}_f}{\partial z^2}+\upsilon_x\frac{\partial\mathcal{T}_f}{\partial x}+\upsilon_y\frac{\partial\mathcal{T}_f}{\partial y}+\upsilon_z\frac{\partial\mathcal{T}_f}{\partial z}+1=0. \qquad \text{(B25)}$$

For three-dimensional diffusion in the absence of external forces the Smoluchowski equation

$$\frac{\partial\rho}{\partial(\Delta t)}=\frac{\partial}{\partial(\Delta x)}\left(\mathcal{D}\frac{\partial\rho}{\partial(\Delta x)}\right)+\frac{\partial}{\partial(\Delta y)}\left(\mathcal{D}\frac{\partial\rho}{\partial(\Delta y)}\right)+\frac{\partial}{\partial(\Delta z)}\left(\mathcal{D}\frac{\partial\rho}{\partial z}\right). \qquad \text{(B26)}$$

Parameters σ and υ in Eq. (B25) are defined similarly to Eqs. (B3) and (B4), for example

$$\upsilon_y=\lim_{\Delta t\to 0}\frac{\langle\Delta y\rangle}{\Delta t}=\lim_{\Delta t\to 0}\frac{\partial\langle\Delta y\rangle}{\partial(\Delta t)}=\lim_{\Delta t\to 0}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\frac{\partial\rho}{\partial(\Delta t)}\Delta y\, d(\Delta x)d(\Delta y)d(\Delta z). \qquad \text{(B27)}$$

Performing calculations similar to Eqs. (B8)–(B13), we obtain

$$\mathcal{D}\left(\frac{\partial^2\mathcal{T}_f}{\partial x^2}+\frac{\partial^2\mathcal{T}_f}{\partial y^2}+\frac{\partial^2\mathcal{T}_f}{\partial z^2}\right)+\frac{\partial\mathcal{D}}{\partial x}\frac{\partial\mathcal{T}_f}{\partial x}+\frac{\partial\mathcal{D}}{\partial y}\frac{\partial\mathcal{T}_f}{\partial y}+\frac{\partial\mathcal{D}}{\partial z}\frac{\partial\mathcal{T}_f}{\partial z}+1=0. \qquad \text{(B28)}$$

In the spherically symmetric case this is equivalent to

$$\mathcal{D}\left(\frac{d^2\mathcal{T}_f}{dr^2}+\frac{2}{r}\frac{d\mathcal{T}_f}{dr}\right)+\frac{d\mathcal{T}_f}{dr}\frac{d\,\mathcal{D}}{dr}+1=0 \qquad \text{(B29)}$$

or

$$\left(\frac{d^2\mathcal{T}_f}{dr^2}+\frac{2}{r}\frac{d\mathcal{T}_f}{dr}\right)+\frac{d\mathcal{T}_f}{dr}\frac{d\ln\mathcal{D}}{dr}+\frac{1}{\mathcal{D}}=0, \qquad \text{(B30)}$$

which corresponds to Eq. (96) of the main text.

APPENDIX C: DIFFUSION LIMIT FOR THE ON-RATE CONSTANT IN THE CASE OF ROD-SHAPED OBSTACLES

We present two approaches to obtain an approximation of the on-rate constant for thin rod-shaped particles: The first approach utilizes steady-state state distribution of the searching particles around an obstacle. The second approach estimates the rate constant from the probability for the single searching particle to "hit" the obstacle. Both approaches lead to Eq. (121) of the main text.

1. The first approach

In this case we represent the obstacle as a cylinder [Fig. 8(a)]. Let $c_s(r)$ be the concentration of the searching particle at the distance r from the obstacle. A steady-state distribution of concentration satisfies the equation

$$\nabla^2 c_s=0. \qquad \text{(C1)}$$

If the searching particle is close to the surface of the obstacle, the distribution of the searching particles would be approximately cylindrically symmetric, so Eq. (C1) is converted to

$$\frac{d^2c_s}{dr^2}+\frac{1}{r}\frac{dc_s}{dr}=0. \qquad \text{(C2)}$$

In the opposite case, when the distance r is much larger than the length of the obstacle $2a_l$, then the obstacle "looks like" a point object, so the distribution of concentration of the searching particles around it would be approximately spherically symmetric, so Eq. (C1) is converted to

$$\frac{d^2c_s}{dr^2}+\frac{2}{r}\frac{dc_s}{dr}=0. \qquad \text{(C3)}$$

Let us designate the solutions of Eq. (C2) and Eq. (C3) as c_{s1} and c_{s2}, respectively. Then

$$c_{s1}=A_{11}\ln r+A_{12}, \qquad \text{(C4)}$$

$$c_{s2}=\frac{A_{21}}{r}+A_{22}, \qquad \text{(C5)}$$

where A_{ij} are some constants. At some critical distance r_c (which is about the length of the obstacle) there would be a transition between the solutions Eq. (C4) and Eq. (C5). Thus, for continuity at the critical distance

$$c_{s1}(r_c)=c_{s2}(r_c), \qquad \text{(C6)}$$

$$\frac{dc_{s1}}{dr}(r_c)=\frac{dc_{s2}}{dr}(r_c). \qquad \text{(C7)}$$

"Unperturbed" concentration of the searching particle far away from the obstacle is

$$c_{s2}(\infty)=c_\infty \qquad \text{(C8)}$$

and on the surface of the obstacle

$$c_{s1}(a_{se}) = 0. \tag{C9}$$

From Eqs. (C4)–(C9) we obtain

$$c_{s1} = \frac{c_\infty}{1 + \ln \frac{r_c}{a_{se}}} \ln \frac{r}{a_{se}} \approx \frac{c_\infty}{\ln \frac{a_l}{a_{se}}} \ln \frac{r}{a_{se}}. \tag{C10}$$

(In the right-hand part of the equation we took into account that $r_c \sim a_l$, and $a_l/a_{se} \gg 1$.) The diffusion limit for the reaction rate is equivalent to the flux of the searching particles through the surface of the obstacle. Thus

$$k_{\text{onc}}\, c_\infty = 2\pi\, a_{se} 2a_l\, D \frac{dc_{s1}}{dr}(a_{se}). \tag{C11}$$

Substituting Eq. (C10) into Eq. (C11), we finally obtain

$$k_{\text{onc}} = 4\pi\, D \frac{a_l}{\ln \frac{a_l}{a_{se}}} \sim D \frac{a_l}{\ln \frac{a_l}{a_{se}}}, \tag{C12}$$

which is equivalent to Eq. (121) from the main text.

2. The second approach

For this approach, we represent the rod-shaped obstacle as a string of spherical beads [Fig. 8(b)] with the radius a_{se}, and the total number

$$n = \frac{2a_l}{2a_{se}} = \frac{a_l}{a_{se}}. \tag{C13}$$

We numerate the beads starting from the end of the obstacle and introduce the following notations:

$\omega_i(r_i)$ is the probability that the searching particle initially localized at the distance r_i from the bead number i will reach this bead before leaving the volume of the radius R ($R > r_i$) around the obstacle.

$\psi_i(r_i)$ is defined in the same way as $\omega_i(r_i)$ plus an additional requirement that the particle will reach the bead number i before it reached any of other beads within the obstacle.

u_{ij} is the probability that the searching particle initially localized on the bead number i will reach the bead number j before leaving the volume of the radius R around the obstacle. Since the distance between the beads within the same obstacle is much smaller than R, the distance R in this case could be assumed to be infinitely long, in which case u_{ij} is inversely proportional to the distance between the respective beads r_{ij} [37]:

$$u_{ij} \approx \frac{a_{se}}{r_{ij}}. \tag{C14}$$

In the case of the straight string of beads shown in Fig. 8, Eq. (C14) is equivalent to

$$u_{ij} \approx \frac{1}{|i-j|}. \tag{C15}$$

For $j = i$ we postulate that

$$u_{ii} = 1. \tag{C16}$$

The total probability Ψ that the searching particle hits the obstacle is the sum of probabilities of independent events that it hit any of the beads first:

$$\Psi = \sum_{i=1}^{i=n} \psi_i. \tag{C17}$$

The probability that the searching particle hits the obstacle is proportional to k_{onc} multiplied by the time that the searching particle would spend in the volume R. Thus, $k_{\text{onc}} \sim \Psi$ with some coefficient of proportionality that does not depend upon the shape or the size of the obstacle. Consequently, to evaluate k_{onc}, we have to evaluate Ψ. For that, we note that the sum of pathways that lead to hitting a given bead consists of all possible pathways, in which either this bead was hit first, or any other bead was hit first, and the given bead was hit after that. Thus

$$\omega_j = \sum_{i=1}^{i=n} \psi_i u_{ij}. \tag{C18}$$

By summation of Eq. (C18) over the j index we obtain

$$\sum_{j=1}^{j=n} \omega_j = \sum_{i=1}^{i=n} \psi_i \sum_{j=1}^{j=n} u_{ij}. \tag{C19}$$

From Eqs. (C15) and (C16), the sum

$$\sum_{j=1}^{j=n} u_{ij} = 1 + \sum_{j=1}^{j=i-1} \frac{1}{i-j} + \sum_{j=i+1}^{j=n} \frac{1}{j-i}$$
$$= 1 + \sum_{j=1}^{j=i-1} \frac{1}{j} + \sum_{j=1}^{j=n-i} \frac{1}{j} \approx \ln i(n-i). \tag{C20}$$

For large n, $\ln i(n-i)$ is roughly between $\ln n$ and $2\ln n$. Thus, for large n

$$\sum_{i=1}^{i=n} \psi_i \ln n < \sum_{i=1}^{i=n} \psi_i \sum_{j=1}^{j=n} u_{ij} < 2 \sum_{i=1}^{i=n} \psi_i \ln n. \tag{C21}$$

From that, we can approximate

$$\sum_{i=1}^{i=n} \psi_i \sim \frac{\sum_{i=1}^{i=n} \psi_i \sum_{j=1}^{j=n} u_{ij}}{\ln n}, \tag{C22}$$

where the proportionality coefficient is between 0.5 and 1. Thus, from Eqs. (C17), (C19), and (C22),

$$\Psi = \sum_{i=1}^{i=n} \psi_i \sim \frac{\sum_{j=1}^{j=n} \omega_j}{\ln n}. \tag{C23}$$

If the initial distances between the searching particle and the beads within the obstacle are much larger than the distances between beads within the obstacle, then we can neglect the differences in the initial distances between the searching particle and different beads within the obstacle, and assume that all these initial distances are equal to some distance r, that could be defined as a distance between the searching particle and the center of the obstacle.

In this approximation, all probabilities ω_j are the same and could be approximated by probability for an isolated bead [see the main text, Eq. (61)]:

$$\omega_j = a_{se}\left(\frac{1}{r} - \frac{1}{R}\right), \quad \text{(C24)}$$

and from Eqs. (B13), (B23), and (B24),

$$\Psi \sim \frac{na_{se}}{\ln n}\left(\frac{1}{r} - \frac{1}{R}\right) = \frac{a_l}{\ln\frac{a_l}{a_{se}}}\left(\frac{1}{r} - \frac{1}{R}\right). \quad \text{(C25)}$$

If the obstacle comprised one isolated bead, then Ψ would be defined by Eq. (C24), and, according to the Smoluchowski formula, k_{onc} would be proportional to $D\,a_{se}$. Thus, since the proportionality coefficient between k_{onc} and Ψ should not depend upon the shape and the size of the obstacle, for the rod-shaped obstacle we again arrive at

$$k_{\mathrm{onc}} \sim D\frac{a_l}{\ln\frac{a_l}{a_{se}}}. \quad \text{(C26)}$$

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