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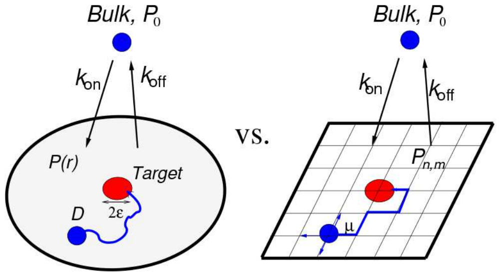
Surface-Assisted Dynamic Search Processes

Jaeoh Shin[†] and Anatoly B. Kolomeisky*[,†,‡]

[†]Department of Chemistry, Rice University, Houston, Texas 77005, United States

[‡]Center for Theoretical Biological Physics, Rice University, Houston, Texas 77005, United States



ABSTRACT: Many chemical and biological systems exhibit intermittent search phenomena when participating particles alternate between dynamic regimes with different dimensionalities. Here we investigate theoretically a dynamic search process of finding a small target on a two-dimensional surface starting from a bulk solution, which is an example of such an intermittent search process. Both continuum and discrete-state stochastic descriptions are developed. It is found that depending on the scanning length λ, which describes the area visited by the reacting molecule during one search cycle, the system can exhibit three different search regimes: (i) For small λ values, the reactant finds the target mostly via three-dimensional bulk diffusion; (ii) for large λ values, the reactant molecule associates to the target mostly via surface diffusion; and (iii) for intermediate λ values, the reactant reaches the target via a combination of three-dimensional and two-dimensional search cycles. Our analysis also shows that the mean search times have different scalings as a function of the size of the surface segment depending on the nature of the dynamic search regime. Search dynamics are also sensitive to the position of the target for large scanning lengths. In addition, it is argued that the continuum description underestimates mean search times and does not always correctly describe the most optimal conditions for the surface-assisted dynamic processes. The importance of our findings for real natural systems is discussed.

■ INTRODUCTION

In many natural and technological systems participating particles switch between spatial regions that are characterized by different geometries and dimensionalities. Examples include heterogeneous chemical catalysis when reacting molecules have to be absorbed to the solid catalysts before the reaction can take place,[1−3] transcription proteins finding the specific target sequences on DNA at the start of most major biological processes,[4−11] and viruses searching for membrane receptors to enter host cells.[2,12] Such complex processes with intermittent search dynamics have been intensively studied in recent years, but the molecular mechanism of underlying phenomena remains not well understood.[8−11,13−23]

One of the most intriguing fundamental issues for processes with intermittent search dynamics is the question of how such alternating behaviors of reactant particles modify and optimize the overall dynamics in the system. This has been widely discussed in the context of protein searches for targets on DNA,[8−10,14−16,22,24−28] where experimental observations suggest that some proteins can significantly increase the apparent association reaction rates to the target sequences. It has been argued first that such an acceleration is the result of the lowering of dimensionality when the protein alternates between the 3D bulk search and 1D nonspecific scanning along the DNA chain.[8,9] However, this view has been challenged, and it was suggested that faster effective association rates are due to the increased mobility of the protein molecules as a result of the nonspecific interactions between proteins and DNA molecules.[10,14]

Theoretical discussions have extended to systems where a small target is located on the 2D surface segment.[18,19,29−31] Recent in vitro experiments have shown that in the process of single-stranded DNA hybridization with a complementary DNA segment attached to the surface, reacting molecules employ a combination of bulk and surface diffusion, which enhances the association rate significantly.[32,33] It was also shown that the time to find the target depends on the physical−chemical properties of the surface.[33] This problem has been addressed theoretically before,[19,20,30] but the results are quite controversial. Theoretical models that neglect correlations in the rebinding of the molecules to the surface from the bulk predict a monotonic dependence of the search times on the dissociation rates,[20,30] while taking these correlations into account suggests that the search times are nonmonotonic.[19] Although existing theoretical studies[18−20,30] have clarified some aspects of the surface-assisted target search processes, there are several issues with these approaches. Theoretical calculations utilized only continuum methods, while it has been shown before for protein search phenomena that the continuum description leads to unphysical behavior at some limits.[14] In many systems, it is much more realistic to view the surface diffusion as a discrete hopping process. Furthermore, only symmetric cases with spherical surfaces bounding bulk volumes and symmetrically positioned targets have been considered so far, while experimental systems clearly deviate from these ideal

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geometries.[32,33] In addition, a full analysis of different search regimes has not been fully explored.

In this paper we present a comprehensive theoretical approach to describe the search process for the target, which is localized on a 2D surface, with the reacting species starting in the bulk solution around the surface segment. Both continuum and discrete-state stochastic methods are developed and compared with each other. We identified three major search regimes which are characterized by comparing the surface scanning length of the reacting molecules with the size of the surface segment. A full analytical description of the search dynamics is obtained for all ranges of parameters, which is also tested by extensive Monte Carlo computer simulations. In addition, the role of the surface segment size and the location of the target are evaluated.

METHODS AND RESULTS

Continuum Model. We will start our theoretical analysis with the simplest continuum description for the surface-assisted search process. In this model, the surface is viewed as a circle of radius R, and the target of radius ϵ is in the center of the circle, as shown in Figure 1. The particle can bind to the surface segment with a total adsorption rate k_{on} (the adsorption rate per unit area is $k_{on}/\pi R^2$), and it can be released back into the bulk solution with a desorption rate k_{off}. As expected, the adsorption rate is proportional to the concentration of the reactants. Here, to simplify calculations, we use a single-molecule description of the search process, i.e., the bulk region, which we consider to contain on average one searching molecule. However, the analysis can be easily extended to general bulk concentrations of reactant molecules, assuming that they are not interfering with each other, as typically is the case in many chemical and biological processes with intermittent search dynamics. The surface-bound reactant undergoes a diffusive motion along the surface with a diffusion constant D. We assume here that from the bulk the reactant can bind to any position (r, θ) on the surface segment with the same probability irrespective of the previous occupation site. This assumption is reasonable if the molecule diffuses very fast in the bulk solution (or the surface segment is quite small) so that the memory of the previously bound site on the surface is totally lost.

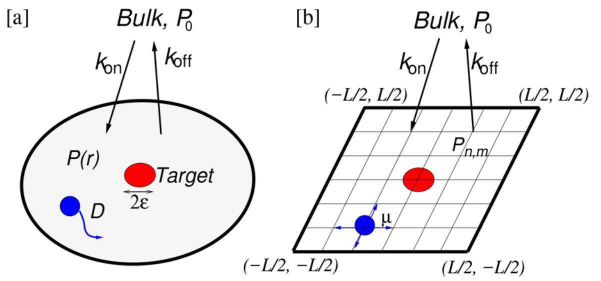

Figure 1. A schematic view of the search for a target on a surface: (a) a continuum description and (b) a discrete-state description. A reactant (shown in blue) is adsorbed to and desorbed from the surface with the rate k_{on} and k_{off}, respectively. On the surface, the reactant undergoes a surface diffusion with diffusivity D (continuum model) or a diffusive random walk with the rate μ (discrete-state model). A target (shown in red) has a size of radius ϵ (a) or occupies one lattice site (b).

Assuming that the reacting molecule starts in the bulk solution, we might calculate a mean search time T of finding the target for the first time by using a so-called flux-over population method.[34] In this approach, a steady-state situation is considered. It is assumed that as soon as the particle finds the target, a new particle is created in the bulk and the search process is repeated again. Knowing the steady-state flux J of the particles to the target, the search time is simply given by $T = 1/J$. One can define $P_0(t)$ as the probability of finding the reacting molecule in the bulk at time t, while $P(r, \theta, t)$ gives the probability density of finding the particle on the surface at the point (r, θ) at time t. The dynamics of the system are described then by the following master equations

$$\frac{\partial P_0(t)}{\partial t} = -\left(1 - \frac{\epsilon^2}{R^2}\right)k_{on}P_0(t) + k_{off}\int_{\epsilon}^{R} P(r, \theta, t)r\,dr\,d\theta + 2\pi\epsilon D\frac{\partial P(r, \theta, t)}{\partial r}\Big|_{r=\epsilon} \tag{1}$$

$$\frac{\partial P(r, \theta, t)}{\partial t} = -k_{off}P(r, \theta, t) + \frac{k_{on}}{\pi R^2}P_0 + D\Delta P(r, \theta, t) \tag{2}$$

where Δ is the Laplacian operator. In eq 1 the first term describes the negative flux to the surface but not to the target, the second term corresponds to the positive flux from the surface to the solution, and the last term is the contribution due to the flux into the target area from the surface that in the flux-over population method is assumed to go immediately into the solution. Similarly, in eq 2, the first term is the negative flux from the surface into the bulk solution, the second term is the positive flux from the bulk to the surface, and the last term corresponds to diffusional fluxes along the surface. At the stationary state, we have $\frac{\partial P_0(t)}{\partial t} = \frac{\partial P(r,\theta,t)}{\partial t} = 0$, and from now on we will consider only the steady-state quantities. Due to the symmetry of the system, $P(r, \theta) = P(r)$, i.e., it depends only on the radial distance r from the center of the circle and not on the angle. The boundary conditions are the following: $-D\frac{\partial P(r)}{\partial r}\big|_{r=R} = 0$ and $P(r)|_{r\le\epsilon} = 0$. The first condition is a reflecting boundary condition, and the second one assures that as soon as the reactant finds the target, it is adsorbed immediately. Finally, the total probability for the reactant molecule to be found anywhere in the system is conserved

$$P_0 + 2\pi\int_{\epsilon}^{R} P(r)r\,dr = 1 \tag{3}$$

These equations can be solved by assuming a solution in the form $P(r) = f(r) + C$, where C is a position-independent constant. By substituting this into eq 2 we obtain at the stationary state

$$0 = -k_{off}[f(r) + C] + \frac{k_{on}}{\pi R^2}P_0 + D\Delta f(r) \tag{4}$$

Now we require that the constant C be given by

$$\frac{k_{on}}{\pi R^2}P_0 = k_{off}C \tag{5}$$

This leads then to the following equation for the function $f(r)$

$$D\left[\frac{\partial^2 f(r)}{\partial r^2} + \frac{1}{r}\frac{\partial f(r)}{\partial r} - \frac{1}{\lambda^2}f(r)\right] = 0 \tag{6}$$

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where $\lambda \equiv (D/k_{\text{off}})^{1/2}$ is defined as a scanning length. The physical meaning of λ is that it is proportional to the average length that the reactant molecule diffuses on the surface after adsorption and before dissociating back into the bulk. Because this length describes the diffusional motion *after* binding to the surface, this quantity is independent of the association rate k_{on}. The general solution of eq 6 is $f(r) = A_1 I_0(r/\lambda) + A_2 K_0(r/\lambda)$, where $I_0(x)$ and $K_0(x)$ are the modified Bessel functions of the first kind and the second kind, respectively. The coefficients A_1 and A_2 can be determined from the boundary conditions. The final form of the probability function $P(r)$ can be written as

$$P(r) = C\left[1 - \frac{I_0(r/\lambda) + \frac{I_1(R/\lambda)}{K_1(R/\lambda)}K_0(r/\lambda)}{I_0(\epsilon/\lambda) + \frac{I_1(R/\lambda)}{K_1(R/\lambda)}K_0(\epsilon/\lambda)}\right] \tag{7}$$

with the constant C given by

$$C^{-1} = \pi(R^2 - \epsilon^2) + \frac{\pi R^2 k_{\text{off}}}{k_{\text{on}}} - \frac{2\pi\lambda\epsilon\left(\frac{I_1(R/\lambda)}{K_1(R/\lambda)}K_1(\epsilon/\lambda) - I_1(\epsilon/\lambda)\right)}{I_0(\epsilon/\lambda) + \frac{I_1(R/\lambda)}{K_1(R/\lambda)}K_0(\epsilon/\lambda)} \tag{8}$$

The expression for the probability to be found in the bulk, P_0, can be found from eqs 5 and 8 and is given as

$$P_0 = \frac{\frac{\pi R^2 k_{\text{off}}}{k_{\text{on}}}}{\pi(R^2 - \epsilon^2) + \frac{\pi R^2 k_{\text{off}}}{k_{\text{on}}} - \frac{2\pi\lambda\epsilon\left(\frac{I_1(R/\lambda)}{K_1(R/\lambda)}K_1(\epsilon/\lambda) - I_1(\epsilon/\lambda)\right)}{I_0(\epsilon/\lambda) + \frac{I_1(R/\lambda)}{K_1(R/\lambda)}K_0(\epsilon/\lambda)}} \tag{9}$$

The flux to the target region is equal to $J = k_{\text{on}}\left(\frac{\epsilon}{R}\right)^2 P_0 + 2\pi\epsilon D \frac{\partial P(r)}{\partial r}\big|_{r=\epsilon}$, which (using eqs 5, 7, and 8) can be rewritten as $J = k_{\text{on}}P_0 - k_{\text{off}}(1 - P_0)$. This expression has a simple physical meaning: the flux to the target is the difference between the total flux to the surface (including the target region) and the flux out of the surface (not including the target region). Finally, the mean search time can be calculated explicitly from $T = 1/J$. One should also note that similar results, although using a different method with somewhat more complex mathematical and physically less transparent expressions, have been obtained before.[18] However, our approach provides a very clear physical explanation of the intermittent search dynamics in the continuum description.

Mean search times to find the target on the surface in the continuum model are presented in Figure 2 for different kinetic parameters. We emphasize that the important dimensionless parameters that specify the dynamics in the system are ratios of the relevant lengths λ/ϵ and λ/R. The nonmonotonic dependence as a function of the scanning length λ is observed (see Figure 2a). The limit of $\lambda/\epsilon \ll 1$ describes the case where the reactant molecules are strongly repulsed by the surface and the search for the target is essentially three-dimensional with occasional bindings to the surface. In the opposite limit, when $\lambda/R \gg 1$, the reactant has a strong affinity to the surface, so it remains on the surface until the target is found. In this situation, the search is effectively two-dimensional. At the intermediate values of λ where $\epsilon < \lambda < R$ (where the attractive and repulsive interactions with the surface are not too strong), the particle undergoes a number of adsorption and desorption events, and when it is bonded to the surface it scans for the target. The search process is a combination of 2D and 3D motions. The continuum model thus predicts that this intermittent search regime minimizes the mean search time T for all sets of parameters. Increasing the association rate k_{on} reduces the mean search times, except for large scanning lengths λ, when the diffusion along the surface is a rate-limiting step (Figure 2a).

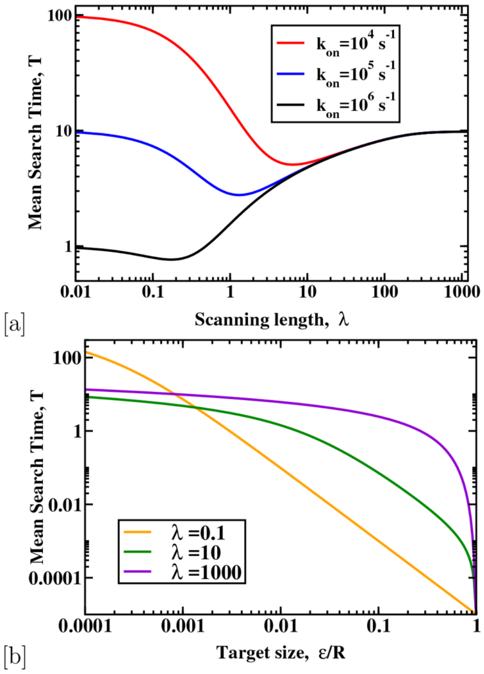

Figure 2. (a) Mean search time T as a function of the scanning length λ in the continuum model. The parameters utilized in calculations are $R = 1001/\sqrt{\pi}$, $\epsilon = 1/\sqrt{\pi}$, and $D = 10^5$ s^{-1}. (b) Mean search time T as a function of the target size ϵ for different scanning lengths. The following parameters were utilized in calculations: $R = 1001/\sqrt{\pi}$, and $D = k_{\text{on}} = 10^5$ s^{-1}.

Our results also indicate that the search process via 2D diffusion ($\lambda/R \gg 1$ limit) can be faster or slower than in 3D bulk diffusion ($\lambda/\epsilon \ll 1$), depending on the specific values of the kinetic rates. This observation contrasts with a widely expressed "belief" that reducing dimensionality should always accelerate the target search dynamics.[8,9] Clearly, the "lowering of dimensionality" is not the correct mechanism to describe intermittent search processes.

In addition, our theoretical calculations suggest that the search dynamics strongly depend on the size of the target ϵ. When $\epsilon = R$, i.e., the target covers the whole surface segment, as expected we obtain $P_0 = 1$ and $T = 1/k_{\text{on}}$. In the opposite limit, $\epsilon \to 0$, the mean search times increase without limit, as shown in Figure 2b. Similar behaviors have been observed also in the continuum models for the protein search for targets on DNA, and it seems to be unphysical in application to real phenomena.[14]

Discrete-State Stochastic Model. It is much more realistic to view the surface-assisted dynamic processes utilizing a discrete-state stochastic view, as presented in Figure 1b. This is because the position of the target and the locations of where the reactant molecules can be found at the surfaces are usually discretized. This is a consequence of the underlying structure of the surface segments.

So now we consider a discrete-state stochastic model where the surface is viewed as an $[(L + 1) \times (L + 1)]$ (L is even) square lattice segment along which the reactant molecule might undergo a random walk. The particle can bind from the bulk to any sites of the lattice with equal probability with a total rate k_{on} (the association rate per site is $k_{\mathrm{on}}/(L + 1)^2$). On the lattice, the particle can jump to one of its neighboring sites with the same rate μ, or it can dissociate into the bulk with the rate k_{off} (see Figure 1). There are four neighboring sites except at the boundary of the lattice (so the total jumping rate is 4μ). In the simplest symmetric case we assume that the target is located at the origin. It is important to note that the discrete-state stochastic model is a more general approach, and the continuum model results might be obtained in the limit when the scanning length is much larger than the target size, which we take as a unity.

Although we were not able to find the mean search times for general conditions in the system, our analysis, outlined below, provided exact formulas in the limit of $\lambda\left(\equiv\left(\frac{\mu}{k_{\mathrm{off}}}\right)^{1/2}\right) \ll 1$ and $\lambda \gg L$. In addition, we found an approximate description for the intermediate λ values, which shows an excellent agreement with Monte Carlo computer simulations.

First, we investigate all possible dynamic regimes in the discrete-state stochastic model of the surface-assisted search using computer simulations, and the results are presented in Figure 3. As in the continuum model, three dynamic phases are observed: (1) for short scanning lengths ($\lambda \ll 1$) the search is mostly 3D, as the reactant molecules can only bind and unbind to the lattice sites and cannot slide on the surface; (2) for very large scanning lengths ($\lambda \gg L$) the search is mostly 2D, as after the initial binding the particle will not dissociate until the target is found; and (3) for intermediate scanning lengths ($1 < \lambda < L$) the reactant molecule alternates between 2D and 3D motions in searching for the target, and multiple binding/unbinding events take place in this situation.

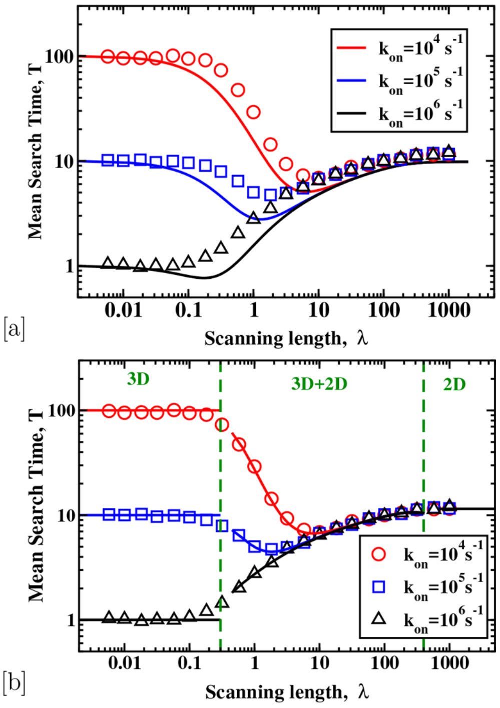

Figure 3. Mean search times T as a function of the scanning length λ for different association rates k_{on}. (a) Simulation data are shown as symbols, and solid lines are from the continuum model predictions. (b) The same simulation data as in panel (a) are shown, and the solid lines are from the discrete-state stochastic description. Vertical dashed lines show separations into three dynamic search regimes. The following parameters were utilized in calculations: $L = 1000$ and $\mu = 10^5$ s^{-1}.

To explain these observations, we decided first to apply the continuum model developed above with the parameters adjusted so that $(L + 1)^2 = \pi R^2$, $1/(L + 1)^2 = (\epsilon/R)^2$, and $\mu = D$. Surprisingly, although qualitative features are reproduced, the continuum description failed to agree quantitatively with computer simulations for the discrete-state stochastic model, as one would naively expect. The continuum model significantly underestimates mean search times in the surface-assisted search processes, and the largest deviations are found for the intermediate scanning lengths λ. In addition, there are conditions (e.g., for $k_{\mathrm{on}} = 10^6$ s^{-1} in Figure 3a) at which only the monotonic dependence of T versus λ is observed, and this result disagrees with the predictions of the continuum model that the fastest search is always at some specific intermediate scanning length.

We speculate that deviations between the predictions from the continuum and discrete-state models are related to the different symmetries of the systems. Radial symmetry is assumed in the continuum description, while quadratic surfaces are analyzed in the discrete-state stochastic approach and in the computer simulations. One can see (Figure 3) that even for large λ values both approaches do not fully agree, and the geometry of the surface is probably the main reason for this. However, discrete-state and continuum descriptions give the same predictions for $\lambda \to 0$. This can be explained in the following way. In this limit, the target can be reached only from the bulk. The fluxes can be written as $J_{\mathrm{cont}} = P_0 k_{\mathrm{on}}(\epsilon/R)^2$ and $J_{\mathrm{discr}} = P_0 k_{\mathrm{on}}(1/(L + 1))^2$ for the continuum and discrete-state models, respectively. However, because we assume that in both approaches targets occupy the same fraction of the surface, $1/(L + 1)^2 = (\epsilon/R)^2$, both fluxes are equal and the search times coincide.

To develop a better theoretical description, we turned to a method of first-passage processes[35,36] that was found to be successful in analyzing complex phenomena associated with the protein search for targets on DNA.[14,24,25] One can define $F_{n,m}(t)$ and $F_0(t)$ as probability density functions of reaching the target at the site (n_0, m_0) for the first time at time t if at $t = 0$ the reactant molecule started at the surface site (n, m) and in the bulk (subindex zero), respectively. The dynamic evolution of these probability functions is governed by backward master equations:[14,35,36]

$$\frac{\mathrm{d}F_0(t)}{\mathrm{d}t} = \sum_{n,m=-L/2}^{L/2} \frac{k_{\mathrm{on}}}{(L + 1)^2} F_{n,m}(t) - k_{\mathrm{on}} F_0(t) \tag{10}$$

$$\begin{aligned}\frac{\mathrm{d}F_{n,m}(t)}{\mathrm{d}t} &= \mu[F_{n-1,m}(t) + F_{n+1,m}(t) + F_{n,m-1}(t) \\ &\quad + F_{n,m+1}(t)] + k_{\mathrm{off}} F_0(t) - (4\mu + k_{\mathrm{off}}) F_{n,m}(t)\end{aligned} \tag{11}$$

The initial condition is $F_{n_0,m_0}(t) = \delta(t)$, which means that if the particle is at the target at $t = 0$ the process will end immediately. These equations can be conveniently written in the Laplace transformation language, $\tilde{f}(s) \equiv \int_0^\infty \exp(-st)\, f(t)\, \mathrm{d}t$, where s is the Laplace variable

$$(s + k_{on})\widetilde{F_0}(s) = \sum_{n,m=-L/2}^{L/2} \frac{k_{on}}{(L+1)^2}\tilde{F}_{n,m}(s) \tag{12}$$

$$\begin{aligned}(s + 4\mu + k_{off})\,\widetilde{F_{n,m}}(s) &= \mu[\widetilde{F_{n-1,m}}(s) + \widetilde{F_{n+1,m}}(s) + \widetilde{F_{n,m-1}}(s) \\ &\quad + \widetilde{F_{n,m+1}}(s)] + k_{off}\tilde{F}_0(s)\end{aligned} \tag{13}$$

The initial condition is now $\widetilde{F_{n_0,m_0}}(s) = 1$ in the Laplace domain.

Although we were not able to solve these master equations in general, full analytical solutions are possible for small scanning lengths $\lambda \ll 1$. In this case, the molecule is not moving on the surface, and we can assume that the diffusion rate is $\mu = 0$. Then, from eqs 12 and 13 it can be derived that

$$\widetilde{F_0}(s) = \frac{k_{on}(s + k_{off})}{(L+1)^2(s + k_{on})(s + k_{off}) - ((L+1)^2 - 1)k_{on}k_{off}} \tag{14}$$

This allows us to calculate explicitly the mean search time T in this dynamic regime

$$T = \int_0^\infty tF_0(t)\, \mathrm{d}t = -\frac{\partial \widetilde{F_0}(s)}{\partial s}\Big|_{s=0} = \frac{(L+1)^2}{k_{on}} + \frac{(L+1)^2 - 1}{k_{off}} \tag{15}$$

This result has a very clear physical interpretation: on average, the reacting molecule should make $(L + 1)^2$ bindings while scanning for the target and $(L + 1)^2 - 1$ dissociations from the surface into the bulk solution. The number of dissociations is one less than the number of associations because the final binding to the surface will be successful and the target will be found. We predict that the mean search times in this regime (3D search) become independent of the scanning length λ, which is in excellent agreement with computer simulations, as one can see from Figure 3b. Theoretical predictions start to deviate from computer simulations only for $\lambda > 0.3$ when the assumption of zero diffusion along the surface starts to break.

There is another dynamic regime which can also be fully analyzed. For $\lambda \gg L$ (effective 2D search), the reactant molecule will bind to the surface and it will not dissociate into the solution until the target is found. Then, the mean search time can be written as

$$T = \frac{1}{k_{on}} + \frac{1}{(L+1)^2}\sum_{n,m=-L/2}^{L/2} T_{n,m}{}^{(0)} \tag{16}$$

In this equation, the first term corresponds to the association to the surface. The second term is the average over all possible nontarget binding positions for the mean search time of finding the target, where $T_{n,m}{}^{(0)}$ is the search time without dissociation from the surface. The last contribution to T essentially describes a purely 2D search problem, which has been explicitly analyzed before,[37,38] and we can utilize the corresponding analytical expressions. As illustrated in Figure 3b, our theory perfectly describes the dynamic regime for large scanning lengths. In this regime, the mean search time will be also independent of the scanning length because as long as $\lambda \gg L$ the search dynamics depend only on the surface diffusion.

To explain the search dynamics in the regime for intermediate values of the scanning lengths $1 < \lambda < L$ (2D+3D search), we notice that every time the reactant molecule binds the surface, on average, it visits A lattice sites. Then, the mean number of search cycles before the target can be found can be estimated as $(L + 1)^2/A$, and we can write the expression for the mean search time, which is similar to eq 15, as

$$T = \frac{(L+1)^2}{A}\frac{1}{k_{on}} + \left[\frac{(L+1)^2}{A} - 1\right]\frac{1}{k_{off}} \tag{17}$$

The parameter A has been intensively investigated for random walk problems.[39−41] There are several approximate expressions for this quantity, and in this work we employ a simple approximation[40]

$$A(n) \simeq \frac{\pi n}{\ln(5.692n)} \tag{18}$$

where $n = 4\ \mu/k_{off} = 4\ \lambda^2$ is the number of steps that the reacting molecule makes on the surface segment during one adsorption period. Using this formula, the mean search time T is easily calculated, and the results are presented in Figure 3b. Excellent agreement with Monte Carlo computer simulations is observed, supporting the validity of our approximate theory. Note that this theory cannot be applied for $\lambda < 0.5$ because the approximation[39] works only for $n \geq 1$. This explains a small gap in the theoretical description of the mean search times, as shown in Figure 3b.

Now that we have a comprehensive theoretical description of all dynamic regimes in the surface-assisted target search, different properties of the system can be studied in more detail. Let us investigate first a dependence of the search times on the size of the surface segments L. The results of computer simulations, which are the same as analytical calculations as explained above, for different scanning lengths λ are presented in Figure 4. One can see that for $\lambda > L$ the mean search time scales as $T \sim L^2 \ln(L)$ (see Figure 4a). This is an expected result because in this dynamic regime the search is effectively two-dimensional, and the 2D search times have been asymptotically evaluated before.[39] A different scaling is observed in the 3D dynamic regimes when the scanning lengths are small ($\lambda < 1$). Here we find $T \sim L^2$. This is a consequence of the simple observation that due to the absence of memory in the system in this dynamic regime the reacting molecule must check on average $\sim L^2$ sites before finding the target. For intermediate values of $1 < \lambda < L$, our calculations predict a crossover behavior for the mean search times as a function of the surface segment size L: for small L we observe $T \sim L^2 \ln(L)$, which changes for large L into $T \sim L^2$.

Another interesting feature of the intermittent search process is the role of the target position on the surface segment. Up to now, we considered only the cases where the target was always at the center of the lattice. To examine how the mean search time T depends on the target position, the target is moved along the diagonal axis of the square lattice segment (see Figure 1b). Thus, the target is located at (m_0, m_0) with $0 \leq m_0 \leq L/2$. Figure 5 presents the changes in the mean search times as the target position is varied from the center of the surface segment to its boundary for different λ values. Our calculations show

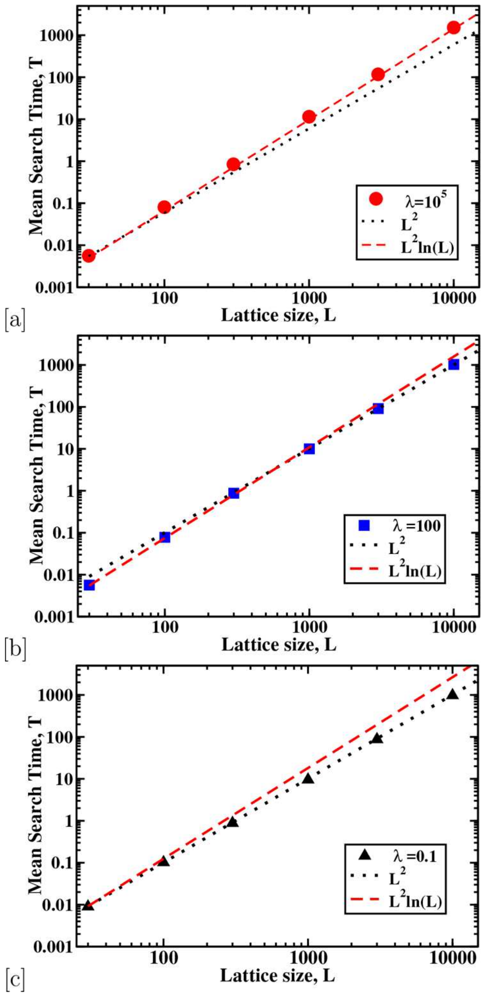

Figure 4. Mean search time T as a function of the lattice size L for different screening lengths λ. (a) $\lambda = 10^5$, (b) $\lambda = 100$, and (c) $\lambda = 0.1$. The following parameters were utilized in calculations: $\mu = k_{on} = 10^5$ s^{-1}.

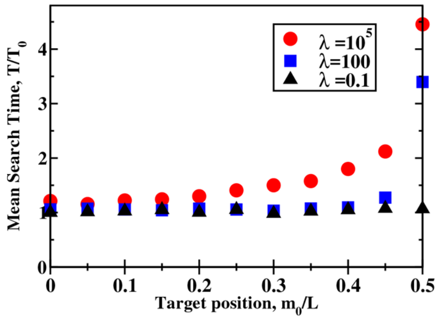

Figure 5. Normalized mean search times as a function of the normalized target position. The position of the target is moved along the diagonal points (m_0, m_0) with $0 \leq m_0 \leq L/2$. T_0 is the mean search time for a 3D search when the target is at the center of the lattice. The following parameters were utilized in calculations: $L = 1000$ and $\mu = k_{on} = 10^5$ s^{-1}.

that there is a dependence on the target position for large scanning lengths, while the search time is independent of the target location for small scanning lengths. For $\lambda > L$, the reactant molecule makes only one adsorption and the search is mostly two-dimensional. Then the mean search time depends on the average distance between the landing position of the reactant and the target site. This distance is smallest when the target is in the center of the segment and largest when the target is at the boundary. Thus, the mean search time grows as a function of the relative position of the target site, m_0/L, for large λ (see Figure 5). For $\lambda < 1$ the situation is different. The target is located via 3D search motions. In this case, the position of the target is not important at all (Figure 5). For scanning lengths $1 < \lambda < L$ the dynamic behavior is intermediate between these two limiting cases: some dependence on the target position is observed, and the magnitude of the effect is proportional to the scanning length λ and how close the target is to the border of the surface segment.

We speculate that this might be a strategy that nature utilizes to defend against viruses infecting healthy biological cells.[12] It is known that viruses associate to specific receptors on cell membranes before they can enter into the cells.[2] Typically these receptors are not uniformly distributed but are clustered together at specific locations, which in our language would correspond to putting the target in the middle of the surface segment and moving the target to the boundaries of the surface, respectively. Thus, the clustering of membrane receptors lowers the probability of viruses finding them, increasing the chances for the cell not to be infected. We also notice that our theoretical analysis can be applied to problems of molecular ligands searching for specific receptors on biological cells.[2]

■ SUMMARY AND CONCLUSIONS

We developed a comprehensive theoretical framework for understanding intermittent search phenomena that involve finding a target on a surface starting from the bulk solution. Two main theoretical approaches are presented here. First, the continuum model of the surface-assisted target search is analyzed, and the full analytical description is obtained. Our theoretical calculations suggest that the search dynamics strongly depend on the magnitude of the scanning length λ for the reactant molecule on the surface as well as on the relative size of the target region. The continuum model predicts that the most optimal search is realized for intermediate values of λ when there is a balance for the reacting molecule to be found at comparable times in the 2D and 3D regions. It is also argued that the "lowering of dimensionality" is not a valid mechanism for the intermittent search processes. Second, a more realistic discrete-state stochastic model for the surface-assisted target search is investigated using extensive Monte Carlo computer simulations and several analytical methods. Three dynamic regimes in the search process are identified depending on the relative values of the target size, scanning length, and the size of the whole surface. If the scanning length is much smaller than the target size (for the single-site target), then there is no sliding along the surface and the search is effectively three-dimensional. For very large scanning lengths (larger than the surface size), the reacting molecule after the initial association to the surface is involved only in a 2D surface search. For intermediate scanning lengths, the reactant molecule undergoes multiple cycles of binding to the surface, scanning the surface and dissociating into the solutions. Analytical calculations based on the method of first-passage times are performed in the regime of an effectively 3D search, and exact solutions are also obtained for an effectively 2D regime using known theoretical results for the surface search. For the intermediate 2D+3D regime, we developed an approximate description that takes into account the number of lattice sites scanned by the reactant molecule during each search cycle. Excellent agreements with computer simulation results are found in all regimes, suggesting that our theoretical methods correctly capture the molecular mechanisms of the intermittent search.

Our theoretical analysis also shows that the mean search times scale differently with the sizes of the surface segments, depending on the nature of the dynamic search regime. For the 2D search phase, the calculations suggest that $T \sim L^2 \ln(L)$, while for the 3D search regime we observe $T \sim L^2$. In the 2D +3D search regime, the crossover behavior interpolating between two limiting cases is observed. We also investigated the effect of the target position on the search dynamics. Again, it is found that the behavior is determined by the nature of the search regime. In the 2D search phase the dynamics are strongly influenced by the target position, while in the 3D search phase they become independent of the specific location of the target. In addition, it was argued that these results might be important for understanding the mechanisms of how viruses infect biological cells.

Furthermore, we compared the application of the continuum and discrete-state stochastic model for analysis of the systems to a surface-assisted target search. It is found that the application of the continuum model provides only a qualitative, not quantitative, description of the process. The mean search times calculated in the continuum model are significantly underestimated, and the largest difference is observed in the realistically most significant 2D+3D search regime. These arguments suggest that it is not reasonable to apply the continuum model framework for understanding the molecular mechanisms of the surface-assisted search phenomena, especially for quantitative analysis.[32,33] It is important to note also that the more general discrete-state stochastic analysis did not assume the radial symmetry of the problem, as was done for the continuum model, so that all main conclusions of our work remain generally valid for all symmetries.

Although our theoretical method is probably capturing most of the relevant dynamic properties of the complex processes associated with the surface-assisted target search, there are several important features that are not taken into account in our analysis. It is assumed that the probability of binding to any site on the surface is the same, which is reasonable for relatively small surface segments and/or very fast bulk solution diffusion. However, for some systems it is more realistic to consider very large surfaces and relatively slow diffusion in the 3D region, which leads to correlations in the dissociation and association positions of the reacting molecules. It seems that our method might be extended to investigate this phenomenon. Another complication that frequently takes place in real natural systems is the presence of other molecules that prevent free diffusion of the reactants. Such crowding effects might strongly affect the search dynamics, especially in biological systems.[26−28] It will be important to investigate these possibilities in more advanced theoretical and experimental studies. This will further clarify the molecular mechanisms of intermittent search processes.

AUTHOR INFORMATION

Corresponding Author

*E-mail: tolya@rice.edu.

ORCID

Anatoly B. Kolomeisky: 0000-0001-5677-6690

Notes

The authors declare no competing financial interest.

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