Intermittent search strategies

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This review examines intermittent target search strategies, which combine phases of slow motion, allowing the searcher to detect the target, and phases of fast motion during which targets cannot be detected. It is first shown that intermittent search strategies are actually widely observed at various scales. At the macroscopic scale, this is, for example, the case of animals looking for food; at the microscopic scale, intermittent transport patterns are involved in a reaction pathway of DNA-binding proteins as well as in intracellular transport. Second, generic stochastic models are introduced, which show that intermittent strategies are efficient strategies that enable the minimization of search time. This suggests that the intrinsic efficiency of intermittent search strategies could justify their frequent observation in nature. Last, beyond these modeling aspects, it is proposed that intermittent strategies could also be used in a broader context to design and accelerate search processes.

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CONTENTS

I. INTRODUCTION

A. General scope and outline

What is the best strategy for finding a missing object? Anyone who has ever lost keys has already faced this problem. This everyday life situation is a prototypical example of a search problem, which under its simplest form involves a searcher—a person, an animal, or any kind of organism or particle—in general able to move across the search domain and one or several targets. Even if it is schematic, the search problem as stated turns out to be a universal question, which arises at different scales and in various fields, and has generated an increasing amount of work in recent years, notably in the physics community.

Theoretical studies of search strategies can be traced back to World War II, during which the U.S. Navy tried to efficiently hunt for submarines and developed rationalized search procedures (Champagne *et al.*, 2003; Shlesinger, 2009). Similar search algorithms have since been developed and utilized in the context of castaway rescue operations (Frost and Stone, 2001), or even for the recovery of an atomic bomb lost in the Mediterranean Sea near Palomares in 1966. One example is the rescue of the Scorpion, a nuclear submarine lost near the Azores in 1968 (Richardson and Stone, 1971). At the macroscopic scale, other important and widely studied examples of search processes concern animals searching for a mate, food, or shelter (Charnov, 1976; O'Brien *et al.*, 1990; Bell, 1991; Viswanathan *et al.*, 1999; Bénichou *et al.*, 2006; Shlesinger, 2006; Edwards *et al.*, 2007), which will be discussed in more detail in this review. Even prehistoric migrations, apart from classical archaeological literature, have also been studied as a search problem, in which human groups search for new profitable territories (Flores, 2007). At the microscopic scale, search processes naturally occur in the context of chemical reactions, for which the encounter of reactive molecules—or, in other words, the fact that one searcher molecule finds a reactive target site—is a required first step. An obvious example is the theory of diffusion-controlled reactions, initiated years ago by the work of von Smoluchowski (1917) and developed by innumerable researchers [see, for instance, the review by Hanggi *et al.* (1990)]. More recently this field has regained interest in the context of biochemical reactions in cells, where the sometimes very small number of reactive molecules makes this first step of the search for a reaction partner crucial for the kinetics. Consider, for instance, reactions involved in genomic transcription, a representative example of which is the search for specific DNA sequences by transcription factors (Berg *et al.*, 1981; Von Hippel, 2007; Bonnet *et al.*, 2008; Gorman and Greene, 2008; Mirny, 2008).

In all these examples, the time needed to discover a target is a limiting quantity, and consequently minimization of this search time often appears as essential. In order to gain intuition into what could be an efficient search strategy on general grounds, let us go back to the everyday-life example mentioned above (see Fig. 1). We consider a searcher who lost a small object—for instance, a key—on a large sandy beach, where the key is so small that it cannot be detected if

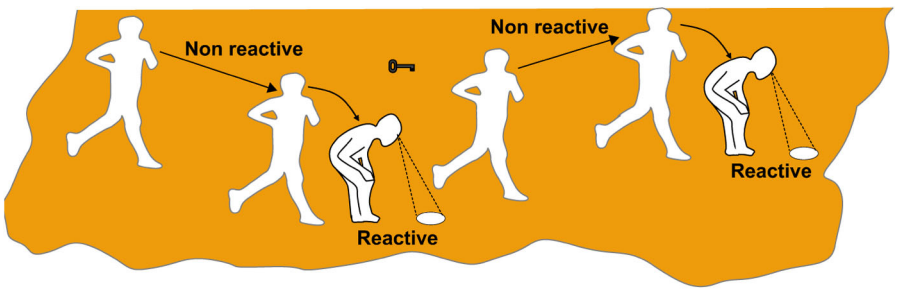


FIG. 1. Intermittent reaction paths illustrated by an everyday-life example of a search problem. The searcher looks for a target. The searcher alternates fast relocation phases, which are not reactive as they do not allow for target detection, and slow reactive phases, which permit target detection.

the searcher passes by too fast. In addition, we assume that the searcher has no prior information on the position of the key, except that the key is in a bounded domain (the beach). What is then the best strategy for the searcher to find the key as fast as possible? A first strategy consists in a slow and careful exploration (to make sure that the key will be detected upon encounter) of the sand all along the beach. In the case of a very large beach, the search time can then be very long. An alternative strategy consists in interrupting the slow and careful exploration of the sand by displacement phases, during which the searcher relocates on the beach very fast, but without even trying to detect the key (typically the searcher ''runs''). Hereafter the term ''intermittent search strategies'' is used for such processes that combine two distinct phases: a phase of slow displacement that enables target detection, and a phase of faster motion during which the target cannot be detected [note that the word ''intermittent'' has also been used recently by Bartumeus (2009) with another definition].

The efficiency of such intermittent strategies results from a trade-off between speed and detection and can be qualitatively discussed. Intuitively, the advantage of the fast relocation phases for the searcher is to reach unvisited regions. The drawback is, however, that during these phases time is consumed without any chance of detecting the target. Determination of the net efficiency of this strategy is therefore not trivial, and in recent years many works have focused on the following questions: (i) Can phases of fast motion that disable detection make the global search more efficient? (ii) If so, is there an optimal way for the searcher to share the time between the two phases? (iii) Are these intermittent search patterns relevant to the description of real situations?

The goal of this article is to review these works while giving explicit answers to these questions. More precisely, it is first shown that intermittent transport patterns are actually widely *observed* at various scales. At the macroscopic scale, this is, for example, the case of foraging animals (see Sec. II); at the microscopic scale, intermittent transport patterns are shown to be involved in the reaction pathway of DNA-binding proteins as well as in intracellular transport (see Sec. III). Second, generic stochastic models are used to show that intermittent strategies are *efficient* strategies that allow minimization of the search time (see Secs. II, III, and IV), and therefore suggest that this efficiency might justify their frequent observation in nature. Last, beyond these modeling aspects, it is proposed that intermittent strategies could also be used in a broader context to *design and accelerate* search processes.

B. General framework and first definitions

The search problem can take multiple forms (da Luz *et al.*, 2009); in this section we define more precisely the framework of this review—namely, random intermittent search strategies—and introduce the main hypothesis that will be made.

1. Searching with or without cues

Although in essence in a search problem the target location is unknown and cannot be found from a rapid inspection of the search domain, in practical cases there are often cues that restrict the territory to be explored or give indications of how to explore it. A classical example is chemotaxis (Berg, 2004), which keeps raising interest in the biological and physical communities [see, for example, Park *et al.* (2003), Kafri and Da Silveira (2008), and Tailleur and Cates (2008)]. Bacteria like *E. coli* swim with a succession of ''runs'' (approximately straight moves) and ''tumbles'' (random changes of direction). When they sense a gradient of chemical concentration, they swim up or down the gradient by adjusting their tumbling rate: When the environment is becoming more favorable, they tumble less, whereas they tumble more when their environment is degrading. This behavior results in a bias toward the most favorable locations of high concentration of chemoattractant, which can be as varied as, for example, salts, glucose, amino acids, or oxygen. Recently it has been shown that a similar behavior can also be triggered by other kinds of external signal such as temperature gradients (Maeda *et al.*, 1976; Salman *et al.*, 2006; Salman and Libchaber, 2007) or light intensity (Sprenger *et al.*, 1993).

Chemotactic search requires a well-defined gradient of chemoattractant and is therefore applicable only when the concentration of cues is sufficient. In contrast, at low concentrations cues can be sparse, or even discrete signals that do not allow for a gradient-based strategy. This is, for example, the case of animals sensing odors in air or water, where the mixing in the potentially turbulent flow breaks up the chemical signal into random and disconnected patches of high concentration. Vergassola *et al.* (2007) proposed a search algorithm, which they called ''infotaxis,'' designed to work in this case of sparse and fluctuating cues. This algorithm, based on a maximization of the expected rate of information gain, produces trajectories such as ''zigzagging'' and ''casting'' paths, which are similar to those observed in the flight of moths (Balkovsky and Shraiman, 2002).

This review focuses on the extreme case where no cue is present that could lead the searcher to the target. This assumption applies to targets that can be detected only if the searcher is within a given detection radius a which is much smaller than the typical extension of the search domain. In particular, this assumption covers the case of search problems at the scale of chemical reactions and, more generally, the case of searchers whose motion is independent of any exterior cue that could be emitted by the target.

2. Systematic versus random strategies

Whatever the scale, the behavior of a searcher relies strongly on its ability, or incapability, to keep memories of its past explorations. Depending on the searcher and on the space to be explored, this kind of spatial memory can play a more or less important role (Moreau *et al.*, 2009). In an extreme case the searcher, for instance, human or animal, can have a mental map of the exploration space and can thus perform a systematic search. Figure 2 presents several systematic patterns: lawn mower, expanding square, and spiral [for more patterns, see, for example, Champagne *et al.* (2003)]. These types of searches have been extensively studied, in particular, for designing an efficient search operated by humans (Dobbie, 1968; Stone, 1989).

In the opposite case where the searcher has low—or no—spatial memory abilities the search trajectories can be qualified as random, and the theory of stochastic processes

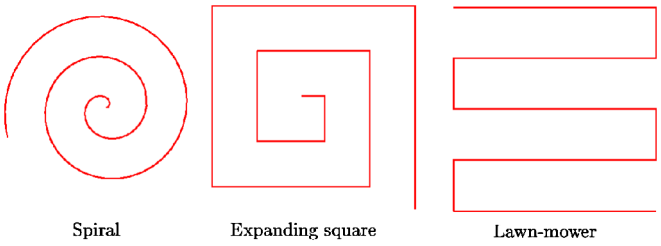


FIG. 2. Examples of patterns for systematic exploration of space.

provides powerful tools for their quantitative analysis (for a reminder on random walks, see Appendix A). This is obviously the case for "molecular" searchers at the microscopic scale that are subject to thermal Brownian motion, but also at larger scales of animals with low cognition skills. This review is mainly focused on random search problems, and effects of spatial memory will be discussed in the last section.

Note that we use the word "strategy" for animals with low cognitive abilities and even for molecules, although such searchers are not able to design strategies themselves since, of course, their dynamics are simply governed by the laws of physics. In the context of proteins searching for targets on DNA, we mean that the search time depends on parameters such as the ionic strength or the protein-DNA affinity, which, if varied, can lead to a minimization of the search time. In the case where the search kinetics is a limiting constraint, such good or even optimal values of these parameters might have been selected in the course of evolution. This very fact that physical parameters can be tuned (implicitly by evolution) to optimize a biological function is termed "strategy." Note, however, that the real optimization problem depends on many parameters and constraints. The models studied in this review are restricted to kinetic constraints, which can be dominant at both the microscopic and macroscopic scales, as discussed in Secs. II and III. This key assumption will be used throughout the review.

3. Framework

To summarize, this review focuses on intermittent search strategies for targets that emit no cue. The searchers will be assumed to have no (or low) memory skills, so that their trajectories are intermittent random walks. Depending on the example to be treated, different quantities can be used to assess the efficiency of search strategies, such as the energy necessary for reaching the first prey, the number of preys collected in a given time, or the time taken to encounter the first prey. In this review we discuss the efficiency of search strategies uniquely from a kinetic point of view. We mainly consider the mean first-passage time to a target as a quantitative measure of the search efficiency and study the minimization of this quantity. Note that the full distribution of the first-passage time is *a priori* needed to quantify the search kinetics on all time scales. However, in most of the situations considered in this review, it can be checked numerically that the distributions of the search time can be well approximated by an exponential, which means that the kinetics is fully characterized by the mean first-passage time.

II. INTERMITTENT SEARCH STRATEGIES AT THE MACROSCOPIC SCALE

Searching for a randomly located object is one of the most frequent tasks of living organisms, be it for obtaining food, a sexual partner, or a shelter (Bell, 1991). In these examples, the search time is generally a limiting factor that has to be optimized for the survival of the species. The question of determining the efficiency of a search behavior is thus a crucial problem of behavioral ecology, which has inspired numerous experimental (O'Brien *et al.*, 1989; O'Brien *et al.*, 1990; Bell, 1991; Kramer and McLaughlin, 2001) and theoretical (Viswanathan *et al.*, 1996; Viswanathan *et al.*, 1999; Bénichou *et al.*, 2005b; Bénichou *et al.*, 2006; Boyer *et al.*, 2006; Lomholt *et al.*, 2008) works. In this context, Lévy walk strategies have been proved to play a crucial role in such optimization problems. In this section, we first discuss why these Lévy walks are advantageous with respect to simple random walks when searching randomly, as first mentioned by Shlesinger and Klafter (1986). We recall the pioneering model of Viswanathan *et al.*, which has played a major role in the development of ideas on random search strategies. We also show how intermittent strategies are naturally involved as soon as hidden targets are considered and define a basic model relying on intermittent strategies, introduced to account for the search behavior of "saltatory" animals. This one-dimensional model is then extended to a bidimensional model, which is shown to be a minimal model optimizing the search time. Last, we discuss the relationships between these two main classes of search strategies—Lévy and intermittent—and return to the well-known "albatross story."

A. The Lévy strategies

1. The advantage of Lévy walks with respect to simple random walks

The ballistic phases interspersed with turns of animal trajectories have often been interpreted as Lévy walks (Viswanathan *et al.*, 1999; Viswanathan *et al.*, 2008). Actually, Shlesinger and Klafter (1986) first reported that, due to their weak oversampling properties (see Fig. 3), Lévy walks could be an efficient way to explore space and could be used to model, in particular, trajectories of foraging animals. In fact, the mean number of distinct sites visited in n steps—which is a measure of the territory explored—is known to behave for a standard random walk like n in dimension $d > 2$ and like $n^{d/2}$ if $d \leq 2$. This is less efficient in low dimensions than a Lévy walk, which has jump probability in dimension d of the form $p(r) \propto r^{-\beta-1}$ (where β is the index of the walk), for which the mean number of distinct sites visited in n steps behaves like n, as long as $\beta < d$. From the point of view of the territory extension explored after a given number of steps, the advantage of Lévy walk patterns over standard random walks is thus clear, and this effect turns out to be as strongly marked as the number of searchers involved in the process is high (Viswanathan *et al.*, 1996).

2. Optimizing the encounter rate with Lévy walks: How and when?

These observations led Viswanathan *et al.* (1999) to propose the following Lévy search model, in the presence

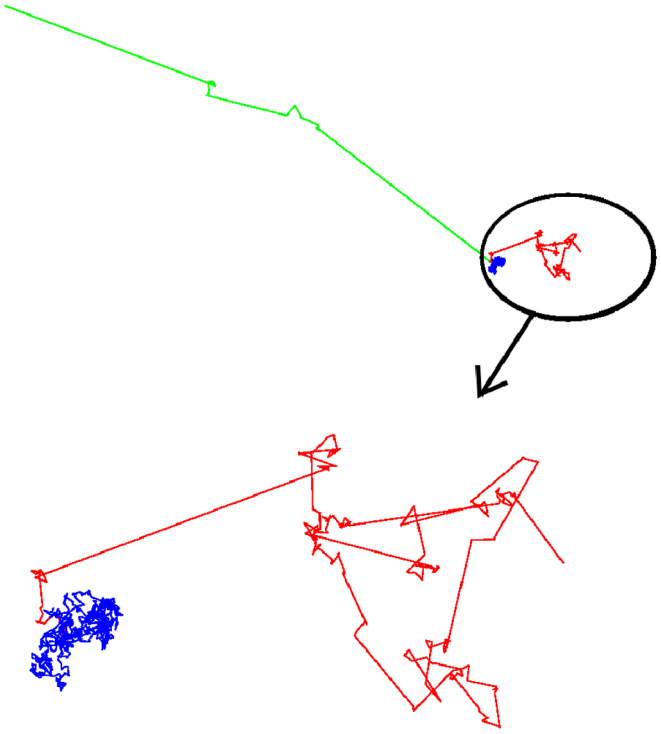


FIG. 3. Example of Lévy walks, with $\mu = 1.5$ (not present on the zoom), $\mu = 2$, and $\mu = 3$. The total path length is the same for the three examples.

of fixed targets randomly and sparsely distributed: Consider a searcher performing a ballistic step at constant speed and detecting targets closer than r_v. A target is found when the searcher encounters it for the first time. The step lengths are drawn from a Lévy distribution $p(l) \propto l^{-\mu}$, with $1 < \mu < 3$. For $\mu \leq 1$, the probability distribution is not defined. For $1 < \mu \leq 2$, the distribution has no mean and no variance. For $2 < \mu < 3$, the distribution has a mean but no variance. For $\mu \geq 3$, the distribution has both a mean and a variance; thus it obeys the central limit theorem: After enough steps, the probability distribution of the difference between the starting point and the last position is a Gaussian, as if the process were diffusion, with the mean square distance scaling linearly with time.

Viswanathan *et al.* (1999) are interested in the mean number of targets detected after a large observation time t. More precisely, they asked the following question: Is it possible to optimize this number with respect to the exponent μ characterizing the motion of the searcher? To answer, they actually considered two different types of target, which lead to two different optimal strategies.

(i) In the first case of what they call "revisitable targets"—meaning that, as soon as detected, a target reappears *at the same location*—they rely on a mean-field approximation of the problem and find that the encounter rate is optimized for a Lévy exponent $\mu \simeq 2$.

(ii) In the second case of "nonrevisitable targets" (or destructive search) where each target can be found only once or there is a single available target, the optimal strategy proposed by Viswanathan *et al.* (1999) is no longer of Lévy type, but reduces to a simple linear ballistic motion.

Several extensions of this pioneering model have been proposed. Bartumeus *et al.* (2002) studied the case of nonrevisitable moving targets. They showed that a Lévy strategy with $\mu = 2$ is often better than a "Brownian" one ($\mu \geq 3$). However, James *et al.* (2008) extended the study to ballistic motion, which outperformed these Lévy strategies.

An intermediate situation between revisitable and nonrevisitable targets has been studied by Raposo *et al.* (2003) and Santos *et al.* (2004). In these works, the immobile target is destroyed upon encounter, but regenerates after a time τ at the same place (for example, a plant bearing new fruits after previous fruits have been eaten). Two regimes are found. When τ is large [$> \tau_c$, a critical time evaluated by Raposo *et al.* (2003) and Santos *et al.* (2004)], the simple ballistic motion remains the best strategy. When $\tau < \tau_c$, the best μ is between 1 and 2. However, it could be argued that in this regime the simple strategy where the searcher does not move but waits for the renewal of the target outperforms a search for a hypothetical other target.

In the work of Bartumeus and Levin (2008), the targets are in patches (such as fish schools) or are Lévy distributed. Even if the targets are destroyed upon encounter, finding a target means that the presence of other targets in the vicinity is likely, which is close to the case of revisitable targets. Hence, as for revisitable targets, the optimum is achieved for a Lévy distribution, with $\mu \simeq 2$.

In the work of Reynolds and Bartumeus (2009), the optimum for destructive targets is $\mu \to 1$ except in two cases (where $1 < \mu^{\text{opt}} \leq 2$). On the one hand, the optimum is not ballistic when the searcher can fail in capturing a detected target. On the other hand, for targets destroyed upon encounter, and for the specific one-dimensional case, because the measure of efficiency is the number of targets captured during a long time, the searcher is after some time in a situation with a target close on one side, but the next target on the other side very far away: a pure ballistic motion is not favored because it can take the wrong direction.

Finally, in the case of revisitable targets and the related cases (regenerating targets, patches, failed capture), the Lévy strategy $\mu = 2$ emerges as a compromise between trajectories returning always to one and the same target zone, and straight ballistic motion, which is, indeed, the best way to explore space. Note, however, that, as stated above, in this case the strategy that consists simply in waiting for target renewal performs even better. In the case of nonrevisitable targets—the generic situation considered hereafter—the best strategy for the searcher is a mere ballistic motion without reorientations.

In all these Lévy walks models, the searcher is assumed to be able to detect targets all along its trajectory. Qualitatively, it corresponds to the case of targets "not too difficult" to detect. However, as it was the case with the example of the lost small key given in the Introduction, it is evident that in some situations the velocity degrades the perception. What happens if the targets are really "hidden," that is to say more precisely, if searching and moving are incompatible? In recent years, many works have been devoted to answering this question. Most of them rely on the following simple two-state model, historically

introduced to account for the search behavior of the "saltatory animals."

B. A basic model of intermittence

1. Observations: The case of saltatory animals

Anyone who has ever lost keys knows that an intermittent behavior combining local scanning phases and relocating phases is often adopted instinctively. Indeed, numerous studies of foraging behavior of a broad range of animal species show that such intermittent behavior is commonly observed and that the durations of search and displacement phases vary widely (O'Brien *et al.*, 1990; Bell, 1991; Kramer and McLaughlin, 2001). The spectrum, which goes from cruise strategy (for large fishes that swim continuously, such as tuna) to ambush or sit-and-wait search, where the forager remains stationary for long periods (such as a rattlesnake), has remained uninterpreted for a long time. As explained in the Introduction, the interest of this type of intermittent strategy, often referred to as "saltatory" (O'Brien *et al.*, 1990; Kramer and McLaughlin, 2001) in the context of foraging animals, can be understood intuitively when the targets are "difficult" to detect and sparsely distributed, as is the case for many foragers (such as ground foraging birds, lizards, planktivorous fish[1]): Since a fast movement is known to significantly degrade perception abilities (O'Brien *et al.*, 1990; Kramer and McLaughlin, 2001), the forager must search slowly. Then, it has to relocate as fast as possible in order to explore a previously unscanned space, and search slowly again.

Even though numerous models based on optimization of the net energy gain (Knoppien and Reddingius, 1985; O'Brien *et al.*, 1989; Anderson *et al.*, 1997) predict an optimal strategy for foragers, the large number of unknown parameters used to model the complexity of the energetic constraints renders a quantitative comparison with experimental data difficult. In the model presented in this section, the search time is assumed to be the relevant quantity optimized by the forager in order to obtain a sufficient daily amount of food and to precede other competing foragers. The energy cost is treated only as an external constraint that sets the maximal speed of the animal. As explained in the next sections, this purely kinetic model of target search captures the essential features of saltatory search behavior observed for foragers in experiments (Kramer and McLaughlin, 2001), when the predator has no information about the prey location.

2. Model

The central point of this schematic model (Bénichou *et al.*, 2005b) is that it relies on the explicit description of searching trajectories as intermittent. In the following it is assumed that the searcher displays alternately two distinct attitudes (see Fig. 4):

(i) A scanning phase, named phase 1, during which the sensory organs of the searcher explore its immediate vicinity. This phase is modeled as a "slow" diffusive movement (a continuous random walk with diffusion coefficient D). The target is found when this movement reaches the target location for the first time. As focusing and processing the information received by sensory organs require a minimum time, the scan phase cannot be too short, which implies a minimal mean time spent in this phase, $\tau_1^{\min}$.

(ii) A motion phase, named phase 2, during which the searcher moves "fast" and is unable to detect targets. These relocating moves are characterized by a ballistic motion (at constant velocity V). In the case of animals, there are usually correlations in the angles between two successive ballistic phases (O'Brien *et al.*, 1990). We limit ourselves here to the case of high correlations, which allow us to consider an effective one-dimensional problem for both phases, with phase 2 always in the same direction.

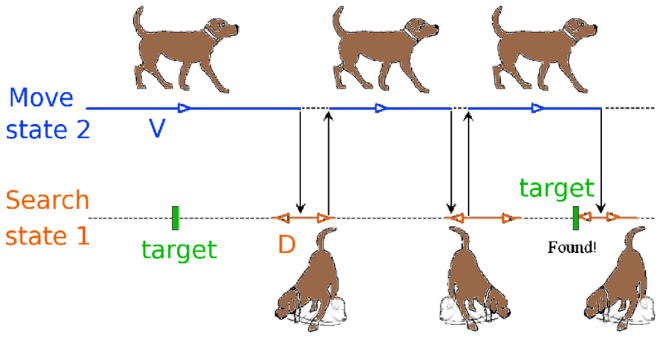


FIG. 4. Basic model for intermittent search.

Next, it is assumed that the searcher randomly switches from phase 1 (2) to phase 2 (1) with a fixed rate per unit time, λ_1 (λ_2), that is, with no temporal memory. It leads to exponentially distributed phase durations, in agreement with numerous experimental studies (Pierce-Shimomura *et al.*, 1999; Hill *et al.*, 2000; Fujiwara *et al.*, 2002; Li *et al.*, 2008), the mean duration of phase i being $\tau_i = 1/\lambda_i$. Last, the preys are assumed to be immobile (see Sec. V.D for a discussion of moving versus immobile targets).

3. Equations

We now evaluate the average time needed to find a target. The chosen geometry is a single target in $x = 0$ on a segment of size L with periodic boundary conditions. This geometry is equivalent to the case of regularly spaced targets or to the case of one target centered in a finite domain with reflective boundaries. L is thus the typical distance between targets, or the size of the search domain. The instantaneous state of the searcher can be described by its position x on the segment and by an index i, which specifies its motion: 1 corresponds to the slow detection phase, and 2 to the ballistic nonreactive phase. The survival probability $p_i(t, x)$ that, when the searcher starts at time $t = 0$ from x and in state i, the target has not yet been found at time t is known to satisfy the backward Chapman-Kolmogorov differential equations (Gardiner, 1996; Redner, 2001):

$$D\frac{\partial^2 p_1}{\partial x^2} + \frac{1}{\tau_1}[p_2(t,x) - p_1(t,x)] = \frac{\partial p_1}{\partial t}, \tag{1}$$

[1]Note that there are counterexamples such as birds of prey that can detect targets even at large velocities.

$$-V\frac{\partial p_2}{\partial x}+\frac{1}{\tau_2}[p_1(t,x)-p_2(t,x)]=\frac{\partial p_2}{\partial t}. \quad (2)$$

Since $t_i(x)$, the mean first-passage time at the target, starting from x in phase i, is given by

$$t_i(x)=-\int_0^\infty t\frac{\partial p_i(t,x)}{\partial t}dt=\int_0^\infty p_i(t,x)dt, \quad (3)$$

it is easily found from Eqs. (1) and (2) to satisfy

$$D\frac{d^2t_1}{dx^2}+\frac{1}{\tau_1}[t_2(x)-t_1(x)]=-1, \quad (4)$$

$$-V\frac{dt_2}{dx}+\frac{1}{\tau_2}[t_1(x)-t_2(x)]=-1. \quad (5)$$

These differential equations have to be completed by boundary conditions. Since we have periodic boundary conditions and the target at $x=0$ can be found only in state 1, we get $t_1(0)=t_1(L)=0$, $t_2(0)=t_2(L)$.

4. Results

The average search time $\langle t\rangle$ is defined as the average of $t_1(x)$ over the initial position x of the searcher, which is uniformly distributed over the segment $[0,L]$, as the searcher initially does not know the target's location. It is found to be given by Bénichou *et al.* (2005b):

$$\langle t\rangle=(\tau_2+\tau_1)\left(\frac{L}{2}\frac{(e^{\alpha+\beta}-1)\sqrt{1+4r}+(1+2r)(e^{\beta}-e^{\alpha})}{\sqrt{1+4r}(e^{\beta}-1)(e^{\alpha}-1)\tau_2V}-\frac{1}{r}-1\right), \quad (6)$$

with

$$r=\frac{\tau_2^2V^2}{D\tau_1}, \quad (7)$$

$$\alpha=\frac{L}{2}\left(-\frac{1}{\tau_2V}+\sqrt{\frac{1}{\tau_2^2V^2}+4\frac{1}{D\tau_1}}\right), \quad (8)$$

$$\beta=-\frac{L}{2}\left(\frac{1}{\tau_2V}+\sqrt{\frac{1}{\tau_2^2V^2}+4\frac{1}{D\tau_1}}\right). \quad (9)$$

In the limit of $L\gg V\tau_2,\sqrt{D\tau_1},D\tau_1/V\tau_2$, this simplifies:

$$\langle t\rangle\simeq\frac{L(\tau_2+\tau_1)(D\tau_1+2\tau_2^2V^2)}{2\tau_2V\sqrt{D\tau_1}\sqrt{D\tau_1+4\tau_2^2V^2}}. \quad (10)$$

Note that, because of intermittence, $\langle t\rangle\propto L$, whereas for diffusion alone the mean detection time is $t_{\rm diff}=L^2/12D$. Intermittence is thus favorable (meaning that the gain, defined as $t_{\rm diff}/\langle t\rangle$ is greater than 1), at least for L large enough.

Intermittence is favorable and the strategy can even be optimized. The mean search time is minimized for $\tau_1^{\rm opt}=\tau_1^{\rm min}$ and $\tau_2^{\rm opt}$, satisfying the relation [see Bénichou *et al.* (2005c) for details]

$$\tau_1^3+6\frac{\tau_1^2\tau_2^2}{\tau}-8\frac{\tau_2^5}{\tau^2}=0, \quad (11)$$

where $\tau=D/V^2$ is an extra characteristic time, depending on the searcher's characteristics. This minimum takes a simple form in two different regimes.

(i) If $\tau_1\gg\tau$, the minimum of the search time is for $\tau_1=\tau_1^{\rm min}$ and

$$\tau_2^{\rm opt}=\left(\frac{3\tau\tau_1^2}{4}\right)^{1/3}. \quad (12)$$

In this regime, denoted by "S" for "searching," one has $\tau_1>\tau_2$: The searcher spends more time scanning than moving.

(ii) If $\tau_1\ll\tau$, the minimum of the search time is for $\tau_1=\tau_1^{\rm min}$ and

$$\tau_2^{\rm opt}=\left(\frac{\tau^2\tau_1^3}{8}\right)^{1/5}. \quad (13)$$

In this regime, denoted by "M" for "moving," one has $\tau_1<\tau_2$, which means that the searcher spends more time moving than scanning.

5. Comparison with experimental data

These results have been compared to experimental data from O'Brien *et al.* (1990) and Kramer and McLaughlin (2001), who provided the average duration of detection and ballistic phases, characterizing the saltatory behavior of 18 different species, as various as planktivorous fish, ground foraging birds, and lizards. The optimal strategy obtained above is shown to account reasonably well for these data [see Fig. 5 and Bénichou *et al.* (2005b); Bénichou *et al.* (2005c); Bénichou *et al.* (2005d) for further details].

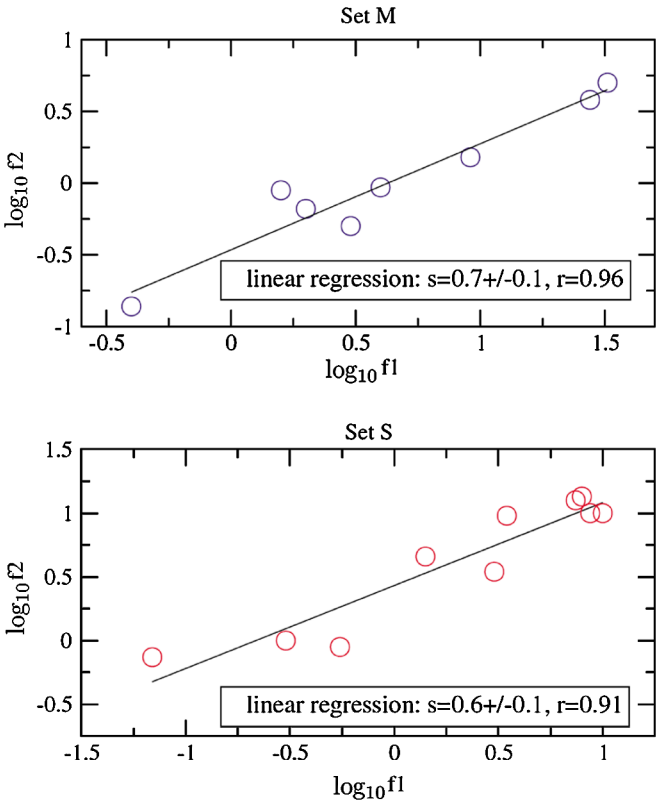


FIG. 5. Log-log plot of experimental data (O'Brien *et al.*, 1990; Kramer and McLaughlin, 2001; Bénichou *et al.*, 2005b) of saltatory search behaviors and their linear regression. Here $f_i=1/\tau_i$.

These results show that the saltatory patterns observed are a way to optimize the search, and that it is probably a reason why this type of pattern is observed so often, as it could have been favored by natural selection.

C. Two-dimensional intermittent search processes: An alternative to Lévy strategies

1. Motivation

The model of intermittent search presented previously was one dimensional, with ballistic phases infinitely correlated, in the sense that the direction taken is always the same. Here we present a model of intermittent search strategies in dimension 2 (Bénichou *et al.*, 2006; Bénichou *et al.*, 2007), which encompasses a much broader field of applications, in particular, for animal or human searchers. It is shown that bidimensional intermittent search strategies do optimize the search time for nonrevisitable targets, i.e., targets that are destroyed upon discovery (see Sec. II.A.2). The optimal way to share the time between the phases of nonreactive displacement and of reactive search is explicitly determined. Technically, this approach relies on an approximate analytical solution based on a decoupling hypothesis, which proves to reproduce quantitatively numerical simulations over a wide range of parameters.

2. Model

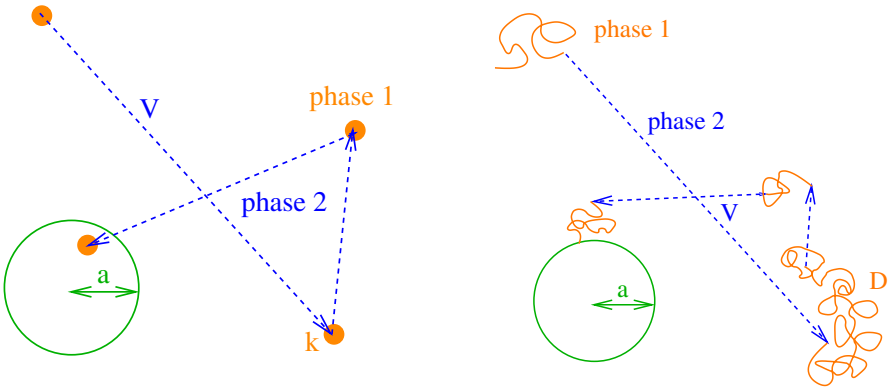
Following the previous model, we consider a two-state searcher (see Fig. 6) of position $\mathbf{r}$ that performs slow reactive phases (denoted 1), randomly interrupted by fast relocating ballistic flights of constant velocity V and random direction (phases 2). The duration of each phase i is assumed to be exponentially distributed with mean τ_i. As fast motion usually strongly degrades perception abilities, we consider again that the searcher is able to find a target only during reactive phases 1. The detection phase involves complex biological processes that we do not aim at modeling accurately here. However, we put forward here two modes of detection. The first one, referred to in the following as the "diffusive mode," corresponds to a diffusive modeling (with diffusion coefficient D) of the search phase as in the previous model, in agreement with observations for vision (Huey, 1968), tactile sense, or olfaction (Bell, 1991). The detection is assumed to be infinitely efficient in this mode: A target is found as soon as the searcher-target distance is smaller than the reaction radius a. On the contrary, in the second mode, denoted as the "static mode," the reaction takes place with a finite rate k, but the searcher is immobile during search phases. Note that this description is commonly adopted in reaction-diffusion systems (Rice, 1985) or operational research (Frost and Stone, 2001). A more realistic description is obtained by combining both modes and considering a diffusive searcher with diffusion coefficient D and finite reaction rate k. In order to reduce the number of parameters and to extract the main features of each mode, we study them separately by taking successively the limits $k \to \infty$ and $D \to 0$ of this general case. More precisely, in these two limiting cases, we address the following questions: What is the mean time it takes the searcher to find a target? Can this search time be minimized? And, if so, for which values of the average durations τ_i of each phase?

3. Basic equations

We now present the basic equations combining the two search modes introduced above in the case of a pointlike target centered in a spherical domain of radius b with reflexive boundary. Note that this geometry mimics both relevant situations of a single target and of infinitely many regularly spaced nonrevisitable targets. As in the previous model, the mean first-passage time to a target satisfies the backward equations (Redner, 2001) (see Sec. IV.B.2 for derivation):

$$D\nabla_{\mathbf{r}}^2 t_1 + \frac{1}{2\pi\tau_1}\int_0^{2\pi}(t_2 - t_1)d\theta_{\mathbf{V}} - k\mathrm{I}_a(\mathbf{r})t_1 = -1, \qquad (14)$$

$$\mathbf{V}\cdot\nabla_{\mathbf{r}} t_2 - \frac{1}{\tau_2}(t_2 - t_1) = -1, \qquad (15)$$



Static mode. The slow reactive phase is static and detection takes place with finite rate k.

Diffusive mode.The slow reactive phase is diffusive and detection is infinitely effcient.

FIG. 6. Two models of intermittent search: The searcher alternates slow reactive phases (regime 1) of mean duration τ_1 and fast nonreactive ballistic phases (regime 2) of mean duration τ_2.

where t_1 is the mean first-passage time starting from state 1 at position $\mathbf{r}$, and t_2 is the mean first-passage time starting from state 2 at position $\mathbf{r}$ with velocity $\mathbf{V}$, of direction characterized by the angle $\theta_{\mathbf{V}}$. Here $I_a(\mathbf{r}) = 1$ if $|\mathbf{r}| \leq a$ and $I_a(\mathbf{r}) = 0$ if $|\mathbf{r}| > a$. In the present form, these integro-differential equations do not seem to allow for an exact resolution with standard methods. We thus resort to an approximate decoupling scheme, which relies on the following idea. If the searcher initially starts in phase 2, and if the target is close, its initial direction matters. But as soon as the initial position is far from the target, there are numerous reorientations before finding the target, implying that the initial direction does not matter. Consequently, if $b \gg a$ and once the mean search time has been averaged over the starting position, the effect of the initial direction can be neglected. This allows us to make an approximation and solve the system [for more technical details, see Appendix B and Bénichou *et al.* (2006); Bénichou *et al.* (2007)].

4. Results for the diffusive mode of detection

For the diffusive mode of detection ($k \to \infty$), an analytical approximation for the search time can be obtained (see Appendix B). In the case of low target density ($a \ll b$), which is most relevant for hidden-target search problems, three regimes arise. In the first regime $a \ll b \ll D/V$, the relocating phases are not efficient and intermittence is useless. In the second regime $a \ll D/V \ll b$, it can be shown (see Appendix A.2.b) that the intermittence can significantly speed up the search (typically by a factor of 2), but that it does not change the order of magnitude of the search time. On the contrary, in the last regime $D/V \ll a \ll b$, the optimal strategy, obtained for

$$\tau_1^{\mathrm{opt}} \sim \frac{D}{2V^2}\frac{\ln^2(b/a)}{2\ln(b/a)-1}, \qquad \tau_2^{\mathrm{opt}} \sim \frac{a}{V}[\ln(b/a)-1/2]^{1/2}, \tag{16}$$

leads to a search time arbitrarily smaller than the nonintermittent search time when $V \to \infty$. Note that this optimal strategy corresponds to a scaling law

$$\frac{\tau_1^{\mathrm{opt}}}{\tau_2^{\mathrm{opt}}} \sim \frac{D}{a^2}\frac{1}{[2-1/\ln(b/a)]^2}, \tag{17}$$

which does not depend on V.

5. Results for the static mode of detection

We now turn to the static mode ($D \to 0$) (see Appendix B.1). In this case, intermittence is trivially necessary to find the target, and the optimization of the search time leads for $b \gg a$ to

$$\tau_{1,\min} = \left(\frac{a}{Vk}\right)^{1/2}\left(\frac{2\ln(b/a)-1}{8}\right)^{1/4}, \tag{18}$$

$$\tau_{2,\min} = \frac{a}{V}[\ln(b/a)-1/2]^{1/2}, \tag{19}$$

corresponding to the scaling law $\tau_{2,\min} = 2k\tau_{1,\min}^2$, which still does not depend on V.

6. Conclusion

This bidimensional two-state model of search processes for nonrevisitable targets closely relies on the experimentally observed intermittent strategies adopted by foraging animals. Using a decoupling approximation numerically validated, it can be analytically solved, allowing us to draw several conclusions. (i) The mean search time $\langle t \rangle$ presents a global minimum for finite values of the τ_i, which means that intermittent strategies constitute optimal strategies, as opposed to Lévy walks, which are optimal only for revisitable targets. (ii) The optimal τ_1^{opt} values obtained for two modes of detection are different and depend explicitly on D and k, leading to different scaling laws that are susceptible to discriminate between the two search modes. (iii) A striking and nonintuitive feature is that both modes of search studied lead to the same optimal value of τ_2^{opt}. As this optimal time does not depend on the specific characteristics D and k of the search mode, it seems to constitute a general property of intermittent search strategies. The robustness of these conclusions will be discussed further in Sec. IV in the framework of a more general model.

D. Should foraging animals really adopt Lévy strategies?

As seen before, intermittent strategies are an alternative to Lévy walks (defined in Sec. II.A) for interpreting trajectories of foraging animals. However, the Lévy walks are often thought to be optimal and widespread in nature. Is this really true?

1. The albatross story

Many foraging animals, including albatrosses, deer, and bumblebees to name a few, have long been thought to adopt Lévy strategies described in the pioneering work of Viswanathan *et al.* (1999). These foraging behaviors were repeatedly accounted for by stating in the more general framework of search processes that Lévy walks are optimal search strategies, as they constitute the best way to explore space. Recently Edwards *et al.* (2007) reanalyzed these data, completed by newly gathered data on foraging albatrosses, and showed that, in fact, there was no experimental evidence for the Lévy walk behavior.[2] This study questions the interpretation of several experimental works, but also raises a new important and puzzling question: Why do animals not adopt the Lévy walk strategy which has, however, been reported to be an optimal search strategy? Here we clarify this apparently paradoxical situation.

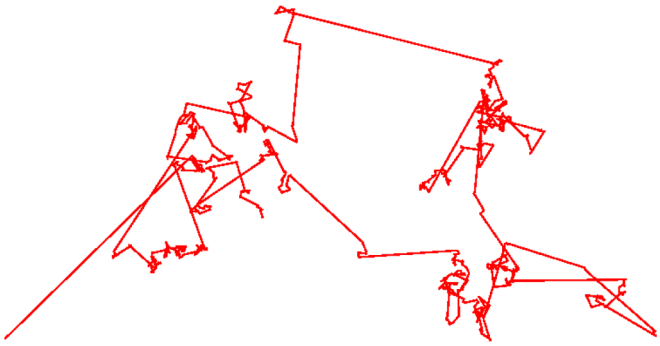
2. Do animals really perform Lévy walks?

As the optimality of Lévy strategies crucially requires conditions on the targets (regenerated at the same place,

[2]Albatrosses' behavior was followed by a humidity sensor on the birds. Flights were taken as the "dry" phases, interspersed with humid phases, when the birds touched the ocean. Very long "flights" eventually proved to be rest time, when the bird was in its nest. Once these misinterpreted dry phases were removed, the distribution of flights' durations is no longer a power law.

patched, or not easily captured) and conditions on the searcher (no switch when a target is found, which is a very simple form of memory), it cannot be taken as a general rule even if realistic for certain species. On the contrary, we argue that the general question of determining the best strategy for finding a single hidden target belongs to the situation of destructive search, where, in the framework of the Viswanathan *et al.* (1999) model, the most efficient way to find a randomly hidden target is simply a linear ballistic motion and not a Lévy strategy (see Sec. II.A). As a consequence, there is no paradox: The reason that Lévy walks are not observed in the work of Edwards *et al.* (2007) is probably because they do not constitute robust optimal search strategies.

And what about other experimental observations? Among experimental studies analyzing organisms' trajectories as a succession of segments interspersed with turns, an important proportion reports times between turns distributed exponentially [a list of examples, far from exhaustive: *C. Elegans* worm (Pierce-Shimomura *et al.*, 1999; Fujiwara *et al.*, 2002), fish (Hill *et al.*, 2000), plankton in some of the conditions studied by Bartumeus *et al.* (2003), amoebae (Li *et al.*, 2008), etc.]. However, apart from the controversial albatross study (Edwards *et al.*, 2007), there is a boom in articles claiming that Lévy behavior is observed for some animal species. Some of them can be dismissed as evidence of Lévy behavior. On the one hand, as explained in detail in Edwards *et al.* (2007), due to experimental limitations, most data cover only a very limited range, which makes difficult a reliable identification of power laws. On the other hand, patterns and processes should not be confused, as emphasized by Benhamou (2007). The same observed patterns can often be explained by different models. It is not because a trajectory is similar to Lévy walk trajectories that the underlying process is necessarily a Lévy walk. For example, a composite classical random walk can look very similar to a Lévy walk for a short enough time (see Fig. 7). Nonetheless, not all studies should be discarded, since limited studies neither prove nor rule out Lévy strategies. [See Viswanathan *et al.* (2008) for a review.] As underlined by Viswanathan *et al.* (2008), other selection pressures could be predominant. For example, when a target's location is known, exploitation could be optimized instead of search, and Lévy walks could emerge from interactions between the environment and the searcher [see Boyer *et al.* (2006), Santos *et al.* (2007), and Jiang *et al.* (2009)].



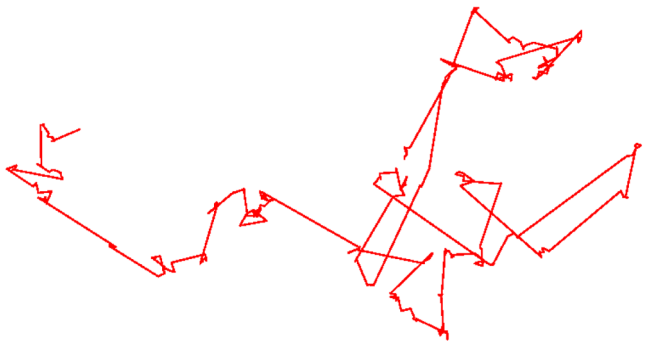


FIG. 7. Comparison between a Lévy walk and a composite random walk: They are not easy to distinguish at short time scales.

E. Conclusion on animal foraging

Lévy walks are a fashionable model for interpreting trajectories of foraging animals. However, on the one hand, there is controversy about at least some of the experimental data that were thought to support Lévy walks. On the other hand, the conditions in which Lévy walks are optimal are very restrictive. However, this does not rule out any contribution of Lévy statistics in the context of search processes. For example, as discussed by Lomholt *et al.* (2008) and in Sec. V.C.2, Lévy statistics can be advantageously used in the context of intermittent trajectories. Additionally, we argue that some animals cannot detect their target when they are moving ballistically, and, in fact, alternate these fast but blind phases with detection phases. The mean search time with intermittence can be smaller than with a detection phase alone, and it can be minimized by tuning the mean durations of each phase. Intermittent search strategies, because they rely on the experimental observation that speed degrades perception, and because they prove optimal and robust, are good candidates for interpreting animal trajectories.

III. INTERMITTENT SEARCH STRATEGIES AT THE MICROSCOPIC SCALE

It was shown in the previous section that intermittent search strategies are observed at the macroscopic scale. They are also observed at the microscopic scale. In the following, we focus on two examples: the localization by a protein of a specific DNA sequence and the active transport of vesicles in cells.

A. Protein-DNA interactions

1. Biological context

Various functions of living cells—and therefore at larger scales of living organisms—are regulated by coordinated chemical reactions between specific molecules, which are often present in only a few copy numbers. The importance of the kinetics of such search processes between reaction partners can be illustrated by the bacterial restriction and modification system (Wilson and Murray, 1991), which involves couples of methyltransferase and restriction enzymes

that recognize the same sequence on DNA [for example, *EcoRV* recognizes the sequence *GATATC* (Taylor and Halford, 1989)]. Methyltransferase enzymes methylate this specific sequence on the bacterial DNA in order to protect it from restriction enzymes, whose function is the opposite—to cut the DNA at this specific sequence. This function is first aimed at impairing any intruder viral DNA that enters the cell and that is very likely to contain the target sequence. Indeed, this sequence, typically 4–8 base pairs, is very short as compared to the viral genome, which, depending on the virus, can be made of 10^3–10^6 base pairs (typically 5×10^4 for bacteriophages). The infected bacterium then faces a vital search problem: Restriction enzymes must find their target sequence on the viral DNA reliably to inactivate the virus before it exploits the bacteria machinery and kills it.

More generally, it is well established that some sequence-specific proteins find their target site in a remarkably short time. For the *lac* repressor, for example, Riggs *et al.* (1970) measured association rates orders of magnitude larger than those expected for reactions limited by the classical three-dimensional diffusion [results confirmed by Hsieh and Brenowitz (1997) at different salt concentrations, ruling out electrostatic effects as the only explanation]. Halford (2009) argued that, in fact, only a few enzymes react significantly faster than the three-dimensional (3D) diffusion limit. However, this study underlined that many enzymes react at rates close to the diffusion limit, and that this observation is still impressive. Indeed, classical experiments are performed with a considerable excess of DNA, which is likely to contain sequences similar to the target sequence which therefore act as traps, slowing down the enzymes in their search. In a series of seminal articles, Berg *et al.* (1981), Winter and Von Hippel (1981), and Winter *et al.* (1981), proposed that 3D diffusion (or ''hopping'' or ''jumping'') was not the only motion available to the protein, even if no energy is consumed (unlike some enzymes, which consume energy to scan the DNA molecule sequentially). They suggested that, in some cases, proteins could bind nonspecifically to DNA due to a weak electrostatic interaction and diffuse along the chain in a process named sliding [see Von Hippel (2007) and Dahirel *et al.* (2009)] for more details on the weak electrostatic interaction). It was then argued that the combination of sliding and 3D diffusion, i.e., facilitated diffusion, can make the search for a sequence two orders of magnitude faster than 3D diffusion alone and henceforth sufficiently efficient [see also Adam and Delbruck (1968)].

This search mechanism actually can be classified as intermittent, in the general meaning defined in the Introduction. Indeed, on the one hand, three-dimensional diffusion off the DNA molecule is fast, but it does not allow for target detection. On the other hand, sliding is a phase of motion along DNA, which therefore enables target detection, but which is much slower due to a higher effective friction.

The pioneering studies on facilitated diffusion (Riggs *et al.*, 1970; Berg *et al.*, 1981; Winter *et al.*, 1981; Winter and Von Hippel, 1981) are based on ensemble measurements, which were for a long time the only way to experimentally access protein-DNA interactions. Recently developed techniques make possible the observation of this interaction at the level of a single molecule, with a resolution in space and time

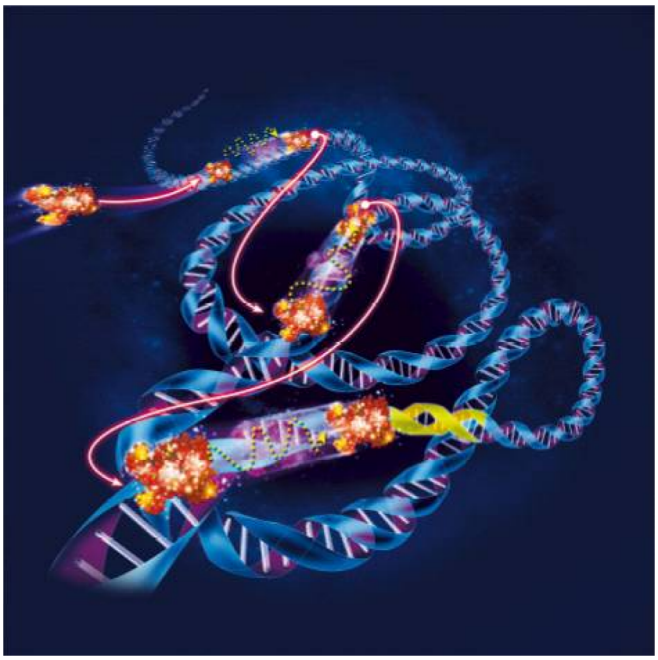


FIG. 8. Artistic view of a DNA-protein interaction, which combines one-dimensional sliding phases and three-dimensional relocation phases. From Virginie Denis, Pour la Science 352, February 2007.

still improving [for a review on the experimental results, see Gorman and Greene (2008)]. It is now confirmed directly that many proteins searching for a specific sequence on DNA combine hopping or jumping and sliding (see Fig. 8). Sliding phases have been clearly identified [both *in vitro* (Kabata *et al.*, 1993) and *in vivo* (Bakk and Metzler, 2004; Wang *et al.*, 2006; Elf *et al.*, 2007)], as well as hopping or jumping phases (Gowers *et al.*, 2005; Bonnet *et al.*, 2008; Komazin-Meredith *et al.*, 2008; van den Broek *et al.*, 2008).

With these new single-molecule experiments, theoretical models have bloomed too. First, we present here a stochastic approach to a simplified version of the problem, which shows that it is the intermittent nature of the trajectories that makes possible such high reaction rates. This minimal model permits one to calculate explicitly the mean search time for such intermittent reaction paths and shows that reactivity can even be optimized by properly tuning simple dynamic parameters of intermittent trajectories. Next, we discuss the different directions of extension of recent theoretical models.

2. Minimal model of intermittent reaction paths

We present here a simple model of intermittent reaction paths with minimal ingredients (Coppey *et al.*, 2004). We first define the model, then explain the main steps of the calculation, and eventually give the results.

a. Definition of the model

We consider a generic protein searching for its target site on a DNA molecule (see Fig. 9). The pathway followed by the protein, considered as a pointlike particle, is a succession of 1D diffusions along the DNA strand (sliding phases denoted phases 1) and 3D excursions in the surrounding solution

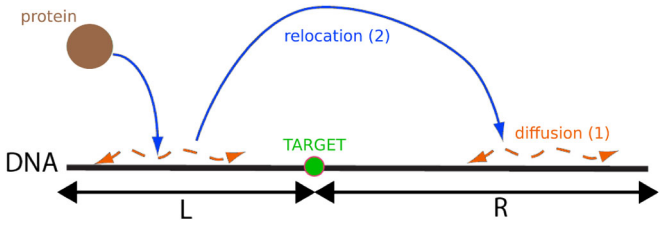


FIG. 9. A model of intermittent transport for DNA-protein interactions.

(denoted phases 2, during which the target is not accessible). In this minimal model we assume that the target site is a perfect reactive point of the DNA molecule, which means that reaction occurs as soon as the target is reached by the protein. Note that in this case the protein can find the target site only by diffusing along DNA, and therefore follows the scheme of intermittent search presented in the Introduction. The key quantity that we evaluate in this section is the search time, or reaction time, defined as the mean first-passage time (Redner, 2001; Condamin *et al.*, 2005a; Condamin *et al.*, 2005b; Condamin *et al.*, 2007; Condamin *et al.*, 2007; Condamin *et al.*, 2007; Bénichou and Voituriez, 2008; Condamin *et al.*, 2008) of the protein at the target, here denoted by $\langle T\rangle$. This quantity gives direct access in a mean-field approximation to the first-order reaction constant $K = 1/\langle T\rangle$ (Berg and Blomberg, 1976).

We now introduce further ingredients of the model. The time spent by the protein on DNA during each sliding phase is assumed to follow an exponential law with dissociation frequency λ_1. The probability density that the protein leaves the DNA at a random time t is then given by $\lambda_1 \exp(-\lambda_1 t)dt$, and the mean duration of a sliding event reads $\tau_1 = 1/\lambda_1$.

The one-dimensional motion on DNA during sliding phases 1 is modeled by a continuous Brownian motion with diffusion coefficient D. We assume that the ends of the DNA chain act on the protein as reflecting boundaries [see, for instance, Jeltsch and Pingoud (1998)], but in practice this assumption is unimportant for long DNA molecules. Moreover, the case of circular DNA, such as plasmids, is readily obtained by taking the particular case $L = R$. We next assume that the 3D excursions of phase 2 are uncorrelated in space. This means that, after dissociation from DNA, the protein will rebind the DNA at a random position independently of its starting position. This is justified when the DNA is in a random coil conformation, as in this case even short 3D excursions can lead to a long effective translocation of the linear position of the protein on DNA. We further assume that the probability density $P_{3D}(t)$ of the duration t of such 3D excursions is exponentially distributed, and write $P_{3D}(t) = \lambda_2 \exp(-\lambda_2 t)$. This assumption is justified, at least for the tail of the distribution, as long as the 3D excursions of the protein are confined in a closed volume, for instance, an experimental volume *in vitro* or *in vivo* the cell or a cell compartment. The mean time $\tau_2 = 1/\lambda_2$ spent in the surrounding solution in phase 2 can then be shown to be proportional to the confining volume (Kac, 1959; Blanco and Fournier, 2003; Bénichou *et al.*, 2005a; Condamin *et al.*, 2005a; ; Condamin *et al.*, 2007; Bénichou *et al.*, 2008).

We next introduce $P_{1D}(t|x)$, which is the conditional probability density that the protein, being on the DNA at position x and at time $t = 0$, will dissociate at time t before any encounter with the target site. We rewrite this quantity as

$$P_{1D}(t|x) = \lambda_1 \exp(-\lambda_1 t) Q(t|x), \tag{20}$$

where $Q(t|x)$ is the conditional probability density that the protein, starting from the position x, does not meet the target site during a single sliding event. The probability density $j(t|x)$ of the first passage to the target site position at time t without dissociation is then related to $Q(t|x)$ according to $Q(t|x) = 1 - \int_0^t j(t'|x)dt'$.

Last, we introduce $\bar{P}_{1D}(t|x)$, which is the conditional probability density that the protein, being on DNA at position x at time $t = 0$, will find the target site for the first time at time t within a single sliding phase 1, without leaving the DNA:

$$\bar{P}_{1D}(t|x) = \exp(-\lambda_1 t) j(t|x). \tag{21}$$

Given these quantities, we show below that the first-passage density of the protein to the target site, and consequently the reaction constant, can be calculated explicitly.

b. First-passage density

By calculating the first-passage density, we obtain the mean reaction time, as well as all associated moments. We assume that the protein starts at $t = 0$ in state 1 (bound to the DNA) at position x. We consider a generic event whose number of 3D excursions is $n - 1$, denote the duration of successive sliding phases $t_1, \ldots, t_n$, and denote the duration of successive 3D excursions $\theta_1, \ldots, \theta_{n-1}$. The probability density of such an event, for which the protein finds the target site for the first time at time $t = \sum_{i=1}^{n} t_i + \sum_{i=1}^{n-1} \theta_i$ is

$$\begin{aligned} P_n(t|x) = {} & \bar{P}_{1D}(t_n) P_{3D}(\theta_{n-1}) P_{1D}(t_n) \cdots P_{1D}(t_2) \\ & \times P_{3D}(\theta_1) P_{1D}(t_1|x), \end{aligned} \tag{22}$$

where $P_{1D}(t)$ and $\bar{P}_{1D}(t)$ are averaged over the initial position of the protein: $P_{1D}(t) = \langle P_{1D}(t|x)\rangle_x$ and $\bar{P}_{1D}(t) = \langle \bar{P}_{1D}(t|x)\rangle_x$. We denote by L the DNA length on the "left" side of the target site and by R the length on the "right" side of the target site. The average of a function f over the initial position x is given by $\langle f(t|x)\rangle_x \equiv \frac{1}{L+R} \int_{-L}^{R} f(t|x)\mathrm{d}x$.

To obtain the density of first passage to the target site $F(t|x)$, we sum over all possible numbers of excursions, and we integrate over all intervals of time, ensuring that $t = \sum_i^n t_i + \sum_i^{n-1} \theta_i$. The average over the initial position of the protein $F(t) = \langle F(t|x)\rangle_x$, can be expressed as follows:

$$\begin{aligned} F(t) = {} & \sum_{n=1}^{\infty} \int_0^{\infty} dt_1 \cdots dt_n d\theta_1 \cdots d\theta_{n-1} \\ & \times \delta\left(\sum_{i=1}^{n} t_i + \sum_{i=1}^{n-1} \theta_i - t\right) \times \left[\prod_{i=1}^{n-1} P_{3D}(\theta_i)\right] \\ & \times \left[\prod_{i=1}^{n-1} P_{1D}(t_i)\right] \bar{P}_{1D}(t_n). \end{aligned} \tag{23}$$

Taking the Laplace transform of $F(t)$, $\hat{F}(s) = \int_0^{\infty} dt e^{-st} F(t)$, we obtain

$$\hat{F}(s) = \langle \hat{j}(\lambda_1 + s|x)\rangle_x \left\{ 1 - \frac{1 - \langle \hat{j}(\lambda_1 + s|x)\rangle_x}{(1 + s/\lambda_1)(1 + s/\lambda_2)} \right\}^{-1}, \tag{24}$$

where $\hat{j}(s|x)$ is the Laplace transform of $j(t|x)$. This expression completely solves the problem for any 1D motion. We see next that the main quantities of physical interest can be extracted from this formula.

c. Optimal search strategy

The relevant quantity to describe the protein-DNA association reaction is the mean time $\langle T\rangle$ necessary for the protein to find the target site (see above). This mean time is obtained from the derivative of the first-passage density by the following relation:

$$\langle T\rangle = -\left(\frac{\partial \hat{F}(s)}{\partial s}\right)_{s=0}, \tag{25}$$

which combined with Eq. (24) gives

$$\langle T\rangle = \frac{1 - \langle \hat{j}(\lambda_1|x)\rangle_x}{\langle \hat{j}(\lambda_1|x)\rangle_x}\left(\frac{1}{\lambda_1} + \frac{1}{\lambda_2}\right). \tag{26}$$

This expression is general and holds for any 1D motion in the slow phase 1. Now, we calculate this quantity in the case where phase 1 is a free 1D diffusion. The one-dimensional Laplace transform of the first-passage probability density is well known [see Redner (2001)] and leads, after averaging over the starting position x to

$$\langle T\rangle = \left(\frac{1}{\lambda_1} + \frac{1}{\lambda_2}\right)\left\{ \frac{\sqrt{\frac{\lambda_1}{D}}(L + R)}{\tanh(\sqrt{\frac{\lambda_1}{D}}L) + \tanh(\sqrt{\frac{\lambda_1}{D}}R)} - 1 \right\}, \tag{27}$$

where D is the diffusion coefficient. This defines as a by-product the association constant of the reaction as $K = 1/\langle T\rangle$. Two initial comments are in order. (i) First, as soon as the length of the DNA strand is large enough (more precisely, as soon as $\sqrt{\lambda_1/D}L \gg 1$ or $\sqrt{\lambda_1/D}R \gg 1$), $\langle T\rangle$ grows linearly with the length of the DNA. This mirrors the efficiency of intermittent reaction paths, as compared to the quadratic growth obtained in the case of pure sliding. In particular, the boundary effects are negligible for this quantity as soon as the overall length is large enough. (ii) Second, this expression is valid for a large class of 3D motions. More precisely, it holds as soon as the mean first return time τ_2 corresponding to the 3D motion is finite and independent of the departure and arrival points.

We now come to an important question recently addressed by Coppey *et al.* (2004) and Slutsky and Mirny (2004), which concerns the *optimization* of such intermittent reaction paths. We assume here that the mean search time is a limiting quantity that might have been minimized in the course of evolution. In this context, we consider $\lambda_1 = 1/\tau_1$, which characterizes the protein-DNA affinity, as the adjustable parameter. Indeed, this quantity depends strongly both on the structure of the protein and on physiological conditions such as the ionic strength, and therefore could widely vary from one protein to another. In contrast, $\lambda_2 = 1/\tau_2$ depends mostly on the properties of the environment, such as the DNA conformation, which is itself subject to very stringent constraints and therefore much less likely to be varied. Another adjustable parameter is the 1D diffusion coefficient D. Optimization of the search time with respect to this parameter is trivial: It is found that D should be as large as possible (assuming that D and λ_1 are independent), but obviously one should keep in mind that D is controlled by the hydrodynamic radius of the protein, which cannot be too small. For these reasons we focus here on λ_1.

It can be seen qualitatively that $\langle T\rangle$ is large for both λ_1 very large (in the limit of infinite λ_1, the protein is never on the DNA) and λ_1 very small (the pure sliding limit which gives a quadratic growth with the DNA length), and could therefore be minimized for an intermediate value of λ_1. The sign of the derivative of the mean search time at $\lambda_1 = 0$ shows that it can indeed be minimized provided that

$$\lambda_2 > 15D\frac{L^2 + R^2 - LR}{L^4 + R^4 + 4LR(L^2 + R^2) - 9R^2L^2}. \tag{28}$$

This condition means that bulk excursions, to be favorable, should be shorter than a fraction of the typical time needed to scan the full DNA molecule by 1D diffusion. In particular, it requires that the DNA length is long enough. If this condition is satisfied, the search time can indeed be minimized (see Fig. 10). A careful analysis of the implicit equation satisfied by λ_1 at the optimum leads to the following expansion for large $\ell = L + R$:

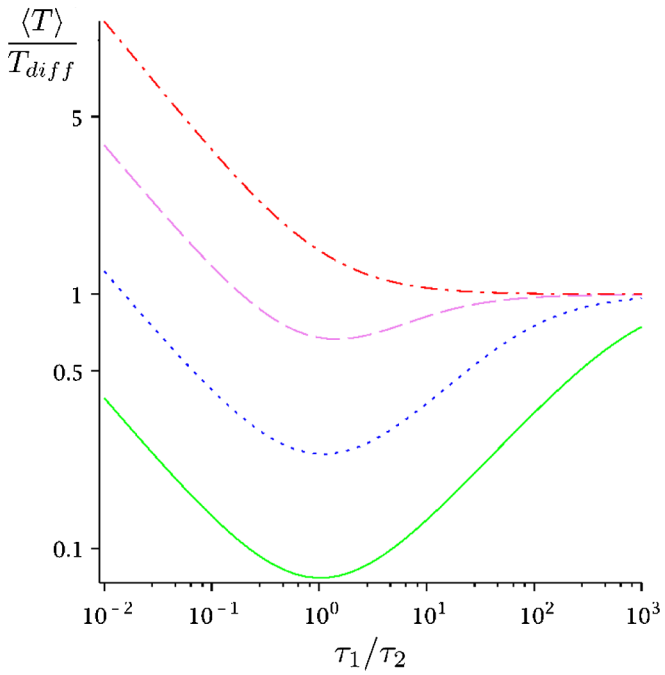


FIG. 10. Mean first-passage time of a DNA-binding protein to its target site, renormalized by the mean first-passage time by diffusion alone ($T_{\rm diff}$), as a function of τ_1/τ_2. $T_{\rm diff}/\tau_2 = 1$ (dash-dotted line), $T_{\rm diff}/\tau_2 = 10$ (dashed line), $T_{\rm diff}/\tau_2 = 100$ (dotted line), and $T_{\rm diff}/\tau_2 = 1000$ (solid line). For a small DNA length ℓ (and therefore small $T_{\rm diff}$) (dash-dotted line), the reaction constant depends monotonically on τ_1 and intermittent reaction paths are inefficient. For larger values of ℓ (other curves), the reaction rate can be optimized as a function of τ_1. Here we averaged over the initial position of the target.

$$\lambda_1 = \lambda_2 - 4\frac{\sqrt{D\lambda_2}}{\ell} - \frac{8D}{\ell^2} - \frac{40D^{3/2}}{\sqrt{\lambda_2}\ell^3} + O\left(\frac{1}{\ell^4}\right). \tag{29}$$

Equations (28) and (29) refine the result of Slutsky and Mirny (2004), which predicts that the optimal strategy is realized when $\lambda_1 = \lambda_2$. This result actually holds in the large-ℓ limit, or more precisely for $\sqrt{\lambda_1/D}\ell \gg 1$. For intermediate values of ℓ, boundary effects become important and the minimum can be significantly different.

The $\langle T\rangle$ value at the minimum is particularly interesting. We compare it to the case of pure sliding where $\langle T_s\rangle = \ell^2/3D$:

$$\frac{\langle T\rangle}{\langle T_s\rangle} = \frac{6}{\ell}\sqrt{\frac{D}{\lambda_1}}. \tag{30}$$

The efficiency of the 3D mediated strategy is therefore much more important when the DNA chain is long. For example, using standard values for λ_1 (a few 10^{-2} s) and D (typically 10^{-2} μm^2/s) and for a DNA substrate of length 10^6 base pairs (bp), the mean reaction time is three orders of magnitude smaller than for a pure sliding strategy. Beyond the importance of such results for understanding the kinetics of gene transcription, this first minimal model shows that intermittent reactive paths are indeed very efficient, and that they can even allow optimization of the reaction kinetics.

3. Toward a more realistic modeling

The model introduced above provides a simple way to discuss the minimization of the search time. Further approaches have been developed to model target search by proteins. We present below the main models used in the literature and discuss their relevance to real target search problems by proteins in cellular conditions.

a. Main approaches

Generally speaking, theoretical models of facilitated diffusion rely on the basic assumption that the protein alternates phases of 1D diffusion along the DNA and phases of free diffusion when the protein is desorbed from the DNA. The existence of two such distinct states, whose dynamics is usually characterized by association-dissociation rates, is supported by direct experimental observations as discussed above. Additionally, molecular dynamics simulations taking into account the electrostatic interaction between the negatively charged DNA and the locally positively charged protein [see, for example, Dahirel *et al.* (2009) and Florescu and Joyeux (2009)] have shown that these two states naturally arise on the basis of the electrostatic interaction only, suggesting the robustness of the facilitated diffusion mechanism. Such studies at the molecular scale could serve as a tool to calculate the association-dissociation rates used in the models of facilitated diffusion discussed in this section, which all take into account effectively only the molecular interactions.

i. Stochastic modeling. The minimal model presented in Sec. III.A.2 relies on the statistical analysis of the trajectory of a single protein and can henceforth be qualified as a stochastic model. Similar stochastic methods have been used and complemented in Lomholt *et al.* (2005), Eliazar *et al.* (2007), Lomholt *et al.* (2007), Eliazar *et al.* (2008), Bénichou *et al.* (2009), Lomholt *et al.* (2009), and Meroz *et al.* (2009)), and have the advantage, when solvable, of giving access to the full distribution of the search time, yielding refined information on the search kinetics. Moreover, they can be adapted in some cases to take into account anomalous transport in both the 1D and 3D phases, as discussed below.

ii. Kinetic approach. The main alternative to the stochastic approach is given by what can be called kinetic models, which assume a steady-state homogeneous concentration of proteins, in contrast with the single-protein description of stochastic models. Such models therefore rely on a mean-field approximation, which proves to be efficient evaluating the mean search time thanks to scaling arguments. A first example is given by Halford and Marko (2004), where scaling arguments are used to roughly estimate the time for the protein to find the DNA coil, and then the time to find the target inside the coil, which eventually yields an optimal sliding length. More generally, the key ingredient of kinetic models, developed mainly by Hu and Shklovskii (2006), Hu *et al.* (2006), and Hu *et al.* (2008), is that the system is assumed to be in a stationary state. Under this hypothesis, the flux of particles delivered by the 3D diffusion into the sphere of influence of the target, whose size is defined as the "antenna length" ξ_a, must be equal to the flux of particles delivered by 1D diffusion into the target. Such a balance equation generically reads

$$J \sim D_3 c_{\text{free}} \xi_a \sim D_1 c_{\text{ads}}/\lambda_a, \tag{31}$$

where the concentrations of free (c_{free}) and adsorbed (c_{ads}) proteins are assumed to be at equilibrium, i.e., satisfying $c_{\text{free}}/c_{\text{ads}} = K$ with K the equilibrium constant associated with the association-dissociation rates. It is important that the antenna length, defined as the typical scale below which the dominant transport is sliding instead of 3D diffusion, has size ξ_a when measured in 3D space, but takes another value λ_a when measured along the DNA. Making assumptions on the DNA conformation (for instance, random coil or fractal globule), different scaling laws between λ_a and ξ_a can be proposed. Equation (31) then permits one to determine ξ_a and henceforth to give the scaling of the mean search time $1/J$. The advantage of this method is that it permits, through the relation between λ_a and ξ_a, various models of DNA conformation to be taken into account, which is much harder to achieve in the stochastic approach. Such models, whose results are compatible with the stochastic approach, provide in addition a useful picture of facilitated diffusion. Indeed, in these models the effect of sliding can be seen as effectively making the target of the size of the antenna length, which is much larger than the real target size, and therefore speeding up the search.

Finally, these two approaches are quite complementary and both require as an input the modeling of 1D and 3D phases. The minimal model of Sec. III.A.2 describes the 1D phase as regular diffusion, while 3D phases are assumed to result in completely random relocations over the DNA. Beyond this minimal model, the specific description of these two phases has motivated numerous works and many refinements have been discussed in the literature. We review in the next

sections the main models that have been proposed to provide a more realistic description of 1D and 3D phases.

b. Descriptions of the 1D phase (sliding and recognition)

i. Anomalous diffusion in the sliding phase. As stated above, the phase of one-dimensional nonspecific interaction of a protein with DNA, sliding, is generally described as Brownian diffusion as in the minimal model of Sec. III.A.2. If this hypothesis seems to be confirmed by *in vitro* experiments (Kabata *et al.*, 1993; Bonnet *et al.*, 2008), it cannot always be the case, in particular, *in vivo*. A first limitation of this simple description appears in the case of many proteins binding to DNA, as is the case *in vivo*, which are likely to create traffic jams (Sokolov *et al.*, 2005; Li *et al.*, 2009). Such crowding effects in one dimension are known to potentially lead to subdiffusive behavior. Additionally, even in the case of a single protein, it should be kept in mind that the DNA sequence is not homogeneous, and the disorder in the sequence can also impact sliding. The heterogeneity in the sequence is often modeled by a disordered energy landscape, whose distribution is Gaussian (Barbi *et al.*, 2004; Hu and Shklovskii, 2006; Wunderlich and Mirny, 2008). Barbi *et al.* (2004) showed that in this case sliding is not purely diffusive: At short times, the protein will be trapped in local minima, leading to subdiffusive behavior. The diffusive behavior is recovered only at larger times, or equivalently for sliding lengths longer than 100 bp.

Anomalous diffusion in the sliding phase has been discussed theoretically by Eliazar *et al.* (2007) [see also Eliazar *et al.* (2008) and Meroz *et al.* (2009)], who extended the minimal model of facilitated diffusion (Coppey *et al.*, 2004) summarized in Sec. III.A.2. In particular, the Laplace-transformed search time distribution is obtained for several non-Brownian sliding motions such as ballistic, self-similar, or halted motions (in particular, when halt durations are widely distributed, leading to subdiffusive behavior), therefore covering standard models of anomalous diffusion. It is important that Eliazar *et al.* (2007) found that, whatever the model of sliding, there are always regimes in which intermittence is favorable, similarly to the case of Brownian sliding. They further showed that in the case of 3D excursions with finite mean durations, the mean search time with an arbitrary sliding mechanism remains of order proportional to ℓ. This indicates that for long enough DNA, intermittence is favorable for a wide range of sliding motions, either normal or anomalous, which supports the robustness of the facilitated diffusion mechanism.

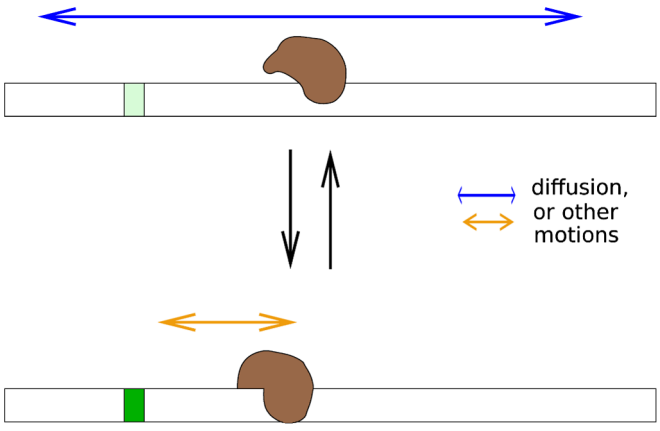


FIG. 11. Sliding is often represented by diffusion with perfect reactivity on the target. The two main directions shown for a more realistic description of the 1D phase: On the one hand, the sliding is not necessarily diffusive, and on the other hand, the 1D phase could be, in fact, a combination of two phases, one fast, but with low recognition, and another slow (or immobile), but with high recognition of the target.

ii. Target recognition. A simplification that is often used in the literature consists in assuming that the target is perfectly reactive, i.e., that reaction occurs with probability 1 at the very first passage of the protein to the target sequence. Slutsky and Mirny (2004), however, stressed that if there is an activation barrier at the target site, the protein has a chance to pass the target without entering the recognition process, and therefore to miss it. The roughness σ of the energy landscape of the sequence can then play a crucial role. If σ is of order $1k_BT$, Slutsky and Mirny (2004) found that the sliding diffusion is fast, but that the protein has a high chance to miss the target. On the contrary, if σ is of order $5k_BT$, the recognition probability is high, but the sliding diffusion coefficient is very low, leading to a long search time. Such a result seems to set conflicting constraints on the search, since an efficient target search process requires both speed and reliability in target recognition. To overcome this paradox, Slutsky and Mirny (2004) proposed on the basis of direct structural observations (Kalodimos *et al.*, 2004) that the protein can perform conformational changes in the sliding phase, and switches between a fast search state (with low σ) and a slow recognition state (with high σ) (see Fig. 11). They showed that if the two energy landscapes are strongly correlated, it is possible to reconcile high speed and efficient recognition. Similar models of two-state proteins in the sliding phase have been studied more quantitatively in the frameworks of both the kinetic [see Hu *et al.* (2008)] and the stochastic approaches [see Bénichou *et al.* (2009)], confirming that such a mechanism indeed permits a fast search with reliable recognition.

c. Descriptions of the 3D phase (jumping or hopping)

We now review the different descriptions of the 3D phase (see Fig. 12). Most of the facilitated diffusion models implicitly require the knowledge of the probability $\pi(x|x_0)$ that a protein which desorbs the DNA at position x_0 will eventually rebind for the first time to the DNA at position x, where the coordinate x measures the distance along the chain. This quantity depends both on the dynamics of the protein and on the conformation of the DNA, and in practice can be determined explicitly only in the case of an ideal infinite cylindrical DNA (see below), which makes assumptions necessary in realistic situations. Depending on the relocation length $|x - x_0|$, 3D excursions have been given different names in the literature, mainly either hops (referring to "small" $|x - x_0|$) and jumps (referring to "large" $|x - x_0|$). Since the definitions of jumps and hops may vary according to authors, the limit between both being somewhat arbitrary, we give below the one that will be used in this review.

i. Jumps. We define as jumps the 3D excursions whose starting and ending points on the DNA sequence are uncorrelated, i.e., such that the relocation probability $\pi(x|x_0)$ is

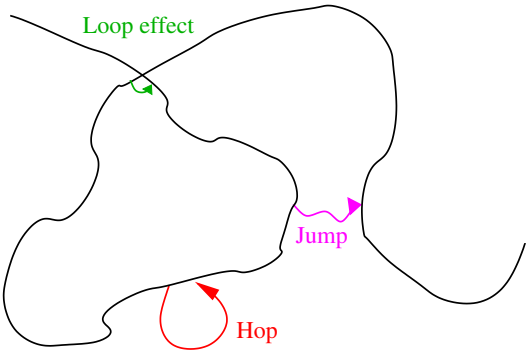


FIG. 12. Description of 3D excursions. Jumps are 3D excursions whose starting and ending points on the DNA sequence are uncorrelated. In practice, for confined DNA conformations as in a cellular medium, jumps have a span (measured along the DNA contour) larger than the density-density correlation length ξ_c of DNA. Conversely, hops are 3D excursions whose starting and ending points on the DNA sequence are correlated, or equivalently 3D excursions whose relocation length is smaller than the correlation length ξ_c.

independent of x. This definition, of course, depends on the DNA conformation and makes sense only for dense enough conformations such as a random coil (for instance, for free DNA in solution) or even denser packings that can be expected *in vivo* [such as fractal globule structures (Grosberg *et al.*, 1988)]. In such structures, sequences that are far apart along the DNA chain can be actually very close in the 3D space. Hence, 3D excursions whose relocation length is larger than the typical distance between DNA segments are likely to end at any remote location on the DNA sequence, and should therefore be considered as jumps according to our definition. The lower bound of the relocation length of jumps therefore strongly depends on the DNA conformation and is in practice hard to evaluate. In the case of interest of a confined DNA (as in cellular conditions), the typical distance between DNA segments can be estimated by the DNA density-density correlation length ξ_c. This suggests an alternative and equivalent definition of jumps as 3D excursions whose relocation length is larger than ξ_c. A widespread assumption used, for example, in the minimal model of Sec. III.A.2 [see also Hu *et al.* (2006) at scales larger then the antenna size or Coppey *et al.* (2004), Eliazar *et al.* (2007), and Bénichou *et al.* (2009)] consists in taking all 3D excursions as jumps, i.e., as random uniform relocations over the DNA. Even if not exact, this assumption has been checked numerically on the example of a quenched self-avoiding DNA and has proved to be very satisfactory (Sheinman and Kafri, 2009) at high enough DNA concentration. Interestingly, this definition of jumps highlights the importance of the effect of the local DNA concentration on the search efficiency, as observed in van den Broek *et al.* (2008); Lomholt *et al.* (2009): the more densely packed the DNA, the smaller the correlation length ξ_c, and therefore the higher the probability of jumps enabling the protein to explore previously unscanned areas, and the less the time spent in 3D phases.

The assumption that all excursions of relocation length larger than the typical distance between DNA segments lead to a completely uniform relocation over the DNA is, however, not exact. Indeed, large-scale correlations in the 3D conformation of the DNA chain may exist, as in the model case of a free random coil conformation. In particular, in eukaryotes, where DNA is packed in the nucleus, recent studies such as that of Lieberman-Aiden *et al.* (2009) support a hierarchical structure of DNA that could induce long-range correlations in the conformation and therefore a nonuniform relocation probability. The impact of DNA conformation on the relocation probability has been tested on the example of an annealed wormlike chain polymer by Díaz de la Rosa *et al.* (2010) who found that at short times, three-dimensional excursions of approximately the DNA persistence length are actually less abundant than both shorter and slightly larger relocations: by definition, closer sequences along the DNA are closer in 3D space, but sequences farther than the persistence length can take advantage of loops and actually be even closer in 3D space. More generally, the loop statistics impacts on the relocation probability and can lead to a nonuniform relocation probability $\pi(x|x_0)$. Lomholt *et al.* (2005) argued that since polymers form loops whose linear size x is distributed according to $p(x) \sim |x|^{-1-\alpha}$ (for instance, $\alpha = 0.5$ for Gaussian chains; $\alpha \simeq 1.2$ for self-avoiding walks), relocations distributed according to the same law are favored and should also be taken into account. In an annealed version of such a model, they showed that depending on α the optimal strategy can vary widely. It should be added that loops can enable another relocation mechanism for proteins with multiple binding sites called intersegmental transfer [see Hu and Shklovskii (2007) and Sheinman and Kafri (2009)], which can be shown for modeling purposes to be widely equivalent to 3D excursions. Finally, the approximation of uniform random relocations has proved to be useful and can be validated numerically for simple DNA conformations (Sheinman and Kafri, 2009), but a better knowledge of the *in vivo* conformation of DNA would be necessary to assess more precisely the relocation probability.

ii. Hops. Echoing the definition of jumps, we define hops as 3D excursions whose starting and ending points on the DNA sequence are correlated, or equivalently as 3D excursions whose relocation length is smaller than the typical distance between DNA segments, which is given by the correlation length ξ_c for confined DNA. Because of their local character, hops are often effectively taken into account in the sliding mechanism [see, for example, Hu *et al.* (2006)]. Although this assumption is useful in practice, it also raises additional questions. (i) First, hops do not continuously explore the DNA, and a protein performing hops have higher chances to miss the target (note that hops permit as a counterpart the bypassing of obstacles on the DNA), and this nonperfect reactivity has to be taken into account. (ii) Second, if hops are included in an effective sliding mechanism, then the effective diffusion coefficient has to be determined, as well as the effective transition rate from this effective sliding state to the jumping state. This last point amounts in practice in calculating the relocation probability $\pi(x|x_0)$ of hops, which gives as a by-product the probability that after desorption from DNA the protein performs a jump rather than a hop.

This problem, which has been studied numerically by Wunderlich and Mirny (2008), can actually be studied

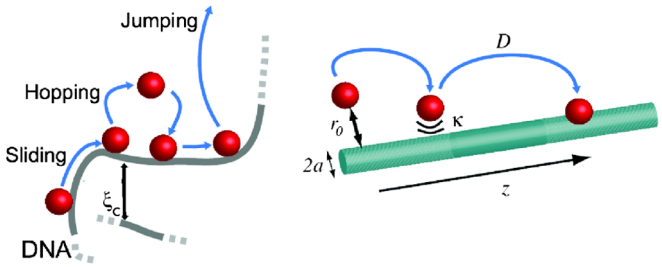


FIG. 13. Facilitated diffusion of a protein on DNA. Left: Schematic definition of sliding, hopping, and jumping. Hops are 3D excursions whose starting and ending points on the DNA sequence are correlated, or equivalently 3D excursions whose relocation length is smaller than the typical distance between DNA segments. In the case of confined DNA, this distance is estimated by the DNA density-density correlation length ξ_c. Right: Model parameters.

analytically (Loverdo *et al.*, 2009), since at the scale of hops, which are smaller than the DNA persistence length ξ_p, the DNA can be simply modeled as a cylinder of effective radius $a = R_{\mathrm{DNA}} + R_{\mathrm{protein}}$ (see Fig. 13, left). Denoting by D the 3D diffusion coefficient of the protein (assumed pointlike), the density probability $\pi(x|\mathbf{r}_0)$ of being adsorbed on the DNA at the longitudinal abscissa x, starting from the point $\mathbf{r}_0$, then satisfies [for further details on derivation, see Berg and Blomberg (1976), Levitz *et al.* (2008), Loverdo *et al.* (2009), Chechkin *et al.* (2009), and Bénichou *et al.* (2010, 2011) for similar analyses]:

$$\Delta_{\mathbf{r}_0}\pi(x|\mathbf{r}_0) = 0. \tag{32}$$

Assuming a radiative boundary condition on the cylinder surface to account for the adsorption rate on DNA,

$$\partial_{r_0}\pi(x|\mathbf{r}_0)(r_0 = a) = \kappa\pi(x|\mathbf{r}_0)(r_0 = a), \tag{33}$$

one can show that

$$\pi(x|\mathbf{r}_0) = \frac{1}{\pi}\int_0^\infty \cos(kx)\frac{K_0(kr_0)}{K_0(ka) + K_1(ka)k/\kappa}dk, \tag{34}$$

where K_i are Bessel functions. This relocation distribution, in good agreement with experimental data from Bonnet *et al.* (2008) obtained on an extended DNA molecule, enables one to address the questions of point (ii) above. First, Eq. (34) gives the analytical distribution of hops, since for $x < \xi_c$ the DNA can be well approximated by a cylinder. In turn, as shown by Loverdo *et al.* (2009), this gives access to the effective diffusion coefficient of a combined motion of sliding and hops. Second, according to our definition, all relocations with $x > \xi_c$ will be jumps. Thus, the probability that a 3D relocation is a jump rather than a hop is given by the complementary cumulative distribution

$$C(x = \xi_c) = \int_{|x|>\xi_c}\pi(x|\mathbf{r}_0)dx \sim \frac{\ln(r_0/a) + 1/\kappa a}{\ln(\xi_c/a)}. \tag{35}$$

Returning to the search problem, in regimes where jumps are favorable, decreasing the correlation length speeds up the search process, as found by van den Broek *et al.* (2008).

iii. Crowding effects. In both prokaryotes and eukaryotes, the cellular medium is very crowded, and 3D excursions of proteins are likely to be hindered. The normal or anomalous nature of transport in cellular medium is still debated. For instance, Dix and Verkman (2008) supported the idea that 3D motion is mostly normal diffusion, whereas Malchus and Weiss (2010) suggested that there is more and more evidence for subdiffusion. Experimentally, it is found that some tracers exhibit transient behavior (subdiffusive at small time scales, diffusive at larger time scales): Measures, however, depend on the size and nature of the tracer, on the time and length scales covered, and on other experimental conditions, which may explain the lack of consensus on the problem. The influence of subdiffusion on the target search will depend on the microscopic mechanism at play. There are three main mechanisms leading to subdiffusion, as outlined in Appendix A: random walk on a fractal medium, random walk with long waiting times (CTRW) [continuous-time random walks], or random walk with long-range correlations such as fractional Brownian motion (FBM). Which of these possibilities best describes transport in crowded environments such as the cellular medium is, however, still unclear [see He *et al.* (2008), Bancaud *et al.* (2009), Szymanski and Weiss (2009), or Tejedor *et al.* (2010) for various opinions on the subject].

Lomholt *et al.* (2007) explored the effect of a crowded environment with subdiffusion $\langle r^2(t)\rangle \propto t^\alpha$ $(0 < \alpha < 1)$ caused by waiting times distributed as $p(t) \sim \tau^\alpha/t^{1+\alpha}$. They argued that because of these waiting times, the probability that the protein has not yet left the DNA at time t and the probability that an unbound protein has not yet bound to DNA after a time t both scale as $1/t^{1+\alpha}$. Their results have two main practical implications. On the one hand, in an experiment, since proteins can remain stuck for very long times, ensemble averages do not lead to the same results as time averages as was also highlighted by He *et al.* (2008). On the other hand, since proteins would slide for a longer time and since it would take them a very long time to return to the DNA, the genes' coding for transcription factors should be close to their target sequences, as also outlined by Wunderlich and Mirny (2008). Analytical determination of the relocation distribution above can be extended to a fractal medium (Loverdo *et al.*, 2009). In this case, using the O'Shaughnessy and Procaccia (1985) formalism, the large-x behavior of the relocation distribution is obtained as $\pi(x|\mathbf{r}_0) \sim r_0^{d_w - d_f^\perp}/x^{1+d_w-d_f^\perp}$, where $d_f^\parallel$ is the dimension of the projection of the fractal on the axis parallel to the cylinder (Loverdo *et al.*, 2009). Hence, the relocation distribution always decays faster than in the case of normal diffusion $\sim 1/(z\ln^2(z/a))$. As a consequence, the proportion of jumps in the case of random conformation of DNA in the fractal type crowding scales as $C(\xi) \sim \xi^{-d_w+d_f^\perp}$: it is much smaller than for regular diffusion, which shows that fractal crowding favors hops and changes the overall intermittent search.

d. Beyond the mean: Variability of the search time

Minimizing the mean search time is the optimization procedure most often used [see, for example, Coppey *et al.* (2004)]. However, the entire distribution of the search time is needed to assess the search kinetics on all time scales. In the case of simple exponential distributions of the search time,

the mean is sufficient to describe the full dynamics. Several models discussed below have shown that the search time distribution is not always a single exponential. Departure from an exponential distribution can have important consequences, such as large fluctuations of the search time, which could be an extra source of variability in gene expression.

i. Effect of trapping sequences. A first possible source of fluctuations in the search time could come from the existence of trapping sequences along the DNA. Since a target sequence is typically 10 bp long, similar sequences are statistically unavoidable and can be expected to be local minima in the protein-DNA interaction energy landscape. Bénichou *et al.* (2009) proposed a model in which the protein can be stuck on such sequences that are similar to the target. The corresponding trapping times naturally introduce new time scales in the problem, which potentially could be very long. In the framework of this model, it is shown that the search time distribution is best described by two exponentials. In particular, the mean search time is controlled by long trapping events even when they are very unlikely, and it can be orders of magnitude larger than the median search time, which is controlled by the trajectories that do not fall into the traps. The main outcome of such a model is that it reconciles the possibility of having long-lived stable complexes (i.e., deep traps), and very fast typical search times, which were cast so far as paradoxical requirements.

ii. Effect of n searchers. The influence of the number of searchers has been discussed by several groups (Sokolov *et al.*, 2005; Eliazar *et al.*, 2007; Eliazar *et al.*, 2008; Meroz *et al.*, 2009). It is important, as stressed by Bénichou *et al.* (2009), that the mean time for n independent searchers is simply given by the mean time divided by the number of searchers only if the search time distribution for a single searcher is a single exponential. In the case of nonexponential distributions (e.g., a sum of weighted exponentials) it can be shown that the effect of the number of searchers can be much stronger, since the weight of long time scales decreases exponentially with increasing n, selecting only the shorter time scale of the problem for n large enough [see Bénichou *et al.* (2009)]. Moreover, if the concentration of searchers increases considerably, searchers cannot be considered as independent any longer and will act as ''roadblocks'' along the DNA molecule. These roadblocks will decrease the effective sliding length, and may also hide the target, overall slowing down the search process. This results in a trade-off, as stressed by Li *et al.* (2009). On the one hand, the more proteins, the more searchers for the target, and the quicker the search. On the other hand, the more proteins, the more crowding, and the less efficient the search of a single protein. They predicted that the optimum is obtained for 10^4–10^5 DNA-binding proteins for *E. Coli*, which is close to the experimental value of 30 000 proteins.

iii. Dependence on the starting point: Colocalization. Another origin of the search time fluctuations can be due to its dependence on the starting position of the protein. Wunderlich and Mirny (2008) showed that a target that is close to the starting point of the protein can be found within a single sliding phase, which yields a very short search time and a rather low variability. In contrast, if the target is far away from the starting point of the protein, it is found after numerous 3D excursions. The mean search time is then much longer, and the spread of the distribution of the search time is larger. Kolesov *et al.* (2007) and Wunderlich and Mirny (2008) then argued that for increasing the efficiency of the transcription factor, its coding sequence (i.e., its starting position) should be colocalized with its target sequence [see also Bénichou *et al.* (2008) and Bénichou and Voituriez (2009) for a further optimization of this colocalization effect with respect to the diffusion coefficient of the protein]. Colocalization is indeed observed in real prokaryote genomes. This mechanism can, however, be invoked only in prokaryotes, where there are no cell compartments separating protein production from DNA.

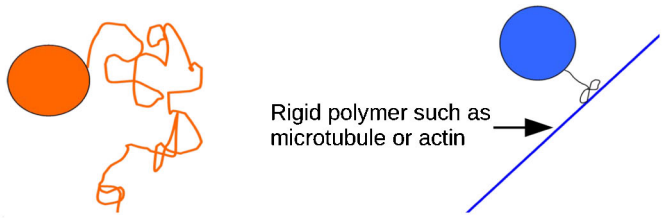
More generally, geometric effects on search kinetics have been discussed by Bénichou *et al.* (2010), where it is shown that low-dimensional effects, such as sliding or diffusion on fractals, can lead to nonexponential distributions that depend strongly on the starting position of the searcher. Such a mechanism could be important for eukaryotes (Bénichou *et al.*, 2011). Indeed, in eukaryotes, DNA is packed inside the nucleus in what is called the chromatin, and some DNA regions might be more or less accessible depending on the chromatin configuration. For example, the DNA close to the nuclear pores is much more accessible to incoming proteins than the DNA buried deep inside the nucleus, leading potentially to different search times. Kampmann (2005) argued qualitatively that proteins binding to DNA could take advantage of the heterogeneities of the chromatin and, depending on the searched sequence, adopt different optimal strategies. The geometric effect can be particularly important in the case of genes that need to be activated simultaneously. Indeed, their colocalization in the nucleus permits sharing the transcription material, since the search time for a transcription factor going from one to the other will be much smaller than in the case of a random localization in the nucleus.

4. Conclusion on protein-DNA interactions

The mechanism of facilitated diffusion of proteins on DNA is intrinsically intermittent in the general meaning defined in this review: It is a combination of one-dimensional motion in close interaction with DNA, called sliding, which enables target detection, and faster 3D excursions. From the theoretical point of view, this further example of an intermittent process has been shown to significantly speed up the search. Over the past few years, strong experimental evidence has been obtained, showing that this mechanism is indeed at play. Interestingly, in this case in the fast phase the searcher is not able to detect the target not because of a lowering of its perception abilities, but simply because the motion takes place in a geometrical space that does not contain the target. Most of the microscopic realizations of intermittence fall in this case as we will see in the next section with a further example.

B. Active transport of vesicles in cells

After this first microscopic example of intermittent search, we turn to another example: active transport of vesicles reacting at specific locations in cells.



Does not need ATP

Distance$^2 \propto Dt$ (or less if subdiffusive)

Diffusion coefficient decreases when the size of the object increases

Consumes ATP

Distance $= Vt$

Velocity ~ 1 μm.s^{-1}, almost independent of the object size (see for example Block et al. (2003))

FIG. 14. Transport options for vesicles inside cells.

1. Active transport in cells

Various motor proteins such as kinesins or myosins are able to convert the chemical fuel provided by adenosine triphosphate (ATP) into mechanical work by interacting with the semiflexible oriented filaments (mainly F-actin and microtubules) of the cytoskeleton (Alberts, 2002). Because many molecules or larger cellular organelles such as vesicles, lysosomes, or mitochondria (hereafter referred to as tracer particles) can randomly bind and unbind to motors, the overall transport of a tracer in the cell can be described as alternating phases of standard diffusive transport (sometimes subdiffusive), and phases of active directed transport powered by motor proteins (Alberts, 2002; Salman *et al.*, 2005), see Fig. 14. In particular, Huet *et al.* (2006) studied the rate of transitions between ballistic, diffusive, and "on the target" states of vesicles, and found that the vesicles studied are much more likely to react in the free diffusive phase than when bound to motors. Active transport in this case is therefore clearly a further example of intermittent behavior. Active transport in cells has been extensively studied both experimentally, for instance, by single particle tracking methods (Sheetz and Spudich, 1983; Howard *et al.*, 1989; Caspi *et al.*, 2000; Caspi *et al.*, 2002), and theoretically by evaluating the mean displacement of a tracer (Shlesinger and Klafter, 1989; Ajdari, 1995; Salman *et al.*, 2005), or stationary concentration profiles (Nedelec *et al.*, 2001). This transport is important, for example, for dynamically regulating the distribution of proteins such as membrane receptors.

Most cell functions are regulated by coordinated chemical reactions that involve low concentrations of reactants (such as ribosomes or vesicles carrying targeted proteins), and that are therefore limited by transport. An analytical model based on the idea of intermittence has been introduced by Loverdo *et al.* (2008) [see also Mirny (2008) and Loverdo *et al.* (2009a)], enables the determination of the kinetic constant of transport limited reactions in active media, and further shows that the kinetic constant can be optimized. We give below the main results of the model; further details can be found in Appendix B.

2. Model

The model relies on the idea of intermittent search strategies and has important similarities with the models of Sec. II, which are discussed in Sec. IV. We consider a tracer particle evolving in a d-dimensional space (in practice $d = 1, 2, 3$), which performs thermal diffusion motions of diffusion coefficient D (denoted phases 1), randomly interrupted by ballistic excursions bound to motors (referred to as phases 2) of constant velocity V and direction pointing in the solid angle $\omega_{\mathbf{V}}$ (see Fig. 15). The distribution of the filaments' orientation is denoted by $\rho(\omega_{\mathbf{V}})$ and will be taken as either disordered or polarized (see Figs. 15, 17, and 19), which schematically reproduces the different states of the cytoskeleton (Alberts, 2002). The random duration of each phase i is assumed to be exponentially distributed with mean τ_i. The tracer T can react with reactants R (supposed immobile) during free diffusion phases 1 only, as T is assumed to be inactive when bound to motors. Reaction occurs with a finite probability per unit of time k when the tracer-reactant distance is smaller than a given reaction radius a. In what follows the kinetic constant K of the reaction $T + R \rightarrow R$ is explicitly determined.

3. Methods

We now present the basic equations in the case of a reactant centered in a spherical domain of radius b with reflecting boundary. This geometry both mimics the relevant situation of a single target and provides a mean-field

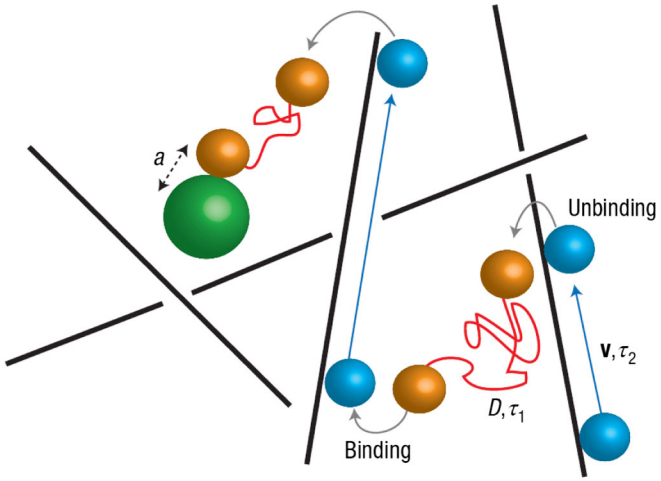


FIG. 15. Vesicle transport in the bulk (three dimensions).

approximation of the general case of randomly located reactants with concentration $c = a^d/b^d$, where b is the typical distance between reactants. We start from a mean-field approximation of the first-order reaction constant (Berg and Blomberg, 1976) and write $K = 1/\langle t \rangle$, where the key quantity of our approach is the reaction time $\langle t \rangle$, which is defined as the mean first-passage time (Redner, 2001; Condamin *et al.*, 2007) of the tracer at a reactant position uniformly averaged over its initial position. t_1 is defined as the mean reaction time if the tracer starts in phase 1 at position $\mathbf{r}$, and t_2 is defined as the mean reaction time if the tracer starts in phase 2 at position $\mathbf{r}$ with velocity $\mathbf{v}$. For the active intermittent dynamics defined above, t_1 and t_2 satisfy the following backward equations (Redner, 2001) (see Sec. IV for derivation):

$$D\Delta_{\mathbf{r}} t_1 + \frac{1}{\tau_1}\int (t_2 - t_1)\rho(\omega_{\mathbf{V}})d\omega_{\mathbf{V}} - k\mathrm{I}_a(\mathbf{r})t_1 = -1,$$
$$\mathbf{V}\cdot\nabla_{\mathbf{r}} t_2 - \frac{1}{\tau_2}(t_2 - t_1) = -1, \tag{36}$$

where $\Delta_{\mathbf{r}}$ and $\nabla_{\mathbf{r}}$ are the Laplacian and the gradient at the initial position, and I_a is the indicator function of the sphere of radius a. As these Eqs. (36) are of integro-differential type, standard methods of resolution are not available for a general distribution ρ.

In the case of a *disordered* distribution of filaments [$\rho(\omega_v) = 1/\Omega_d$, where Ω_d is the solid angle of the d-dimensional sphere], these equations can be solved exactly in dimension 1. In dimensions 2 and 3, an approximate scheme has to be introduced; the details of the calculation are given in Appendix B. We present here simplified expressions of the resulting kinetic constant by taking alternately the limit $k \to \infty$, which corresponds to the ideal case of perfect reaction, and the limit $D \to 0$, which allows us to isolate the k dependence.

4. Active transport in the cytoplasm

We first discuss the $d = 3$ disordered case (see Fig. 15), which provides a general description of the actin cytoskeleton of a cell in nonpolarized conditions, or of a generic *in vitro* active solution. An analytical form of the mean first-passage time $\langle t \rangle = 1/K_{3d}$ is given in Appendix B and plotted in Fig. 16. Strikingly, K_{3d} can be maximized as soon as the reaction radius exceeds a threshold $a_c \simeq 6D/V$ for the following value of the mean interaction time with motors:

$$\tau_{2,3d}^{\mathrm{opt}} = \frac{\sqrt{3}a}{Vx_0} \simeq 1.078\,\frac{a}{V}, \tag{37}$$

where x_0 is the solution of $2\tanh(x) - 2x + x\tanh(x)^2 = 0$. The τ_1 dependence is very weak, but one can roughly estimate the optimal value by $\tau_{1,3d}^{\mathrm{opt}} \simeq 6D/V^2$. This gives in turn the maximal reaction rate

$$K_{3d}^m \simeq \frac{cV}{a}\,\frac{\sqrt{3}[x_0 - \tanh(x_0)]}{x_0^2}, \tag{38}$$

so that the gain with respect to the reaction rate K_{3d}^p in a passive medium is $G_{3d} = K_{3d}^m/K_{3d}^p \simeq CaV/D$ with $C \simeq 0.26$.

Several comments are in order. (i) First, $\tau_{2,3d}^{\mathrm{opt}}$ depends neither on D nor on the reactant concentration. A similar analysis for finite k (in the $D \to 0$ limit) shows that this optimal value does not depend on k either (see Sec. IV), which proves that the optimal mean interaction time with motors is widely independent of the parameters characterizing the diffusion phase 1. (ii) Second, the value a_c should be discussed. In standard cellular conditions D ranges from $\simeq 10^{-2}\ \mu\mathrm{m}^2\,\mathrm{s}^{-1}$ for vesicles to $\simeq 10\ \mu\mathrm{m}^2\,\mathrm{s}^{-1}$ for small proteins, whereas the typical velocity of a motor protein is $V \simeq 1\ \mu\mathrm{m}\,\mathrm{s}^{-1}$, a value that is widely independent of the size of the cargo (Alberts, 2002). This gives a critical reaction radius a_c ranging from $\simeq 10$ nm for vesicles, which is smaller than any cellular organelle, to $\simeq 10\ \mu$m for single molecules, which is comparable to the whole cell dimension. Hence, this shows that in such a three-dimensional disordered case active transport can optimize reactivity for sufficiently large tracers such as vesicles, as motor-mediated motion permits a fast relocation to unexplored regions, whereas it is inefficient for standard molecular reaction kinetics, mainly because at the

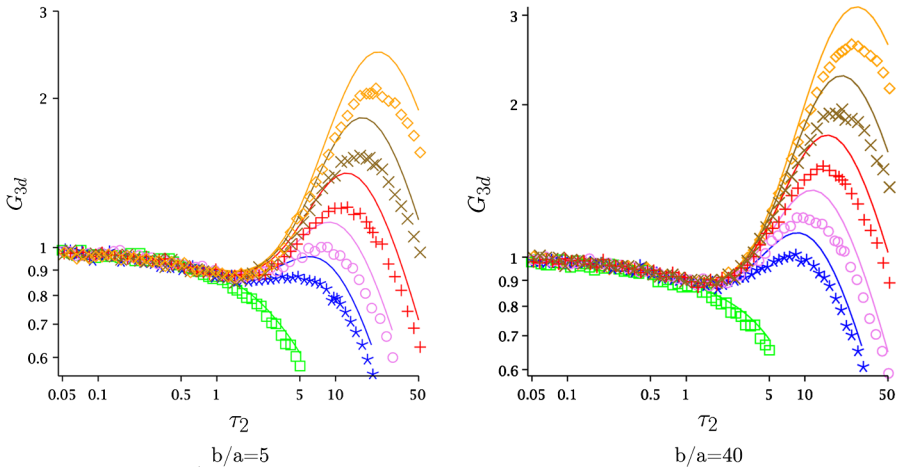


FIG. 16. Optimization of the reaction rate for intermittent active transport. Gain of reactivity due to active transport in three dimensions as a function of τ_2 for different values of the ratio b/a (logarithmic scale). The analytical form (the mean detection time with diffusion alone divided by the mean detection time with intermittence) (plain lines) is plotted against numerical simulations (symbols) for the following values of the parameters (arbitrary units): $a = 1$ (□), $a = 5$ (⋆), $a = 7$ (∘), $a = 10$ (+), $a = 14$ (×), $a = 20$ (◇), with $\tau_1 = 6$, $V = 1$, and $D = 1$. G_{3d} presents a maximum only for $a > a_c \simeq 4$.

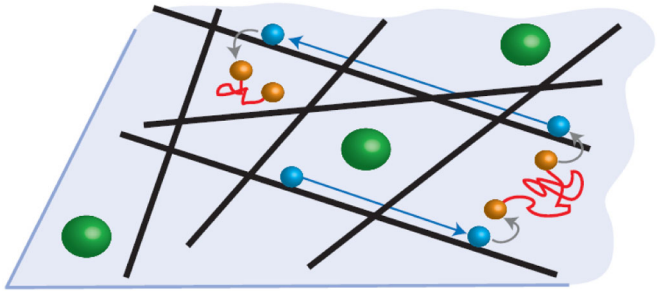


FIG. 17. Planar structures such as membranes and lamellipodia ($d = 2$).

cell scale molecular free diffusion is faster than motor-mediated motion. This could help justify the idea that many molecular species in cells are transported in vesicles. Interestingly, in standard cellular conditions $\tau_{2,3d}^{\rm opt}$ is of order 0.1 s for a typical reaction radius of order 0.1 μm. This value is compatible with experimental observations (Alberts, 2002) and suggests that cellular transport is close to optimum. (iii) Last, the typical gain for a vesicle of reaction radius $a \gtrsim 0.1$ μm in standard cellular conditions is $G_{3d} \gtrsim 2.5$ (see Fig. 16) and can reach $G_{3d} \simeq 10$ for the fastest types of molecular motors [$V \simeq 4$ μm s^{-1}; see Sheetz and Spudich (1983) and Alberts (2002)], independently of the reactant concentration c. As we shall see below, the gain will be significantly higher in lower-dimensional structures such as axons.

5. Active transport at membranes

We now come to the $d = 2$ disordered case (see Fig. 17). Striking examples in cells are given by the cytoplasmic membrane, which is closely coupled to the network of cortical actin filaments, or the lamellipodium of adhering cells (Alberts, 2002). In many cases the orientation of filaments can be assumed to be random. It can be shown that as for $d = 3$ (see Sec. IV), the reaction rate K_{2d} can be optimized in the regime $D/V \ll a \ll b$. Remarkably, the optimal interaction time $\tau_{2,2d}^{\rm opt}$ takes one and the same value in the two limits $k \to \infty$ and $D \to 0$:

$$\tau_{2,2d}^{\rm opt} \simeq \frac{a}{V\sqrt{2}}[\ln(1/c) - 1]^{1/2}, \tag{39}$$

which indicates again that $\tau_{2,2d}^{\rm opt}$ does not depend on the parameters of the thermal diffusion phase, through either D or k. In the limit $k \to \infty$ one has

$$\tau_{1,2d}^{\rm opt} = \frac{D}{8V^2}\frac{\ln^2(1/c)}{\ln(1/c) - 1},$$

and the maximal reaction rate can then be obtained:

$$K_{2d}^m \simeq \frac{cV}{a\sqrt{2\ln(1/c)}}. \tag{40}$$

Comparison of this expression to the case of passive transport yields a gain $G_{2d} = K_{2d}^m/K_{2d}^p \simeq aV\sqrt{\ln(1/c)}/4D\sqrt{2}$. As in the $d = 3$ case, this proves that active transport enhances reactivity for large enough tracers (with a critical reaction radius $a_c \simeq D/V$ of the same order as in the $d = 3$ case), such as vesicles. However, here the gain G_{2d} depends on the reactant concentration c, and can be more significant: With the same values of D, V, and a as given above in standard cellular conditions, and for reactants with low concentration (such as specific membrane receptors) with a typical distance between reactants $b \gtrsim 10$ μm, the typical gain is $G_{2d} \gtrsim 8$ and reaches 10 for single reactants (such as examples of signaling molecules; see Fig. 18).

6. Active transport in tubular structures

The case of *nematic order* of the cytoskeletal filaments, which depicts, for instance, the situation of a polarized cell (Alberts, 2002), can be shown to be equivalent in a first approximation to the one-dimensional case, which is exactly solvable (for calculations, see Appendix B); see Fig. 19. The $d = 1$ case is also important on its own in cell biology

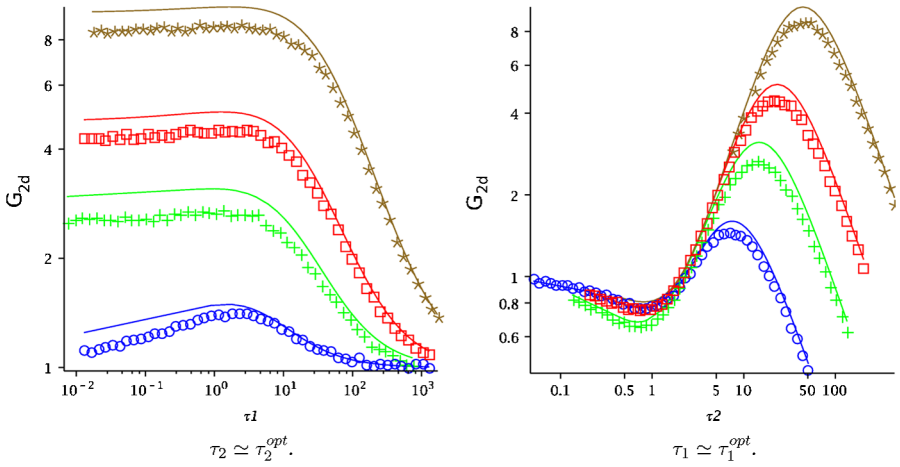


FIG. 18. Optimization of the reaction rate for intermittent active transport. Gain of reactivity due to active transport G_{2d} in two dimensions as a function of τ_1 or τ_2 (logarithmic scale). The analytical form [the mean detection time with diffusion alone divided by the mean detection time with intermittence (B50)] (plain lines) is plotted against numerical simulations (symbols) for the following values of the parameters (arbitrary units): $a = 20$, $b = 2000$ ($\star$); $a = 10$, $b = 1000$ ($\square$); $a = 10$, $b = 100$ ($+$); $a = 2.5$, $b = 250$ ($\circ$); with $V = 1$ and $D = 1$. These curves represent standard cellular conditions (as discussed in the text).

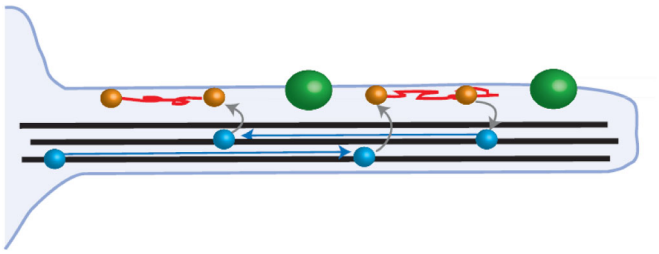


FIG. 19. Tubular structures in cells, such as axons and dendrites ($d = 1$).

as many one-dimensional active structures such as axons, dendrites, or stress fibers are present in living cells (Alberts, 2002). As an illustration, we take the example of an axon, filled with parallel microtubules pointing their plus end in a direction $\mathbf{e}$. We consider a tracer particle interacting with both kinesins (+ end directed motors, of average velocity $V\mathbf{e}$) and dyneins (− end directed motors, of average velocity $-V\mathbf{e}$) with the same characteristic interaction time τ_2 (see Fig. 1). For this type of tracer, the mean first-passage time satisfies Eqs. (36) with an effective nematic distribution of filaments $\rho(\omega_{\mathbf{V}}) = \frac{1}{2}[\delta(\mathbf{V} - \mathbf{e}) + \delta(\mathbf{V} + \mathbf{e})]$. The reaction rate K_{1d} is maximized in the regime $D/V \ll a \ll b$ for the following values of the characteristic times (see Fig. 20):

$$\tau_{1,1d}^{\text{opt}} = \frac{1}{48}\frac{D}{V^2 c}, \qquad \tau_{2,1d}^{\text{opt}} = \frac{1}{\sqrt{3}}\frac{a}{Vc^{1/2}}, \tag{41}$$

for $k \to \infty$. The maximal reaction rate K_{1d}^m is then given by

$$K_{1d}^m \simeq \frac{\sqrt{3}Vc^{3/2}}{2a}, \tag{42}$$

and the gain is $G_{1d} = K_{1d}^m/K_{1d}^p \simeq aV/(2\sqrt{3}Dc^{1/2})$, which proves that active transport can optimize reactivity as in higher dimensions. Interestingly the c dependence of the gain is much more important than for $d = 2, 3$, which shows that the efficiency of active transport is strongly enhanced in one-dimensional or nematic structures at low concentration. Indeed, with the same values of D, V, and a as given above in standard cellular conditions, and for a typical distance between reactants $b \gtrsim 100\ \mu$m (such as low-concentration axonal receptors), one obtains a typical gain $G_{1d} \gtrsim 100$ (see Fig. 20). In the limit of finite reactivity (k finite and $D \to 0$) one has

$$\tau_{1,1d}^{\text{opt}} = \sqrt{\frac{a}{Vk}}\left(\frac{2\ln(1/c) - 1}{8}\right)^{1/4}$$

and the same optimal value (41) of $\tau_{2,1d}^{\text{opt}}$. As in higher dimensions $\tau_{2,1d}^{\text{opt}}$ depends neither on the thermal diffusion coefficient D of phases 1 nor on the association constant k, which shows that the optimal interaction time with motors τ_2^{opt} presents remarkable universal features. Furthermore, this approach permits an estimate of τ_2^{opt} compatible with observations in standard cellular conditions, which suggests that cellular transport could be close to optimum.

7. Conclusion on intermittent active transport

Starting from the observation of vesicles alternating free diffusion and phases bound to motors performing ballistic motion, and from the observation that (at least in some cases), vesicles can react only in the free phase, a model for intermittent active transport has been proposed. The reaction rate, which can be approximated by the inverse of the mean first-passage time, can be explicitly calculated in this model for various cellular geometries (bulk cytoplasm, membranes, and tubular structures). This shows that intermittent transport can indeed increase reaction rates for large objects such as vesicles, and, in particular, in low dimensions. The model for the reactive phase is either diffusive or static (with a reaction rate), and both lead to the same optimal duration of the ballistic phase. The latter point is investigated in more detail in the next section.

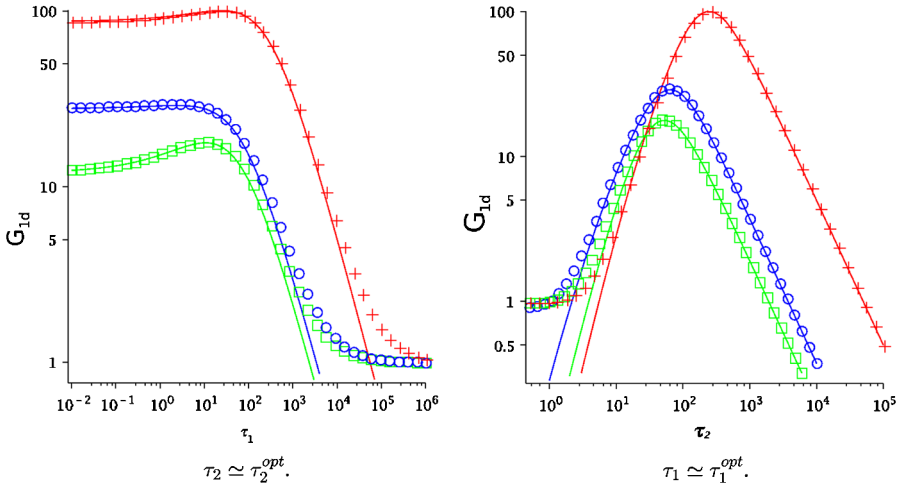


FIG. 20. Optimization of the reaction rate for intermittent active transport. Gain of reactivity due to active transport G_{1d} in one dimension as a function of τ_1 or τ_2 (logarithmic scale). The analytical form [the mean detection time with diffusion alone divided by the mean detection time with intermittence (B23)] is plotted against the exact solution (symbols), for the following values of the parameters (arbitrary units): $D = 1, V = 1$ for all curves and $a = 10, b = 10^4$ (+); $a = 10, b = 10^3$ (∘); $a = 2.5, b = 10^3$ (□). Standard cellular conditions (as discussed in the text) correspond to ∘ and + curves.

IV. INTERMITTENT SEARCH: A ROBUST STRATEGY

As shown, intermittent search strategies are observed at the macroscopic scale (foraging animals) as well as at the microscopic scale (localization of a DNA sequence by a protein, vesicle transport in cells). The models we have used to interpret these findings, in particular, in Secs. II.C and III.B, present similar general features.

Loverdo *et al.* (2009b) introduced a generic model of intermittent search based on these general features and studied systematically in one, two, and three dimensions, and for three different modelings of the detection phase. This rather technical section (completed by Appendix B) gathers the main tools usually involved in the calculation of first-passage properties of intermittent random walks, and utilized throughout this review. Finally, general conclusions on intermittent random walks can be drawn from this systematic study and are summarized in Table I.

A. Introduction

The generic model presented in this section follows the original definition of intermittence given in the Introduction and relies on a succession of slow phases with detection, and ballistic phases without detection, without direction correlation between ballistic phases. This model is minimal in the sense that the searcher has low memory skills. Indeed, without correlations between ballistic phases, there is no spatial memory. We also assume a Markovian searcher, i.e., one with no temporal memory. As previously, we address the following main questions: Is it beneficial for the search to include such fast but nonreactive phases? Is it possible, by properly tuning the kinetic parameters of trajectories (such as the durations of each of the two phases), to minimize the search time? We develop in what follows a systematic analytical study of intermittent random walks in one, two, and three dimensions and fully characterize the optimal regimes. Overall, this systematic approach allows us to identify robust features of intermittent search strategies. In particular, the slow phase that enables detection is often hard to characterize experimentally. Here we propose and study three distinct modelings for this phase, which allows us to assess to what extent our results are robust and model independent. Our analysis covers in detail intermittent search problems in one, two, and three dimensions and is aimed at giving a quantitative basis—as complete as possible—to model real search problems involving intermittent searchers.

We first define the model and introduce the methods. Then we summarize the results for the search problem in dimensions 1, 2, and 3, for different types of motion in the slow phase. Eventually we synthesize the results in Table I where all cases, their differences, and their similarities are gathered. This table finally leads us to draw general conclusions.

B. Model and notations

1. Model

We consider an intermittent searcher that switches between two phases. The switching rate λ_1 (λ_2) from phase 1 to phase 2 (from phase 2 to phase 1) is time independent, which assumes that the searcher has no temporal memory and implies an exponential distribution of durations of each phase i of mean $\tau_i = 1/\lambda_i$.

Phase 1 denotes the phase of slow motion, during which the target can be detected if it lies within a distance from the searcher that is smaller than a given detection radius a, which is the maximum distance within which the searcher can get information about target location. We propose three different modelings of this phase, in order to cover various real-life situations (see Fig. 21).

(i) In the ''static mode,'' the searcher is immobile and detects the target with probability k per unit time if it lies at a distance less than a.

(ii) In the second modeling, called the ''diffusive mode,'' the searcher performs a continuous diffusive motion, with diffusion coefficient D, and finds the target immediately if it lies at a distance less than a.

(iii) In the last modeling, called the ''ballistic mode,'' the searcher moves ballistically in a random direction with constant speed v_l and reacts immediately with the target if it lies at a distance less than a. We note that this mode is equivalent to the model of Lévy walk searches proposed by Viswanathan *et al.* (1999), except for the law of the time between reorientations (see Sec. II.A). It was shown that for destructive search, i.e., targets that cannot be revisited, the optimal strategy is obtained for a straight ballistic motion, without reorientations (see Sec. II.A). In what follows it is shown that if another motion, ''blind'' (i.e., without detection) but with higher velocity, is available, there are regimes outperforming the straight line strategy.

Some comments on these different modelings of the slow phase 1 are in order. First, these three modes schematically cover experimental observations of the behavior of animals searching for food (O'Brien *et al.*, 1990; Bell, 1991), where the slow phases of detection are often described as static, random, or having slow velocity. Several real situations are also likely to involve a combination of two modes. For instance, the motion of a reactive particle in a cell not bound to motors can be described by a combination of the diffusive and static modes. For simplicity, these modes are treated independently, and this approach can therefore be considered as a limit of more realistic models. Finally, combining these three schematic modes covers a wide range of possible motions, from subdiffusive (even static), diffusive, to superdiffusive (even ballistic). Beyond the modeling of real-life systems, studying different detection modes enables us to assess the robustness of the results.

Phase 2 denotes the fast phase during which the target cannot be found. In this phase, the searcher performs a ballistic motion at a constant speed V in a random direction, redrawn for each new phase 2, independently of previous phases. In real examples correlations between successive ballistic phases could exist, as observed for foraging animals (O'Brien *et al.*, 1990). If correlations are very high, it is close to a one-dimensional problem with all phases 2 in the same direction, a different problem already treated in Sec. II.B.

TABLE I. Recapitulation of main results of the generic intermittent search model: strategies minimizing the mean first-passage time on the target. In each cell, validity of the regime, optimal τ_1, optimal τ_2, minimal t_m (t_m with $\tau_i = \tau_i^{\rm opt}$). The values of $\tau_2^{\rm opt}$ independent of the description of the slow detection phase 1 are given in bold. Results are given in the limit $b \gg a$. The complement to the intermediate regime for the diffusive mode in two dimensions is $c = 4[\gamma - \ln(2)]$ with γ the Euler constant; w is a solution of $\frac{2Vb}{wD}\ln[4\ln(w) - 5 + c] = -8(\ln w)^2 + [6 + 8\ln(b/a)]\ln(w) - 10\ln(b/a) + 11 - c[c/2 + 2\ln(a/b) - 3/2]$; in this regime we have $t_m^{\rm opt} \simeq \frac{b^2}{D}\ln(\frac{b}{a})\frac{1}{4\ln(w)-5}[1 + \frac{wD(4\ln(w)-7)}{bV\sqrt{5\ln(w)-5}}][1 + 2\ln(w)\ln(\frac{b}{aw})]$. Adapted from Loverdo *et al.* (2009b).

Static mode		Diffusive mode			Ballistic mode	
1D	Always intermittence	$b < \frac{D}{V}$	$b > \frac{D}{V}$, $a \ll \sqrt{\frac{b}{a}}\frac{D}{V}$	$b > \frac{D}{V}$, $a \gg \sqrt{\frac{b}{a}}\frac{D}{V}$	$v_l < v_l^c$	$v_l < v_l^c \simeq \frac{V}{2}\sqrt{\frac{3a}{b}}$
	$\tau_1^{\rm opt} = \sqrt{\frac{\tau_2^{\rm opt}}{2k}} \simeq \sqrt{\frac{a}{2Vk}}\sqrt[4]{\frac{b}{3a}}$	$\tau_1^{\rm opt} \to \infty$	$\tau_1^{\rm opt} \simeq (\frac{b^2D}{36V^4})^{1/3}$	$\tau_1^{\rm opt} \simeq \frac{Db}{48V^2a}$	$\tau_1^{\rm opt} \to \infty$	$\tau_1^{\rm opt} \to 0$
	$\boldsymbol{\tau_2^{\rm opt} \simeq \frac{a}{V}\sqrt{\frac{b}{3a}}}$	$\tau_2^{\rm opt} \to 0$	$\tau_2^{\rm opt} \simeq (\frac{2b^2D}{9V^4})^{1/3}$	$\boldsymbol{\tau_2^{\rm opt} \simeq \frac{a}{V}\sqrt{\frac{b}{3a}}}$	$\tau_2^{\rm opt} \to 0$	$\boldsymbol{\tau_2^{\rm opt} \simeq \frac{a}{V}\sqrt{\frac{b}{3a}}}$
	$\tau_m^{\rm opt} \simeq \frac{2b}{V}\sqrt{\frac{b}{3a}}\left(1 + \sqrt{\frac{V}{2ka}}\sqrt[4]{\frac{3a}{b}}\right)^2$	$\tau_m^{\rm opt} \simeq \frac{b^2}{3D}$	$\tau_m^{\rm opt} \simeq (\frac{3^5b^4}{2^4DV^2})^{1/3}$	$\tau_m^{\rm opt} \simeq \frac{2b}{V}\sqrt{\frac{b}{3a}}$	$\tau_m^{\rm opt} \simeq \frac{b}{v_l}$	$\tau_m^{\rm opt} \simeq \frac{2b}{V}\sqrt{\frac{b}{3a}}$
2D	Always intermittence	$b < \frac{D}{V}$	$b \gg \frac{D}{V} \gg a$	$b \gg a \gg \frac{D}{V}$	$v_l > v_l^c$	$v_l < v_l^c \simeq \pi V/(4\sqrt{\ln(\frac{b}{a})})$
	$\tau_1^{\rm opt} = \sqrt{\frac{\tau_2^{\rm opt}}{2k}} \simeq \sqrt{\frac{a}{2Vk}}\sqrt[4]{\ln(\frac{b}{a}) - \frac{1}{2}}$	$\tau_1^{\rm opt} \to \infty$	$\tau_1^{\rm opt} \simeq \frac{b^2}{D}\frac{4\ln w - 5 + c}{w^2(4\ln w - 7 + c)}$	$\tau_1^{\rm opt} \simeq \frac{D}{2V^2}\frac{(\ln(\frac{b}{a}))^2}{2\ln(\frac{b}{a})-1}$	$\tau_1^{\rm opt} \to \infty$	$\tau_1^{\rm opt} \to 0$
	$\boldsymbol{\tau_2^{\rm opt} \simeq \frac{a}{V}\sqrt{\ln(\frac{b}{a}) - \frac{1}{2}}}$	$\tau_2^{\rm opt} \to 0$	$\tau_2^{\rm opt} \simeq \frac{b}{V}\frac{\sqrt{4\ln w - 5 + c}}{w}$	$\boldsymbol{\tau_2^{\rm opt} \simeq \frac{a}{V}\sqrt{\ln(\frac{b}{a}) - \frac{1}{2}}}$	$\tau_2^{\rm opt} \to 0$	$\boldsymbol{\tau_2^{\rm opt} \simeq \frac{a}{V}\sqrt{\ln(\frac{b}{a}) - \frac{1}{2}}}$
	$\tau_m^{\rm opt} \simeq \frac{2b^2}{aV}(\sqrt[4]{\ln(\frac{b}{a})} + \sqrt{\frac{V}{2ak}})^2$	$\tau_m^{\rm opt} \simeq \frac{b^2}{2D}\ln(\frac{b}{a})$	$\tau_m^{\rm opt}$, c, w: see Appendix B.2.b	$\tau_m^{\rm opt} \simeq \frac{2b^2}{aV}\sqrt{\ln(\frac{b}{a})}$	$\tau_m^{\rm opt} \simeq \frac{\pi b^2}{2av_l}$	$\tau_m^{\rm opt} \simeq \frac{2b^2}{aV}\sqrt{\ln(\frac{b}{a})}$
3D	Always intermittence	$a \leqslant 6\frac{D}{V}$		$b \gg a \gtrsim 6\frac{D}{V}$	$v_l > v_l^c$	$v_l < v_l^c \simeq 0.6V$
	$\tau_1^{\rm opt} = \sqrt{\frac{\tau_2^{\rm opt}}{2k}} \simeq \sqrt[4]{\frac{3}{10}}\sqrt{\frac{a}{Vk}}$	$\tau_1^{\rm opt} \to \infty$		$\tau_1^{\rm opt} \simeq \frac{6D}{V^2}$	$\tau_1^{\rm opt} \to \infty$	$\tau_1^{\rm opt} \to 0$
	$\boldsymbol{\tau_2^{\rm opt} \simeq 1.1\frac{a}{V}}$	$\tau_2^{\rm opt} \to 0$		$\boldsymbol{\tau_2^{\rm opt} \simeq 1.1\frac{a}{V}}$	$\tau_2^{\rm opt} \to 0$	$\boldsymbol{\tau_2^{\rm opt} \simeq 1.1\frac{a}{V}}$
	$\tau_m^{\rm opt} \simeq \frac{b^3}{Va^2}(\sqrt[4]{\frac{24}{5}} + \sqrt{\frac{V}{ak}})^2$	$\tau_m^{\rm opt} \simeq \frac{b^3}{3Da}$		$\tau_m^{\rm opt} \simeq 2.2\frac{b^3}{Va^2}$	$\tau_m^{\rm opt} \simeq \frac{4b^3}{3a^2v_l}$	$\tau_m^{\rm opt} \simeq 2.2\frac{b^3}{Va^2}$

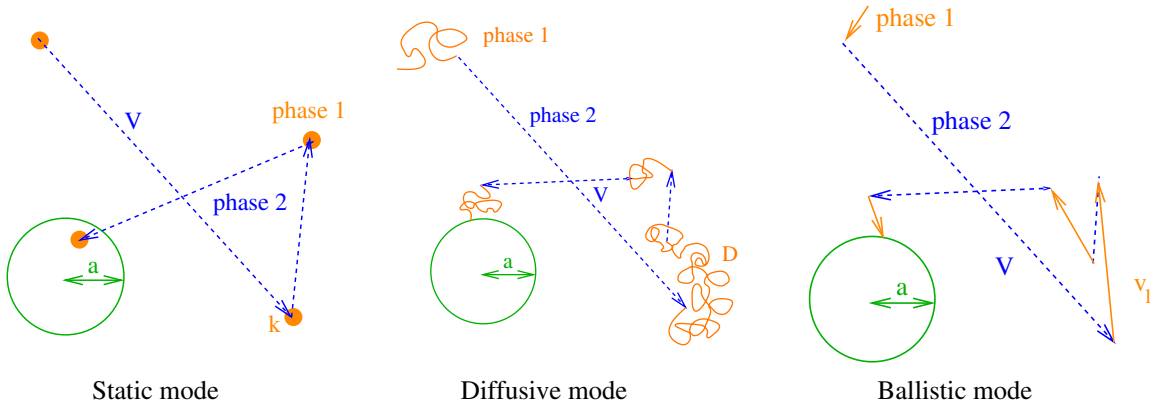


FIG. 21. The three different descriptions of phase 1 (the phase with detection), here represented in two dimensions.

We consider here the limit of low correlation, that is, of a searcher with no memory skills.

We assume that the searcher evolves in a d-dimensional spherical domain of radius b, with reflective boundaries and with one centered immobile target of radius a. As the searcher does not initially know the target's location, we start the walk from a random point of the d-dimensional sphere and average the mean target detection time over the initial position. This geometry models the case of a single target in a finite domain and also provides a good approximation of an infinite space with regularly spaced targets. Such a regular array of targets corresponds to a mean-field approximation of random distributions of targets, which can be more realistic in some experimental situations.

2. Methods

We explain here the general methods and introduce the notation.

We define $s_i(\mathbf{r}, t)$ as the probability that the searcher has not yet found the target at t, *starting* from $\mathbf{r}$ in state i, where state $i = 1$ is the slow-motion phase with detection and state $i = 2$ is the fast-motion phase without target detection. Note that in dimension 1, the space coordinate will be denoted by x, and in the case of a ballistic mode for phase 1, the upper index in $t_i^{\pm}$ stands for ballistic motion with direction $\pm x$. The survival probability $s_i(\mathbf{r}, t)$ is the solution of the following standard backward differential Chapman-Kolmogorov equations (Gardiner, 1996):

$$L_i^{\dagger} s_i(\mathbf{r}, t) + \frac{1}{\tau_i}[s_j(\mathbf{r}, t) - s_i(\mathbf{r}, t)] - k s_i(\mathbf{r}, t) I_a(\mathbf{r}) \delta(i-1) = \frac{\partial s_i(\mathbf{r}, t)}{\partial t}, \tag{43}$$

with $I_a(\mathbf{r}) = 1$ when $r < a$, and 0 else, and $L_i^{\dagger}$ the adjoint operator of the transport operator. For example, $L_i^{\dagger} = D\Delta$ for diffusion and $L_i^{\dagger} = \mathbf{v} \cdot \boldsymbol{\nabla}$ for a ballistic motion of velocity $\mathbf{v}$. The mean first-passage time to the target $t_i(\mathbf{r})$ for a searcher starting in the phase i from point $\mathbf{r}$ is then given by

$$t_i(\mathbf{r}) = -\int_0^{\infty} t \frac{\partial s_i(\mathbf{r}, t)}{\partial t} dt = \int_0^{\infty} s_i(\mathbf{r}, t) dt. \tag{44}$$

Consequently, for each phase i, $t_i(\mathbf{r})$ is the solution of

$$L_i^{\dagger} t_i(\mathbf{r}) + \frac{1}{\tau_i}[t_j(\mathbf{r}) - t_i(\mathbf{r})] - k t_i(\mathbf{r}) I_a(\mathbf{r}) \delta(i-1) = -1. \tag{45}$$

We assume that the searcher starts in phase 1, and to take into account the fact that it does not initially know the target's location, we average the mean detection time over the starting point, leading to the following definition of the mean search time:

$$t_m = \frac{1}{V(\Omega_d)} \int_{\Omega_d} t_1(\mathbf{r}) d\mathbf{r}, \tag{46}$$

with Ω_d the d-dimensional sphere of radius b and $V(\Omega_d)$ its volume. Unless specified, we consider the low-target-density limit $a \ll b$.

Our general aim is to minimize t_m as a function of the mean durations τ_1, τ_2 of each phase and, in particular, to determine under which conditions an intermittent strategy (with finite τ_2) is faster than the usual single-state search in phase 1 only, which is given by the limit $\tau_1 \to \infty$. In the static mode, intermittence is necessary for the searcher to move and is therefore always favorable. In the diffusive mode, we compare the mean search time with intermittence t_m to the mean search time for a single-state diffusive searcher t_{diff} and define the gain as gain $= t_{\mathrm{diff}}/t_m$. Similarly, in the ballistic mode, we compare t_m to the mean search time for a single-state ballistic searcher t_{bal} and define the gain as gain $= t_{\mathrm{bal}}/t_m$. The upper index "opt" is used to denote the value of a parameter or variable at the minimum of t_m.

Calculations are exact in dimension 1, whereas approximation schemes (which can be checked numerically) are needed in dimensions 2 and 3. The main calculation steps are given in Appendix B, and further technical details can be found in Loverdo *et al.* (2009b). We now summarize the main results for each dimension.

C. Dimension 1

Besides the fact that it involves more tractable calculations, the one-dimensional case is also interesting to model real search problems. As discussed, at the microscopic scale

tubular structures of cells such as axons or dendrites in neurons can be considered as one dimensional (Alberts, 2002). The active transport of reactive particles, which alternate between diffusion phases and ballistic phases when bound to molecular motors, can be schematically captured by this generic model with diffusive mode (Loverdo *et al.*, 2008). At the macroscopic scale, one could cite animals such as ants (Dussutour *et al.*, 2005), which tend to follow tracks or one-dimensional boundaries. More generally, borderlines between different habitats, such as a shoreline, can be considered as one dimensional.

It is shown in Appendix B that intermittent search strategies in dimension 1 share similar features for the static, diffusive, and ballistic detection modes. In particular, all modes show regimes where intermittence is favorable and lead to a minimization of the search time. Strikingly, the optimal duration of the nonreactive relocation phase 2 is quite independent of the modeling of the reactive phase: $\tau_2^{\rm opt} = \frac{a}{3V}\sqrt{b/a}$ for the static mode, for the ballistic mode (in the regime $v_l < v_l^c \simeq \frac{V}{2}\sqrt{3a/b}$), and for the diffusive mode (in the regime $b > \frac{D}{V}$ and $a \gg \frac{D}{V}\sqrt{b/a}$). This shows the robustness of the optimal value $\tau_2^{\rm opt}$.

D. Dimension 2

As discussed, the two-dimensional problem is particularly well suited to model animal behaviors; it is also relevant to the microscopic scale, since it mimics, for example, the case of cellular traffic on membranes (Alberts, 2002). While in dimension 1 the mean search time can be calculated analytically, in dimension 2 (and later in dimension 3) approximation schemes are necessary and can be checked by numerical simulations.

Remarkably, for the three different modes of detection (static, diffusive, and ballistic), there is a regime where intermittence minimizes the search time for one and the same $\tau_2^{\rm opt}$, given by $\tau_2^{\rm opt} = \frac{a}{V}\sqrt{\ln(b/a) - 1/2}$. As in dimension 1, this indicates that optimal intermittent strategies are robust and widely independent of the details of the description of the detection mechanism.

E. Dimension 3

The three-dimensional case is also relevant to biology. At the microscopic scale, it corresponds, for example, to intracellular traffic in the bulk cytoplasm of cells, or at larger scales to animals living in dimension 3, such as plankton (Bartumeus *et al.*, 2003) or *Caenorhabditis elegans* in its natural habitat (soil) (Kiontke and Sudhaus, 2005). As was the case in dimension 2, different assumptions have to be made to obtain analytical expressions of the search time. Such assumptions can be checked by numerical simulations using the same algorithms as in dimension 2.

For the three possible modelings of the detection mode (static, diffusive, and ballistic) in dimension 3, there is a regime where the optimal strategy is intermittent. Remarkably, and as was the case in dimensions 1 and 2, the optimal time to spend in the fast nonreactive phase 2 is independent of the modeling of the detection mode and reads $\tau_2^{\rm opt} \simeq 1.1\,\frac{a}{V}$. Additionally, while the mean first-passage time to the target scales as b^3, the optimal values of the durations of the two phases do not depend on the target density a/b.

F. Discussion and conclusion

To summarize, the methods of calculation developed in this section and in Appendix B allow one to show that the mean search time of intermittent random walks can be minimized under broad conditions. Table I summarizes the main results of this minimization. This study shows that the optimal durations of the two phases and the gain of intermittent search (as compared to a single-state search) do depend on the target density in dimension 1. In particular, the gain can be very high at low target concentration. Interestingly, this dependence is smaller in dimension 2 and vanishes in dimension 3. The fact that intermittent search is more advantageous in low dimensions (1 and 2) can be understood as follows. At large scale, the intermittent searcher effectively performs a random walk, and therefore scans a space of dimension 2. In an environment of dimension 1 (and marginally of dimension 2), the searcher therefore oversamples the space, and it is favorable to perform large jumps to go to previously unexplored areas. In contrast, in dimension 3, the random walk is transient, and the searcher on average always scans previously unexplored areas, which makes large jumps less beneficial.

Additionally, these results show that, for various modeling choices of the slow reactive phase, there is one and the same optimal duration of the fast nonreactive phase, which depends only on the space dimension. This further supports the robustness of optimal intermittent search strategies. Such robustness and efficiency could explain why intermittent trajectories are observed so often, as well as in various forms.

V. EXTENSIONS AND PERSPECTIVES

Far from closing the problem, the generic model presented in Sec. IV opens interesting perspectives. In this section, we highlight a few promising directions: (i) The influence of the targets' distribution; and (ii) the effect of taking into account a more involved searcher, enjoying now some orientational and temporal memory. Indeed, in the generic model of Sec. IV, the searcher has minimal memory skills. On the one hand, the phase duration distribution is exponential, which means that there is no temporal memory: The effect of other duration distributions is studied in Sec. V.C. On the other hand, the direction of each new ballistic blind phase is taken at random, independently of the previous phases, meaning that there is no orientational memory: We study the effect of correlations in Sec. V.B. (iii) The effects of moving targets, which can be more realistic at both the microscopic and macroscopic scales. Next, we review in Sec. V.E similar models of intermittent search, which have been proposed recently in other contexts, and finally discuss how further models could also be applied to design efficient searches instead of interpreting biological systems (see Sec. V.F).

A. Influence of the target distribution on the search time

We first study the influence of target distribution on the previous results. For simplicity, we study the one-dimensional model of Sec. II.B.

1. How are real targets distributed?

In the context of foraging animals, target distributions are often described as regular, random, or patched; (Bell, 1991); see Fig. 22. In the models presented, the chosen geometry can be interpreted as one target in a finite domain, or as an infinite array of regularly spaced targets. The regular distribution is representative of the real-life case of targets that repel each other, thus being as far from each other as possible. This distribution is also a mean-field approximation of other distributions. As the regular distribution has already been studied, we discuss the other representative distributions.

If targets are in patches, for example, when they attract each other, when a target is found it is likely that other targets are present in the immediate surroundings. Thus a simple strategy is to switch behavior when a target is encountered, as proposed, for example, by Benhamou (1992). The search is then in two steps: finding a patch, and exploiting it. For the first step, previous results are still valid, except for the density of targets, which has to be replaced by the density of patches.

In the following we focus on the last case of Poissonian targets, which corresponds to situations of noninteracting targets.

2. Analytical results in the case of a Poissonian distribution of targets

In the case of a one-dimensional Poissonian distribution of targets, the distance between two consecutive targets is exponentially distributed. Except for this change, the other parameters remain as defined in the model of Sec. II.B.

The mean search time is, in general, difficult to calculate for a Poissonian target distribution, which can be seen as frozen disorder. However, estimates (for $L \gg D/V$) can be given in three regimes [see Moreau *et al.* (2007) and Moreau *et al.* (2009) for details]:

(i) In the large-ballistic-displacements limit (when $V\tau_2 \gg \sqrt{D\tau_1}$), two successive diffusive phases can be considered as nonoverlapping. It can be shown that in this regime

$$\langle t\rangle \simeq L\frac{\tau_1+\tau_2}{2\sqrt{D\tau_1}}. \tag{47}$$

(ii) In the small-ballistic-displacements limit (when $V\tau_2 \ll \sqrt{D\tau_1}$), successive diffusive phases often overlap. This leads to

$$\langle t\rangle \simeq L\frac{\tau_1+\tau_2}{V\tau_2}. \tag{48}$$

(iii) The most interesting situation is the intermediary regime. Indeed, in the first case (large ballistic displacements), relocations are too long and overshoot the target; and in the second case (small ballistic displacements), there are often repetitive scans of the same areas. In the intermediary regime, the mean first-passage time to the target can be approximated by

$$\langle t\rangle \simeq L\frac{\tau_1+\tau_2}{V\tau_2}\frac{(1+\theta)^2(1+\epsilon\theta)}{1+4\theta+2\epsilon\theta^2}, \tag{49}$$

with $\theta = V\tau_2/\sqrt{D\tau_1}$ and $\epsilon = \sqrt{D\tau_1}/L$.

This last regime enables a discussion of the efficiency of the intermittent search. The efficiency can be quantified by comparing $\langle t\rangle^{\mathrm{opt}}$, the mean search time with intermittence at minimum, with $\tau_{\mathrm{diff}} = L^2/(2D)$, the mean search time with diffusion alone. It can be shown that intermittence decreases the search time in the limit of low target density, and that the mean search time is minimized for τ_1 as small as possible. The optimization with respect to τ_2 leads to two regimes, depending on the minimal value of τ_1 as compared to the previously introduced time scale $\tau = D/V^2$, characteristic of the searcher.

(i) When $\tau_1 \gg \tau$,

$$\frac{\tau_2^{\mathrm{opt}}}{\tau} \sim \sqrt{\frac{7}{4}}\left(\frac{\tau_1}{\tau}\right)^{3/4}. \tag{50}$$

At the optimum, the mean search time is

$$\langle t\rangle^{\mathrm{opt}} \sim \frac{L}{2V}\sqrt{\frac{\tau_1}{\tau}}, \tag{51}$$

and the gain is

$$G \sim \frac{L}{\sqrt{D\tau_1}} = \sqrt{\frac{2\tau_{\mathrm{diff}}}{\tau_1}}, \tag{52}$$

where $\tau_{\mathrm{bal}} = L/V$ is the typical time needed to travel in the ballistic mode the distance between two consecutive targets. As we shall see in the following, in this regime the approximations are very accurate.

(ii) When $\tau_1 \ll \tau$,

$$\frac{\tau_2^{\mathrm{opt}}}{\tau} \sim \frac{1}{2}\sqrt{\frac{\tau_1}{\tau}}. \tag{53}$$

At the optimum, the mean search time is

$$\langle t\rangle^{\mathrm{opt}} \sim \frac{3L}{4V} = \frac{3}{4}\tau_{\mathrm{bal}}, \tag{54}$$

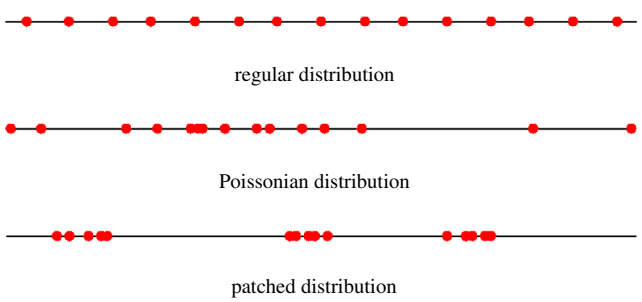
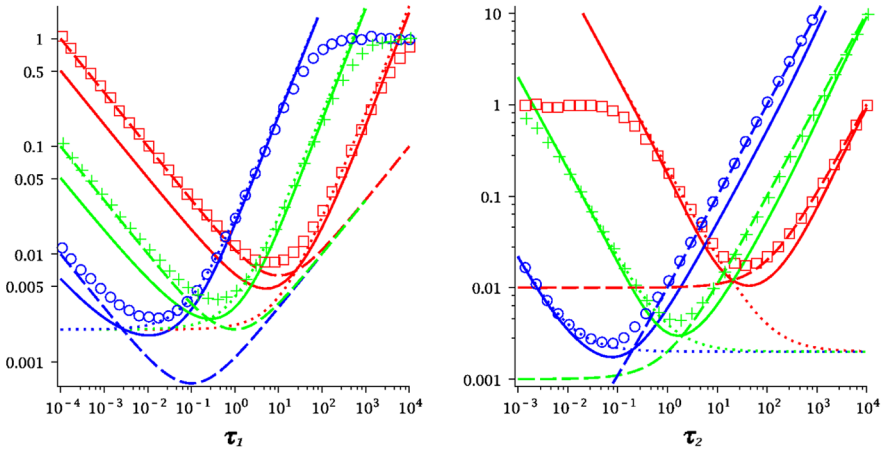


FIG. 22. Examples of target distributions.



$ln(\langle T\rangle/\tau_{\rm diff})$ as a function of $ln(\tau_1)$. $\tau_2 = 10$ (red, □), $\tau_2 = 1$ (green, +), $\tau_2 = 0.1$ (blue, ∘).

$ln(\langle T\rangle/\tau_{\rm diff})$ as a function of $ln(\tau_2)$. $\tau_1 = 100$ (red, □), $\tau_1 = 1$ (green, +), $\tau_1 = 0.01$ (blue, ∘).

FIG. 23. Validity of the approximations. Mean first-passage time to the target, renormalized by the mean first-passage time without intermittence. Small-ballistic-displacements approximation (48) (dashed line). Large-ballistic-displacements approximation (47) (dotted line). Intermediary approximation (49) (line). Numerical simulations (symbols). $D = 1$, $V = 1$, $L = 10^3$.

and the gain is

$$G \sim \frac{2LV}{3D} = \frac{4\tau_{\rm diff}}{3\tau_{\rm bal}}. \tag{55}$$

As we shall see in the following, the approximations are qualitatively good in this regime, but not as precise as in the other regime. Indeed, the gain obtained here would mean that the mean first-passage time to the target is smaller than $\tau_{\rm bal}$, which is the minimal mean time to travel to the target (except if $\tau_{\rm bal} > \tau_{\rm diff}$). In fact, as shown in Fig. 25, simulations predict that $\langle t\rangle^{\rm opt} \longrightarrow \tau_{\rm bal}$. This means that very fast intermittence enables the searcher to retain the best of the two phases: the reactivity of phase 1 and the motion of phase 2.

Figure 23 represents the mean search time $\langle t\rangle$ as a function of τ_1 and τ_2 for typical values of the other parameters. It allows a comparison of the numerical results with the approximations (47) and (48), and with the intermediary approximation (49). It shows that the approximations of large and small ballistic displacements are valid in the expected conditions, and the intermediary approximation (49) correctly reproduces the existence and the position of the minimum of $\langle t\rangle$. Figure 24 supports the scaling laws relating τ_1 and the corresponding optimal waiting time τ_2 at the optimum. The exponent 3/4 of the theoretical scaling law (50) for $\tau \ll \tau_1$ is well confirmed by the simulations. This is not the case for the law (53) for $\tau \gg \tau_1$, which indicates that the approximations should be handled with care for short waiting times τ_1,τ_2, although their results are qualitatively correct. Figure 25 shows the gain as a function of τ_1 for different possible conditions. This supports the conclusions of the theoretical study and, indeed, confirms that the gain due to intermittence can be important if $\tau_{\rm diff} \gg \tau_{\rm bal}$.

3. Conclusion

In the case of a Poissonian distribution of targets, intermittence remains valid as a strategy minimizing the search time. The optimal strategy still consists in taking τ_1 as small as possible. However, $\tau_2^{\rm opt}$ is different from that in the case of regularly spaced targets. The optimal mean duration of ballistic flights scales as $\sqrt{(7/4)}(\tau_1^3\tau)^{1/4}$ in the limit $\tau_1 \gg \tau = D/V^2$. In this regime, at the optimum, $\langle t\rangle \simeq \frac{1}{2}\frac{L}{V}\sqrt{\tau_1/\tau_2}$, with a gain compared to diffusion alone proportional to $L/\sqrt{D\tau_1}$.

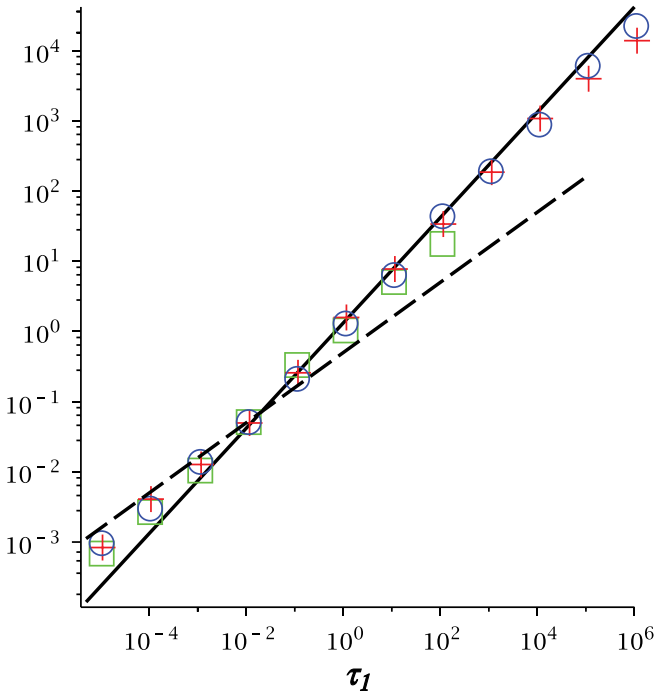


FIG. 24. $\ln(\tau_2^{\rm opt})$ as a function of $\ln(\tau_1)$. Small-τ_1 analytical prediction (53) (dashed line). Large-τ_1 analytical prediction (50) (solid line). Numerical values (symbols), for $L = 10$ (□), $L = 10^3$ (+), and $L = 10^5$ (∘). $D = 1$, $V = 1$.

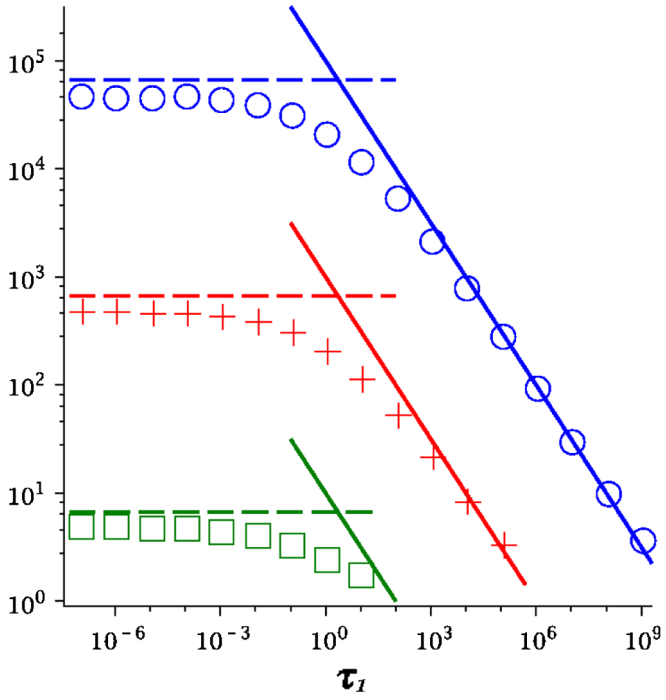


FIG. 25. $\ln(G)$ as a function of $\ln(\tau_1)$ (τ_2 taken optimal). Small-τ_1 analytical prediction (55) (dotted line). Large-τ_1 analytical prediction (52) (solid line). Numerical simulations (points). $L = 10^1$ (□), $L = 10^3$ (+), and $L = 10^5$ (∘). $D = 1$, $V = 1$.

B. Taking into account partial correlations in ballistic phases

1. Motivation

The models developed in Secs. II.B and IV are very similar. The searcher alternates between a slow reactive phase and a fast ballistic blind phase. The main difference is that in Sec. II.B, ballistic phases are always in the same direction, whereas, on the contrary, in Sec. IV, the direction of each new ballistic phase is random and independent of the previous ballistic phase.

In the case of animal trajectories, the successive directions of ballistic phases are usually correlated (O'Brien *et al.*, 1990). We have considered so far two extreme cases: no correlation or infinite-range correlations. In both cases, there are regimes where intermittence is favorable. However, in the case of infinite-range correlations, the shorter the duration of each phase, the smaller the search time. In contrast, in the case without any correlation, the minimal search time is obtained for finite values of τ_1 and τ_2, which even diverge with the system size. In the intermediate case of finite range correlations, determination of the nature of the minimum is an interesting theoretical question. In addition, as real biological systems often present correlations, it is important to take into account correlations in the generic model of intermittence. We present in what follows the simplest case of the static mode of detection in dimension 1.

2. Model

The searcher is either in the reactive phase 1 (where it is immobile and finds the target with probability k per unit time if the target is at a distance smaller than a) or in the ballistic phase 2, of velocity V. For each new ballistic phase, the direction of V is the same as in the previous ballistic phase with probability p, and in the opposite direction with probability $1 - p$. The distribution of the duration of the phases is exponential, of mean τ_i, and the distance between two targets is $2b$.

In the case of no correlations ($p = 1/2$) the mean search time has been calculated in Appendix B.1 [see Eq. (B13)], where it was shown that the optimum is obtained for $\tau_1^{\rm opt} = \sqrt{(a/Vk)}(b/12a)^{1/4}$ and $\tau_2^{\rm opt} = a/V\sqrt{b/3a}$.

In the general case, the methods of Sec. IV can be adapted to calculate analytically the mean search time starting from a random position in state 1, which can be written as

$$t_m = (\tau_2 + \tau_1)\left\{\frac{1}{k\tau_1} + \frac{b-a}{b}\left[\frac{2}{3}\frac{(1-p)(b-a)^2}{\tau_2^2 V^2} + 1 + \frac{1}{k\tau_1} + \frac{u(b-a)}{\sqrt{k\tau_1}\tau_2 V}\coth\left(\frac{\sqrt{k\tau_1}ua}{\tau_2 V(1+k\tau_1)}\right)\right]\right\}, \quad (56)$$

with $u = \sqrt{2(1-p) + k\tau_1}$.

3. Minimization of the mean search time

a. Case of infinite-range correlation $p = 1$

It can be shown that the mean search time is minimized for τ_1 and τ_2 tending to 0, with $\tau_1 = \alpha\tau_2$. We define $w = ak/v$, and depending on this parameter,

(i) $w < 1$: $\alpha^{\rm opt} \simeq (\frac{3}{2w^2})^{1/3}$,

(ii) $1 < w < w^*$: $\alpha^{\rm opt} \simeq \frac{\ln(4w)}{2w}$,

(iii) $w > w^*$: $\alpha^{\rm opt} \simeq \sqrt{\frac{2a}{wb}}$.

w^* is defined as the solution of $\ln(4w^*)/2w^* = \sqrt{2a/w^* b}$. These expressions are in good agreement with the numerical minimization of the exact expression of the mean search time (see Fig. 26).

b. Case of intermediate correlations

The mean search time obtained in (56) is difficult to optimize. An important question raised is to determine whether the mean search time is minimized for finite τ_1 and τ_2 (as in the case $p = 0.5$), or for τ_1 and τ_2 tending to 0 (as in the case $p = 1$). An answer can be obtained by noticing that a lower bound of the mean search time is given by

$$t_m \geq (\tau_1 + \tau_2)\left(\frac{1}{k\tau_1} + \frac{(b-a)^3}{b}\frac{2(1-p)}{3\tau_2^2 V^2}\right). \quad (57)$$

Supposing that the minimum is realized for at least the case of $\tau_i \to 0$, three cases arise.

(i) $\tau_1 \to 0$ with $\tau_1 \ll \tau_2$. In this case $t_m \geq \tau_2/k\tau_1 \to \infty$.

(ii) $\tau_2 \to 0$ with $\tau_2 \ll \tau_1$. In this case $t_m \geq \tau_1 \frac{(b-a)^3}{b} \times \frac{2(1-p)}{3\tau_2^2 V^2} \to \infty$.

(iii) $\tau_1 \sim \tau_2$ and both $\to 0$. In this case $t_m \geq \tau_2 \frac{(b-a)^3}{b} \times \frac{2(1-p)}{3\tau_2^2 V^2} \sim 1/\tau_2 \to \infty$.

Finally, this shows that the minimum is realized for finite values of τ_1 and τ_2 as soon as $p < 1$. Actually, it can be

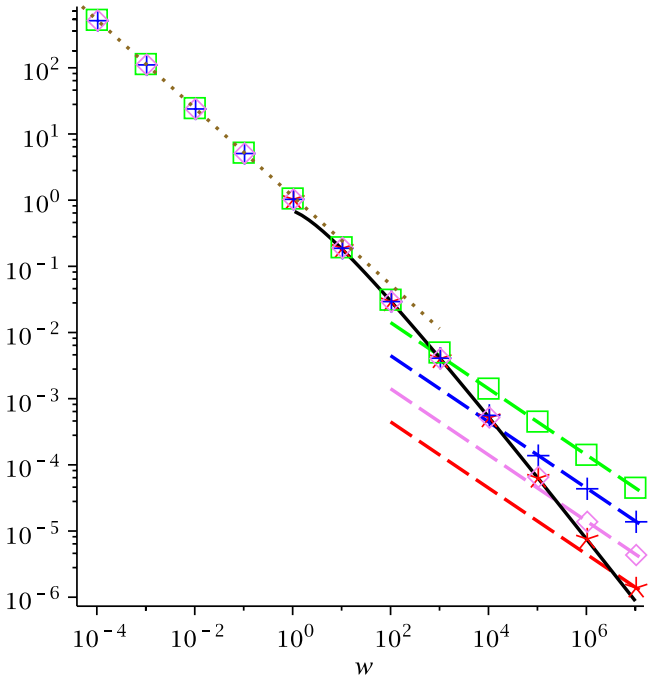


FIG. 26. Minimization of the mean search time for the static mode with infinite correlation ($p = 1$). α^{opt} as a function of w. Theoretical expression for small w (dots), for intermediate w (solid line), and for large w (dashed lines). Optimization of the exact expression (with $\tau_2 \to 0$ and $\tau_1 = \alpha\tau_2$) (symbols). $b = 100$ (□), $b = 10^3$ (+), $b = 10^4$ (◇), and $b = 10^5$ (⋆). $a = 1$, $V = 1$.

shown that, except for p close to 1, the minimum of the search time is obtained for

$$\tau_1^{\mathrm{opt}} = \sqrt{\frac{a}{Vk}}\left(\frac{b}{a}\frac{(1-p)}{6}\right)^{1/4} \tag{58}$$

and

$$\tau_2^{\mathrm{opt}} = \frac{a}{V}\sqrt{\frac{b}{a}\frac{2(1-p)}{3}}. \tag{59}$$

Interestingly, note that the relation $\tau_2^{\mathrm{opt}} = 2k(\tau_1^{\mathrm{opt}})^2$ obtained initially in the case of the absence of correlations (see Table I) still holds in this case.

These expressions are in agreement with the numerical minimization of the exact expression of the mean search time (see Fig. 27), except when $1 - p$ is very small.

4. Conclusion

In the simple case of the static mode in one dimension, the influence of correlations on the mean search time and its minimization can be studied. An exact expression for the mean search time shows that it is minimized for finite values of τ_1 and τ_2 as soon as $p < 1$. When $1 - p \gg a/b$, the optimal durations τ_1^{opt} and τ_2^{opt} can be explicitly given, and they are in continuity with the case without correlation, $p = 0.5$.

C. Other distributions of phase durations

The model presented in Sec. IV is minimal in the sense that the searcher has no memory. As seen in the previous section, one possibility is to add orientational memory. Another possibility is to add temporal memory. In the generic model, we have considered a "Markovian" searcher, in the sense that the rate of switching from one phase to the other is constant. It leads to an exponential distribution of the durations of the phases. In the following, we study the influence of the distribution of the duration of the phases [see also Chechkin *et al.* (2009), Meerschaert *et al.* (2009), and Tejedor and Metzler (2009) for other types of correlation]. A first possibility is to study the effect of distributions that are peaked around the mean duration, or even deterministic (Bénichou *et al.*, 2007). A second possibility is to study the case of Lévy-distributed blind phases as in Lomholt *et al.* (2008).

1. Deterministic durations of the phases

In the generic model described, we considered exponential durations of phases, which correspond to searchers with no temporal memory. In the opposite case, a searcher with full

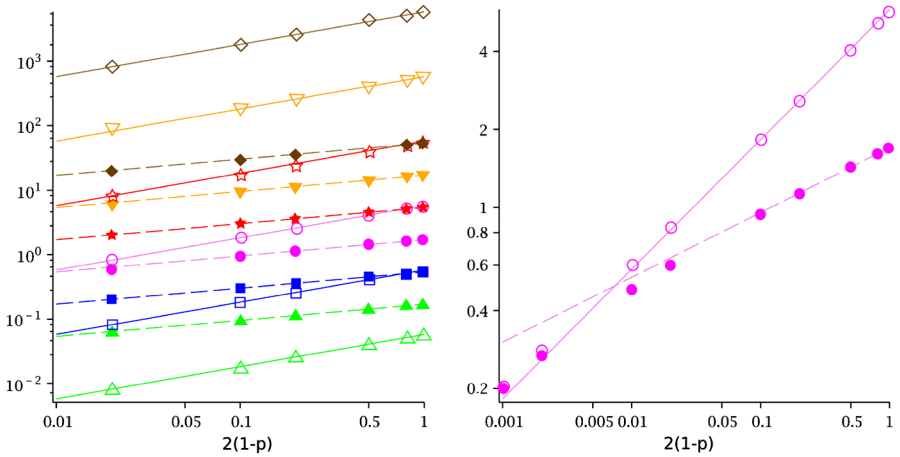


FIG. 27. τ^{opt} as a function of $2(1 - p)$. Theoretical value of τ_1^{opt} (58) (dashed line) and theoretical value of τ_2^{opt} (59) (solid lines), compared to the numerical minimization of the full exact mean search time, leading to τ_1^{opt} (filled symbols) and τ_2^{opt} (empty symbols). $a = 0.01$, $b = 1$ (△); $a = 0.01$, $b = 100$ (□); $a = 1$, $b = 100$ (○); $a = 1$, $b = 10^4$ (★); $a = 100$, $b = 10^4$ (▽); $a = 100$, $b = 10^6$ (◇). $k = 1$, $V = 1$.

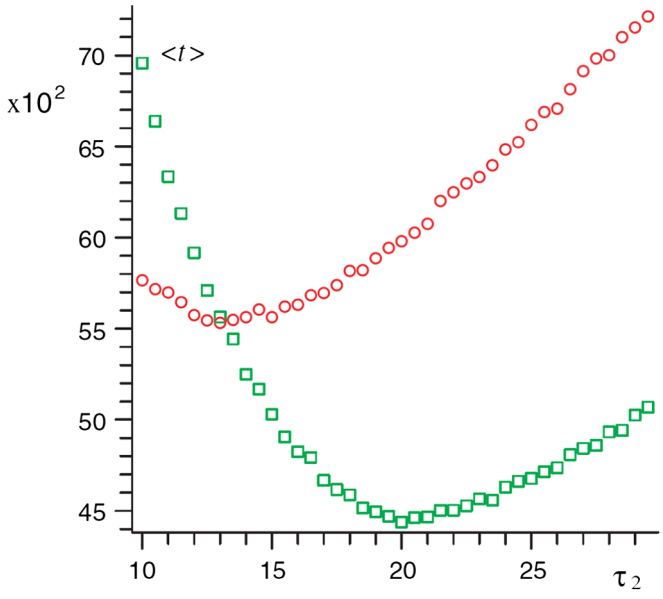


FIG. 28. Comparison between the search without (∘) and with temporal memory (□). Static mode in two dimensions. t_m as a function of τ_2. $k = 1$, $V = 1$, $b = 113$, $a = 10$, $\tau_1 = 2.6$.

memory skills could, for example, switch from one phase to the other at deterministic instead of exponentially distributed times. The corresponding problem is no longer Markovian, which makes its analytical resolution much more complex. We present here a summary of a numerical study of the effect of such temporal memory for a searcher with the static mode of detection in dimension 2 [see Bénichou *et al.* (2007) for details and Bénichou *et al.* (2006) for a semianalytical treatment in one dimension]. First, this study shows that the optimal τ_1^{opt} and τ_2^{opt} are larger than in the case without memory, but are of the same order of magnitude (see Fig. 28). Second, such temporal memory decreases the mean search time. Indeed, a deterministic duration of the relocation phase avoids both the very short and very long relocations, which are inefficient. Third, and importantly, the gain from this temporal memory is quite low (less than 40% in an extended range of parameters, and decreasing with increasing b/a) as compared to the case with no memory (see Fig. 28).

2. Lévy distribution of the fast phase durations

Lomholt *et al.* (2008) studied analytically and numerically a one-dimensional intermittent random walk where the duration of relocation phases is taken from a Lévy law [$p(l) \propto l^{-\alpha-1}$, with $1 < \alpha < 2$]. Apart from this distribution of the duration of ballistic phases, this model is identical to the generic model presented in Sec. IV [see also Bénichou *et al.* (2006)], in the case of a diffusive mode of detection in one dimension (in the particular case of a pointlike target $a \to 0$).

The mean search time is evaluated with the exact formula [Eq. (9) of Lomholt *et al.* (2008)]

$$\langle t \rangle = \sum_{n=1}^{\infty} \frac{2(\tau_1 + \tau_2)}{D\tau_1 k_n^2 + 1 - \lambda(k_n)}, \tag{60}$$

with $k_n = 2\pi n/L$, where L is the distance between targets, and λ is the characteristic function of the distribution: $\lambda(k) = \exp(-\sigma^\alpha |k|^\alpha)$. The relation between σ, α, the velocity V, and τ_2 (the mean duration of phase 2, which is defined since $\alpha > 1$) is given by [Eq. (10) of Lomholt *et al.* (2008)]

$$\sigma = \frac{\pi V \tau_2}{2\Gamma(1 - 1/\alpha)}. \tag{61}$$

A more tractable approximate expression of the mean search time can be derived [Eq. (14) of Lomholt *et al.* (2008)]:

$$\langle t \rangle = 2(\tau_1 + \tau_2)\left[\frac{L}{4\sqrt{D\tau_1}} + \left(\frac{L}{2\pi\sigma}\right)^\alpha \zeta(\alpha)\right], \tag{62}$$

where $\zeta(\alpha) = \sum_{n=1}^{\infty} n^{-\alpha}$ is the Riemann ζ function.

As compared with the generic model of Sec. IV, this model introduces an extra parameter α, which, as could be expected, enables a further minimization of the mean search time. Lomholt *et al.* (2008) claimed that Lévy laws are more efficient than exponential laws because they have no second moment and therefore are not bound to the central limit theorem.

The Lévy distribution, however, is not the optimal distribution of the duration of ballistic phases, and distributions with a finite second moment can perform even better, as opposed to what is claimed by Lomholt *et al.* (2008). Indeed, relocations larger than the distance between two targets L cannot be profitable, and power-law distributions are therefore inefficient in the regime of long times $t > L/V$. A simple example is given by a Lévy distribution with an upper cutoff at L (see Fig. 29). For $L = 10^4$, numerical simulations show that the optimum without cutoff is realized for $\alpha \simeq 1.4$, with $t_m \simeq 195\,000$, and the optimum with a cutoff at L is realized for $\alpha \simeq 1.3$, with $t_m \simeq 188\,000$, that is, $\simeq 3.7\%$ lower. For $L = 10^5$, the optimum without cutoff is realized for $\alpha \simeq 1.3$, $t_m \simeq 3\,260\,000$; the optimum with a cutoff of L is realized for $\alpha \simeq 1.2$, $t_m \simeq 3\,060\,000$, that is, $\simeq 6.5\%$ lower. Truncated distributions with a well-defined second moment therefore outperform Lévy distributions. Hence, intermittent random walks with Lévy-distributed relocations decrease the mean search time more efficiently than in the case of exponentially distributed relocations, but it is not because of their infinite variance, and other distributions with a second moment can perform even better.

Another point discussed by Lomholt *et al.* (2008) is the robustness of the strategy: If L is misevaluated, the efficiency of the intermittent search with exponential relocation durations decreases more than for the Lévy distribution. The truncated Lévy distribution is probably of intermediate robustness.

D. The point of view of the target: Pascal principle

In this review, we have addressed the question of determining optimal search strategies. One could also consider the opposite point of view and try to determine optimal survival strategies of targets. In the case where the target's motion is independent of the searcher's motion, the response is actually given simply by the so-called Pascal principle (Moreau *et al.*, 2003; Moreau *et al.*, 2004) for a broad class of situations.

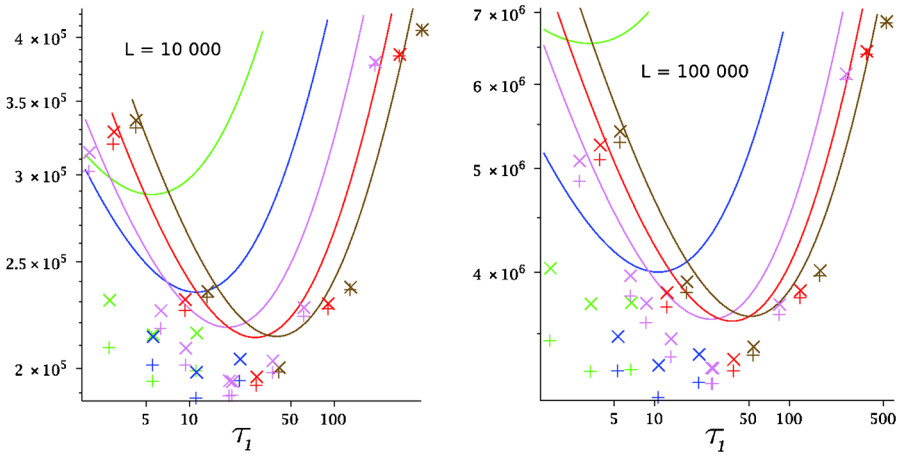


FIG. 29. t_m as a function of τ_1, with σ at the theoretical minimum [numerical minimization of Eq. (62)]. Lines: analytical formula (62). ×: simulations without cutoff. +: simulations with cutoff at L. $D = 1$, $V = 1$. Left: $L = 10^4$, $\alpha = 1.6$; $\alpha = 1.5$; $\alpha = 1.4$; $\alpha = 1.3$; $\alpha = 1.2$. Right: $L = 10^5$, $\alpha = 1.6$; $\alpha = 1.5$; $\alpha = 1.4$; $\alpha = 1.3$; $\alpha = 1.2$.

More precisely, suppose that the motion of the searcher is time and space homogeneous and that it satisfies the following property: Starting from a position x (different from the target position), the transition probability to be at position y at time $t > 0$ is always maximum for $y = x$. Assume that the target can perform any stochastic motion, independently of the searcher, which is assumed to perform a stochastic motion. Then the Pascal principle states that the survival probability of the target is maximum if the target remains immobile at its initial position. Of course, the validity of the Pascal principle is restricted to special motions of the searcher: It holds for a diffusive motion, but not, for instance, if the searcher undergoes a ballistic motion with constant velocity. However, the validity conditions are satisfied if the searcher undergoes ballistic motions with symmetrically distributed stochastic velocities, or if the displacements consist in teleportations, which are distributed symmetrically with respect to the initial position. In these cases, the best strategy for the target is to remain immobile.

E. Other models of intermittent search

In the past few years, several models relying on the mechanism of intermittent search have been developed in different contexts. We review here these models, which are in essence similar to the generic case discussed in Sec. IV, and which broaden the field of application of intermittent search.

1. Oshanin *et al.* (2007, 2009)

Oshanin *et al.* (2007, 2009) proposed a model similar to the diffusive mode in one dimension of the generic model of Sec. IV, but in discrete space, on an infinite lattice. At each time step, with probability α, the searcher jumps to the neighboring node of the line (with equal probabilities for each side, which corresponds to diffusion). With probability $1 - \alpha$, it stays off lattice during a time T and after this time, it lands at a distance L from its initial position (once again, with equal probabilities for each side); see Fig. 30. This phase is equivalent to a ballistic nonreactive phase. Its duration is exactly T, whereas the duration of the diffusive phase with target detection is exponentially distributed, with mean duration $1/(1 - \alpha)$. There is one target, but an infinite set of searchers, initially randomly distributed. The quantity maximized is the probability, that at a given time t, the target has already been found by any of the searchers. Oshanin *et al.* found an optimal α, but dependent on t. If L and T are fixed, then the optimization with respect to α leads to $\alpha^{\text{opt}} \propto t^{1/3}$, which can be very small. If T only is fixed, the optimization with respect to both α and L gives $\alpha^{\text{opt}} = 0.5$ and $L^{\text{opt}} \sim \sqrt{t}/\ln(t)$. Note that in the case $T = 1$, at the optimum the time has to be equally shared between the two phases, which is reminiscent of the result obtained in the framework of the simple model of facilitated diffusion (Sec. III.A.2). Last, if $V = L/T$ is fixed, it is found that $L^{\text{opt}} \sim \sqrt{t}/\ln(t)$, $\alpha^{\text{opt}} \sim 1 - 4V\ln(t)/3\sqrt{t}$, which means that the mean duration of the nearest-neighbor phase is $3/4$ the duration of a large move. This model can actually be seen as the lattice version of the model given by Bénichou *et al.* (2006), where similar results were obtained: (i) the existence of a global minimum of the search time, (ii) the ratio of times spent in both phases at the minimum is given by a numerical constant, and (iii) this numerical constant is equal to $1/2$ in Bénichou *et al.* (2006) (where the time spent off the lattice is exponentially distributed) instead of the $3/4$ given above (for deterministic times off lattice).

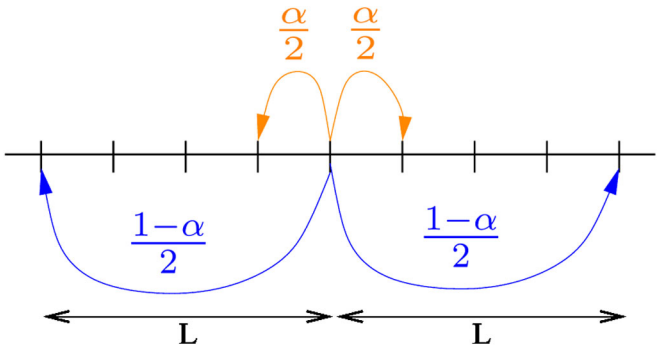


FIG. 30. Model used by Oshanin *et al.* (2007, 2009).

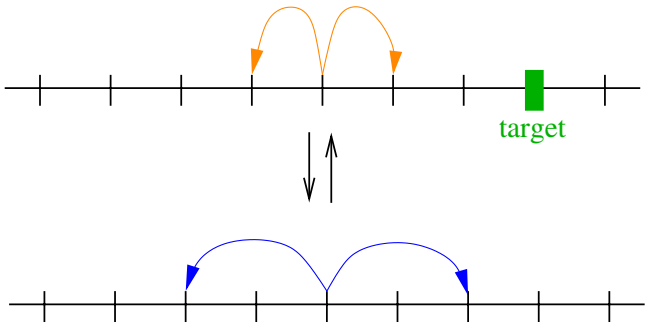


FIG. 31. Model used by Rojo *et al.* (2009).

2. Rojo *et al.* (2009)

Rojo *et al.* (2009) proposed a model that displays some similarities with the previous model (see Fig. 31). The search domain is a one-dimensional discrete infinite lattice with one target, there is also an infinite set of searchers, and the quantity optimized is also the probability that the target is found by any of the searchers at a given t. The detection phase consists of jumps to the nearest neighbors, with a given frequency. Such a rule is equivalent to diffusion. The nonreactive phase consists of jumps to the next nearest neighbors. It is again diffusion, but if the jump frequency is the same as in the other phase, it is a faster diffusion. In both phases, there is a fixed rate of switch to the other phase, leading to exponentially distributed durations of the phases. If one of the mean durations is fixed, the probability that the target is already found at t is minimized for a finite duration of the other phase. But the optimum is for infinitely short phases, enabling the searcher to combine the faster diffusion of one phase and the detection capacities of the other phase.

3. Reingruber and Holcman (2009)

Reingruber and Holcman (2009) proposed a model that is also diffusive-diffusive (see Fig. 32). They studied this model first in one dimension: The searcher's starting point is at one extremity of a segment, a reflecting boundary. The target is at the other end of the segment. However, in phase 1 (diffusion of coefficient D_1), the target can be found, whereas in phase 2 (diffusion of coefficient D_2), both extremities are reflecting. There are fixed rates of switching from one phase to another. The results showed that there are two regimes: If $D_1 > D_2$, straightforwardly, the optimum for the searcher is to be in phase 1 only; if $D_2 > D_1$, the optimum is to switch very rapidly between the two phases, so as to spend almost all the time in the faster phase 2, but not to miss the target. This model is extended to a three-dimensional ball (the initial position is almost without importance in this geometry), but with a target of radius a on the border (which is reflecting everywhere else). The two phases are defined as in one dimension. Reingruber and Holcman (2009) gave two limits in this case. Note that the expression we obtained in the generic model of Sec. IV for the diffusive mode in three dimensions [see Loverdo *et al.* (2009b)] could be used, with $3V^2\tau_2^2 = D_2\tau_2$. In fact, these calculations use a "diffusive-diffusive" approximation, with an effective $D_2^{\text{eff}} = 3V^2\tau_2$. The optimization will be quite different, because the dependence on τ_2 is dramatically changed if instead of a fixed D_2, D_2 is a function of τ_2. Indeed, the optimum for the generic model is for finite τ_1 and τ_2, whereas, even if not explicitly calculated, it is probable that the optimum for diffusion-diffusion in three dimensions is similar to that in the one-dimensional case, i.e., for phase durations as small as possible. The goal of this model is to study cellular signaling, with a ligand binding to a target that will transmit a signal.

4. Bressloff and Newby (2009); Newby and Bressloff (2009)

Bressloff and Newby (2009) presented another model applied to intracellular transport, more precisely here to the transport of mRNA granules inside neurons. They presented a model in one dimension, standing, for example, for an axon with little branching. The starting point is at one extremity, which is reflecting: It models granules produced in the soma of the neuron and that have to be exported to the axon. The target, a synapse, is somewhere in the segment. The other end of the segment is an absorbing boundary, representing that the vesicles containing the mRNA can be degraded, or that there can be other targets farther away in the axon that can absorb the searcher. To complete the idea that there are several targets that are not equivalent, and that these targets are in competition, they also calculated explicitly the probability that the searcher finds a target more often than the others. In this model, there are three states (see Fig. 33): an immobile detection phase, similar to the static mode, switching to ballistic modes with probability α per unit time; a ballistic phase in direction $+$, with speed v_+, and with a transition rate

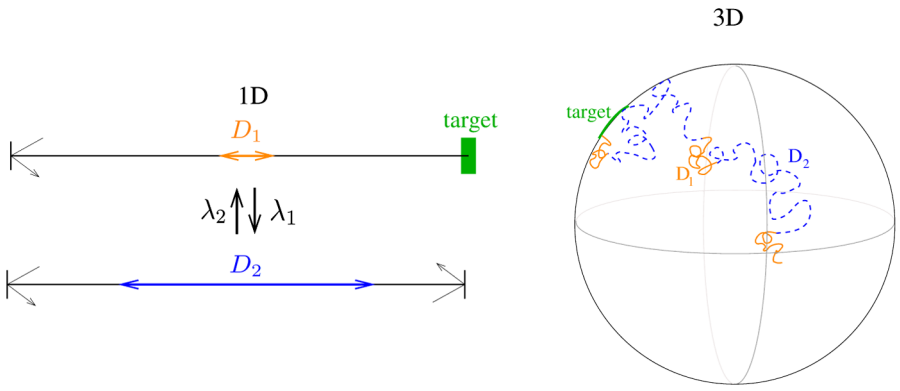


FIG. 32. Model used by Reingruber and Holcman (2009).

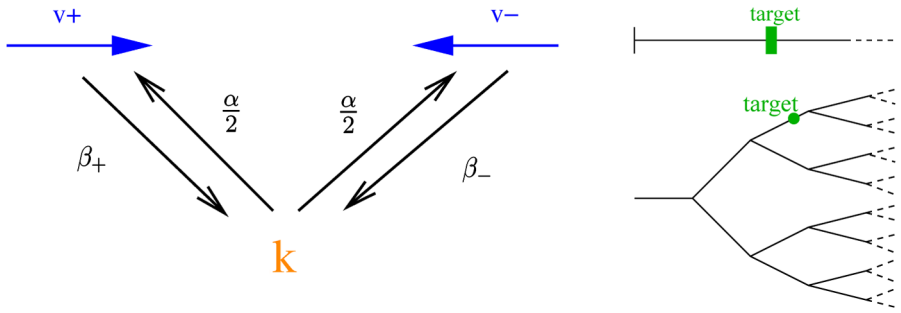


FIG. 33. Model used by Bressloff and Newby (2009) and Newby and Bressloff (2009).

to the detection mode β_+; a ballistic phase in direction $-$, with speed v_-, and with a transition rate to the detection mode β_-. During the two ballistic phases, the searcher cannot detect the target. Movement is biased to the direction $+$ if $v_+/\beta_+ > v_-/\beta_-$.

The results are based on the fact that on the segment there are two contradicting constraints: maximizing the hit probability (as the searcher can be degraded before finding the target), and minimizing the time to find the target when the target is found. Indeed, if there is more bias, the target will be missed more often, but when found, the search time will be smaller. With a fixed hit probability, the mean first-passage time to the target (on the condition that the target is found) is minimized when there is more bias. In other words, unidirectional motion is better than bidirectional motion in this case.

Newby and Bressloff (2009) extended this problem to the case of a directed tree. In this case, unidirectional motion has a drawback: A wrong branch can be taken, annihilating any possibility of finding the target. Biased bidirectional motion can be seen as an effective combination of a ballistic and a diffusive motion. It exists as a critical hit probability p^*. If the mean first-passage time to the target is minimized given that the probability of finding the target is a given $p < p^*$, unidirectional motion is better; but if the given probability is $p > p^*$, there is an optimal finite bias that minimizes the mean search time in case of success.

5. Ramezanpour (2007)

Intermittence in networks is an interesting extension. Ramezanpour (2007) proposes (see Fig. 34) to explore a network in which the degree (equal to the number of neighbors) distribution is $p(k) \propto k^{-3}$, constructed as proposed by Barabasi and Albert (1999), or with some modifications. On this finite network, at each time step the searcher chooses randomly one of the edges connected to the node where it is, and goes to the node connected by this edge. Every t_w, the searcher jumps to a completely random node. The question is whether the mean time to cover the nodes and the edges of the network can be optimized as a function of t_w. For the nodes, the random jumping is a way to visit all the nodes with equal probability; thus t_w should be as small as possible. For the edges, there is an optimal finite t_w. Indeed, if t_w is small, most edges visited will emanate from low-connected nodes (as the low-connected nodes are the more numerous nodes, such edges are more likely to be visited after a random jump), but if t_w is large, the searcher will spend most of its time on the edges connecting high-degree nodes, and will take time to explore the whole network, especially for remote edges connecting nodes of low degree.

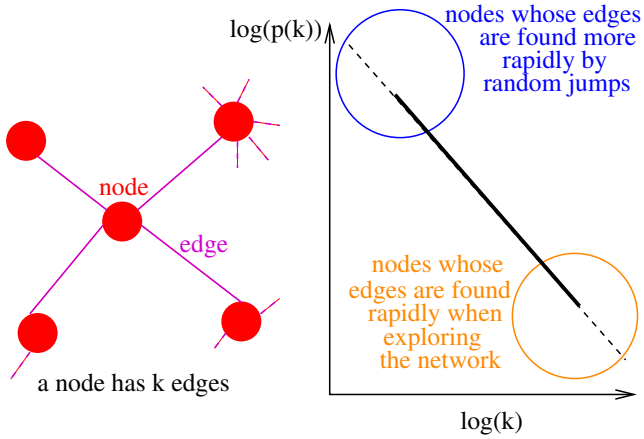


FIG. 34. Model presented by Ramezanpour (2007).

F. Designing efficient searches

As seen, intermittent reaction paths are involved in various search problems involving biomolecules at the microscopic scale, as well as biological organisms at the macroscopic scale. Simple analytical models show that intermittent transport can actually minimize the search time. A reason why such intermittent trajectories are widely observed could be simply that they constitute generic optimal search strategies, and consequently they could have been selected by evolution.

Beyond *modeling* what is observed in real-life biological examples, such intermittent strategies could also be used to *design* searches, at the microscopic and macroscopic scales. We discuss here potential applications at the microscopic scale [for more details see Bénichou *et al.* (2008)].

Heterogeneous chemical reactions, where the reactive targets are located at an interface, either one dimensional (polymer) or two dimensional (surface), are intrinsically intermittent. Indeed, the reactants can either diffuse in the bulk volume, where the target cannot be found, or bind to the interface and diffuse more slowly (see Fig. 35, left).

Beyond obvious optimizations (increasing the target and the reactant concentrations, increasing the diffusion coefficients of the reactant in the bulk or at the interface, etc.), the mean durations of the phases (free or bound to the interface) are the main adjustable parameters enabling minimization

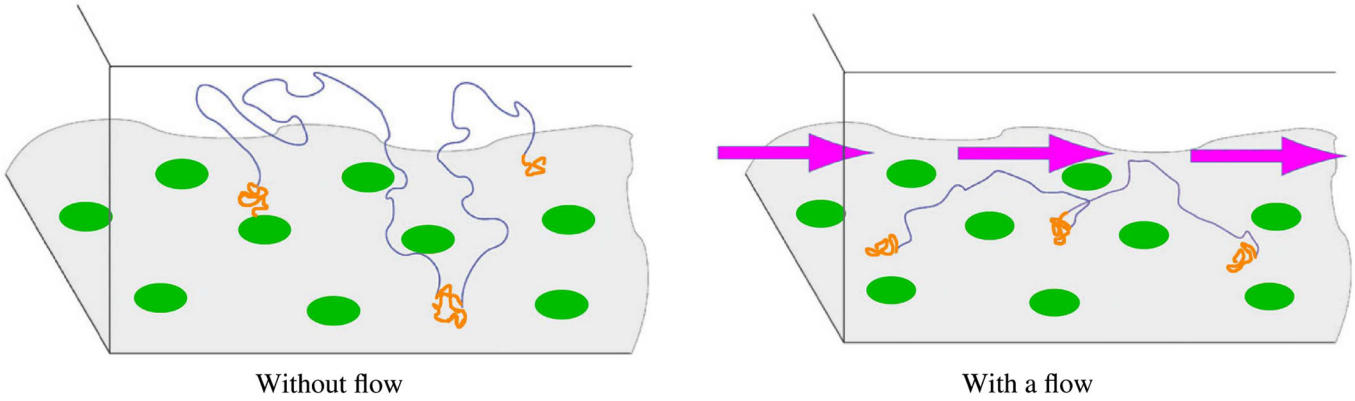


FIG. 35. Design of heterogeneous chemical reactions, with targets (disks) here fixed on a two-dimensional surface. The reactant either diffuses in the volume (thin lines) or diffuses on the surface (thick lines). The flow is represented by arrows.

of the mean search time, and therefore maximization of the reaction rate. The main idea is that in the "teleportation" approximation (see Sec. III.A.2), after a bulk excursion, the distance between the reactant landing point on the surface and its starting point is larger than the typical distance between targets. In such a regime, each new bound phase is independent of the previous one, and the trajectory overlap is limited, which enhances the reactivity.

The mean durations of the phases can actually be tuned in real systems. First, the mean time a reactant remains bound to the interface depends on its affinity with the interface, which could be tuned. Second, the mean time spent in the bulk is mainly controlled by the confinement volume (Blanco and Fournier, 2003; Bénichou *et al.*, 2005a; Condamin *et al.*, 2007). The confinement volume has therefore to be as small as possible, but it should be large enough to make the teleportation approximation valid. This constraint defines a critical volume and can actually be bypassed by applying a hydrodynamic flow parallel to the surface, which makes the teleportation approximation valid even for very short bulk excursions, provided that the velocity of the flow is high enough (see Fig. 35, right). In this regime it can be shown (Bénichou *et al.*, 2008) that the reaction rate can be optimized by tuning the affinity of the reactant for the interface in a similar way as in Sec. III.A.2.

At the molecular level, we stress that intermittent transport could also be useful for *in vitro* chemistry. Indeed, we have shown that intermittent transport naturally pops up in the context of reaction at interfaces, where reactants combine surface diffusion phases and bulk excursions, and could permit the enhancement of reactivity. In this case, chemical adjustment of the typical association time of the reactants with the interface makes it possible to optimize the reaction rate.

VI. CONCLUSION

Intermittent search strategies rely on a simple mechanism: The searcher alternates between two phases, one during which the target can be detected, but with slow motion, and another of faster motion but without target detection. This mechanism of intermittence has emerged from the observation of real-life biological searches at various scales. At the macroscopic scale, a given example is animals searching for hidden food, which alternate between fast ballistic relocation phases with no target detection and phases of slower motion aimed at detecting the target. A simple model based on this observation permits an analytical demonstration that the mean search time can be minimized as a function of the phases' mean duration. There is one single way to share time between the two phases in order to find the target as fast as possible. This intermittent search is then an optimal search strategy. In this respect, this model is an alternative to the famous Lévy walk model, which is optimal only in restrictive conditions.

Intermittence is also observed at the microscopic scale. Indeed, for some biochemical reactions in cells, which involve a very low concentration of reactants, reaction pathways are not always simple Brownian trajectories. They can rather be qualified as intermittent, since they combine slow diffusion phases, on the one hand, and a second mode of faster transport, on the other hand, which can be either a faster diffusion mode as in the case of DNA-binding proteins or a ballistic mode powered by molecular motors in the case of intracellular transport. Analytical models actually show that such intermittent trajectories are very efficient, since they significantly reduce reaction times. Interestingly, it is shown that reaction rates can even be maximized by adjusting simple biochemical parameters. The gain is small in dimension 3, but for lower-dimensional structures, such as membranes (2D) or polymers or tubular structures (1D), the gain can be very large at low target concentration. Such efficiency—and optimality—could explain why intermittent transport is observed in various forms in the context of reactions in cells.

Since these intermittent search strategies are observed at various scales, one could suggest that they constitute a generically efficient search mechanism. Systematic analysis of a generic model in the framework of intermittent random walks, in one, two, and three dimensions, and for three different descriptions of the slow reactive phase, permits a quantitative assessment of the robustness of this mechanism. In fact, this study shows that the optimality of these search strategies is a widely robust result. Finally, if intermittent random walks are observed in real biological systems at various scales, it is probably because they do constitute an efficient search strategy. Beyond these modeling aspects, one

can suggest that such intermittent strategies could also be used to design optimizable search strategies.

ACKNOWLEDGMENTS

The support of ANR Grant DYOPTRI is acknowledged.

APPENDIX A: REVIEW OF RANDOM WALKS AND LéVY PROCESSES

Regular random walks obey Gaussian statistics and have a mean square displacement growing linearly with time: $\langle r^2(t)\rangle \sim t^{\alpha}$, with $\alpha = 1$. Inversely, transport processes characterized by nonlinear scalings with time of the mean square displacement are termed ''anomalous,'' either subdiffusive if $\alpha < 1$ or superdiffusive if $\alpha > 1$. In this review, we make use of standard models of subdiffusion (continuous-time random walks, diffusion on fractals, and fractional Brownian motion) and superdiffusion (Lévy flights and Lévy walks), whose definitions are repeated here for consistency [see, for instance, Ben-Avraham and Havlin (2000) for a complete discussion].

1. Subdiffusion

a. Continuous-time random walks

A first class of models leading to subdiffusion stems from continuous-time random walks (CTRWs) and their continuous-space limit described by fractional diffusion equations. The anomalous behavior in these models originates from a heavy-tailed distribution of waiting times: At each step the walker lands on a trap, where it can remain for extended periods of time. Technically, the CTRW is a standard random walk with random waiting times, drawn from a probability density function $\psi(t)$. The CTRW model has a normal diffusive behavior if the mean waiting time is finite. For heavy-tailed distributions, such that

$$\psi(t) \propto \frac{1}{t^{1+\beta}} \qquad \text{at large times,} \tag{A1}$$

the mean waiting time diverges for $\beta < 1$ and the walk is subdiffusive with $\alpha = \beta$.

When dealing with a tracer particle, traps can be out-of-equilibrium chemical binding configurations, and the waiting times are then the dissociation times; traps can also be realized by the free cages around the tracer in a dense hard spherelike crowded environment, and the waiting times are the lifetimes of the cages (Saxton, 1996; Saxton, 2007; Condamin *et al.*, 2008).

b. Diffusion on fractals

Another kind of model for subdiffusion relies on spatial inhomogeneities as exemplified by diffusion in deterministic (such as Sierpinski gasket) or random fractals (such as critical percolation clusters). The subdiffusive behavior is in this case caused by the presence of fixed obstacles that create numerous dead ends, as illustrated by de Gennes's ant in a labyrinth (de Gennes, 1976; Saxton, 1994). This results in an effective subdiffusion in the embedding space, with an exponent $\alpha < 1$, whose value depends on the fractal structure (d'Auriac *et al.*, 1983; Bunde and Havlin, 1991; Ben-Avraham and Havlin, 2000).

c. Fractional Brownian motion

Fractional Brownian motion (FBM) is a third model of subdiffusion (Mandelbrot and van Ness, 1968; Metzler and Klafter, 2000), usually defined for systems in dimension 1. It was introduced to take into account correlations in a random walk: The state of the system at time t is influenced by the state at time $t' < t$. More precisely, it is a Gaussian process with autocorrelation function of the form

$$\langle X(t_1)X(t_2)\rangle \propto t_1^{2H} + t_2^{2H} - |t_1 - t_2|^{2H}, \tag{A2}$$

with $0 < H < 1/2$, so that $\alpha = 2H < 1$ (FBM can also be defined for $1/2 < H < 1$, but in this case it leads to superdiffusion). Note that Brownian diffusion is recovered for $H = 1/2$. FBM is used to describe the motion of a monomer in a polymer chain or single-file diffusion. Recently, it has also been proposed to underlie the diffusion in a crowded environment (Szymanski and Weiss, 2009).

2. Superdiffusion

a. Lévy flights

Lévy flights are random walks such that, at each step t, the walker jumps in some random uniformly distributed direction, to a distance r drawn from a probability density function

$$p(r) \propto \frac{1}{r^{1+\beta}}. \tag{A3}$$

It can be shown that, if $\beta < 2$, superdiffusion emerges, with $\alpha = 2/\beta$, while, if $\beta > 2$, regular diffusion is recovered.

b. Lévy walks

Lévy walks differ from Lévy flights in that, now, the time to make a step of size r is taken to be proportional to r (Shlesinger *et al.*, 1987). Physically, a Lévy walk can be described as a random walker performing jumps still drawn from the probability density function

$$p(r) \propto \frac{1}{r^{1+\beta}}, \tag{A4}$$

but this time at a constant velocity. The resulting mean square displacement can be given by

$$\langle r^2\rangle \propto \begin{cases} t^2 & \text{if } 0 < \beta < 1, \\ t^2/\ln t & \text{if } \beta = 1, \\ t^{3-\beta} & \text{if } 1 < \beta < 2, \\ t\ln t & \text{if } \beta = 2, \\ t & \text{if } \beta > 2. \end{cases} \tag{A5}$$

Applications of Lévy walks are given in the main text, in the context of random search problems. Note that, in this context, the terms ''Lévy walks'' and ''Lévy flight'' are often used interchangeable to designate Lévy walks.

APPENDIX B: MEAN FIRST-PASSAGE TIMES OF INTERMITTENT RANDOM WALKS

1. Dimension 1

a. Static mode

In this section we assume that the detection phase is modeled by the static mode. Hence the searcher does not move during the reactive phase 1 and has a fixed reaction rate k per unit time with the target if it lies within its detection radius a (see Fig. 21). It is the limit of a very slow searcher in the reactive phase.

i. Equations. Outside the target (for $x > a$), we have the following backward equations for the mean first-passage time:

$$V\frac{dt_2^+}{dx} + \frac{1}{\tau_2}(t_1 - t_2^+) = -1, \tag{B1}$$

$$-V\frac{dt_2^-}{dx} + \frac{1}{\tau_2}(t_1 - t_2^-) = -1, \tag{B2}$$

and

$$\frac{1}{\tau_1}\left(\frac{t_2^+ + t_2^-}{2} - t_1\right) = -1. \tag{B3}$$

Inside the target ($x \le a$), the first two equations are identical, but the third one is written

$$\frac{1}{\tau_1}\frac{t_2^+ + t_2^-}{2} - \left(\frac{1}{\tau_1} + k\right)t_1 = -1. \tag{B4}$$

We introduce $t_2 = (t_2^+ + t_2^-)/2$ and $t_2^d = (t_2^+ - t_2^-)/2$. Then outside the target we have the following equations:

$$V\frac{dt_2}{dx} - \frac{1}{\tau_2}t_2^d = 0, \tag{B5}$$

$$V^2\tau_2\frac{d^2t_2}{dx^2} + \frac{1}{\tau_2}(t_1 - t_2) = 0, \tag{B6}$$

$$\frac{1}{\tau_1}(t_2 - t_1) = -1. \tag{B7}$$

Inside the target the first two equations are identical, but the last one is written

$$\frac{1}{\tau_1}t_2 - \left(\frac{1}{\tau_1} + k\right)t_1 = -1. \tag{B8}$$

Because of the symmetry $x \leftrightarrow -x$, we can restrict the study to the areas $x \in [0, a]$ and $x \in [a, b]$. This symmetry also implies

$$\left.\frac{dt_2^{\text{in}}}{dx}\right|_{x=0} = 0, \tag{B9}$$

$$\left.\frac{dt_2^{\text{out}}}{dx}\right|_{x=b} = 0. \tag{B10}$$

In addition, continuity at $x = a$ for t_2^+ and t_2^- gives

$$t_2^{\text{in}}(x = a) = t_2^{\text{out}}(x = a), \tag{B11}$$

$$t_2^{d,\text{in}}(x = a) = t_2^{d,\text{out}}(x = a). \tag{B12}$$

This set of linear equations enables us to explicitly determine t_1, t_2, and t_2^d inside and outside the target.

ii. Results. An exact analytical expression for the mean first-passage time to the target is then given by

$$t_m = \frac{\tau_1 + \tau_2}{b}\left[\frac{b}{k\tau_1} + \frac{(b-a)^3}{3V^2\tau_2^2} + \frac{\beta(b-a)^2}{V\tau_2}\coth\left(\frac{a}{V\tau_2\beta}\right) + (b-a)\beta^2\right], \tag{B13}$$

where $\beta = \sqrt{(k\tau_1)^{-1} + 1}$.

We obtain in the limit $b \gg a$

$$t_m = (\tau_1 + \tau_2)\left[\frac{b^2}{3V^2\tau_2^2} + \left(\frac{1}{k\tau_1} + 1\right)\frac{b}{a}\right]. \tag{B14}$$

This approximation is accurate (see Fig. 36).

We use this approximation (B14) to find τ_1 and τ_2 values minimizing t_m:

$$\tau_1^{\text{opt}} = \sqrt{\frac{a}{Vk}}\left(\frac{b}{12a}\right)^{1/4}, \tag{B15}$$

$$\tau_2^{\text{opt}} = \frac{a}{V}\sqrt{\frac{b}{3a}}. \tag{B16}$$

It is important that the optimal duration of the relocation phase does not depend on k, i.e., on the description of the detection phase.

b. Diffusive mode

We now turn to the diffusive modeling of the detection phase. The detection phase 1 is now diffusive, with immediate detection of the target if it is within a radius a from the searcher (see Fig. 21).

i. Equations. Along the same lines, the backward equations for the mean first-passage time read outside the target ($x > a$)

$$V\frac{dt_2^+}{dx} + \frac{1}{\tau_2}(t_1 - t_2^+) = -1, \tag{B17}$$

$$-V\frac{dt_2^-}{dx} + \frac{1}{\tau_2}(t_1 - t_2^-) = -1, \tag{B18}$$

$$D\frac{d^2t_1}{dx^2} + \frac{1}{\tau_1}\left(\frac{t_2^+}{2} + \frac{t_2^-}{2} - t_1\right) = -1, \tag{B19}$$

and inside the target ($x \le a$)

$$V\frac{dt_2^+}{dx} - \frac{1}{\tau_2}t_2^+ = -1, \tag{B20}$$

$$-V\frac{dt_2^-}{dx} - \frac{1}{\tau_2}t_2^- = -1, \tag{B21}$$

and

$$t_1 = 0. \tag{B22}$$

Boundary conditions result as previously from continuity and symmetry.

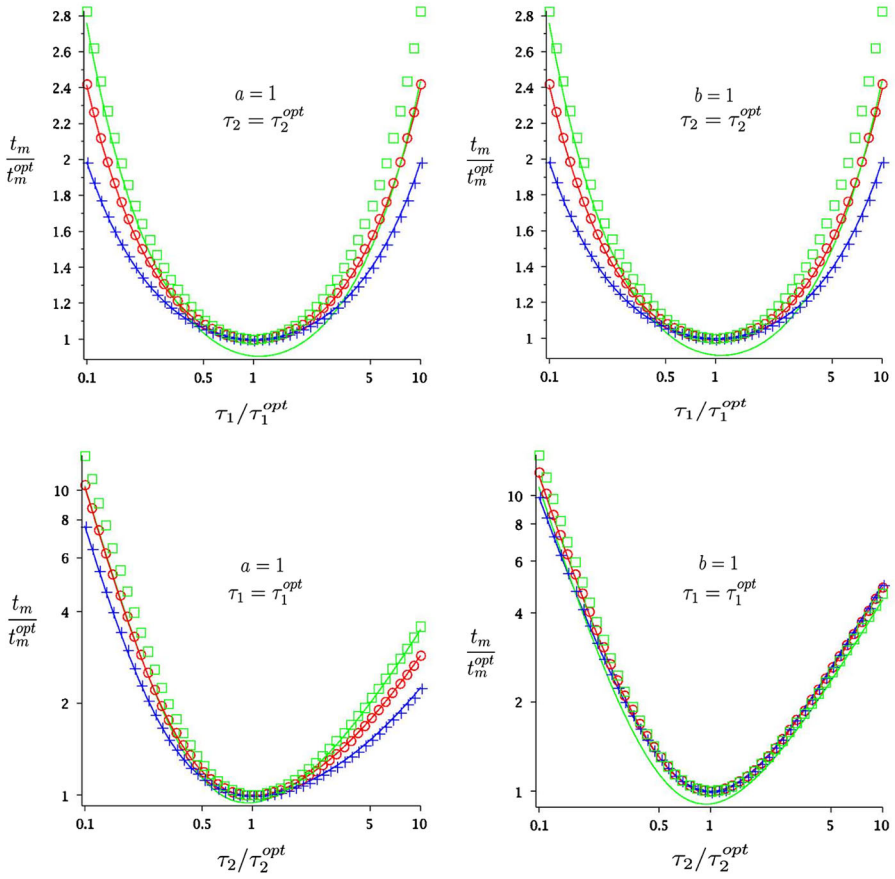


FIG. 36. Static mode in one dimension. Exact expression of t_m (B13) (lines) compared to the approximation of t_m (B14) (symbols), both rescaled by $t_m^{\rm opt}$. $\tau_1^{\rm opt}$ from (B15), $\tau_2^{\rm opt}$ from (B16). $V=1$, $k=1$. $b/a=10$ (□), $b/a=100$ (∘), and $b/a=1000$ (+).

ii. Results. Standard but lengthy calculations lead to an exact expression of the mean first-detection time of the target t_m given by Loverdo *et al.* (2009b). Three regimes can be identified.

(i) In the first regime ($b<D/V$) intermittence is not favorable.

(ii) For $b>D/V$ and $bD^2/a^3V^2<1$ intermittence is favorable. In the low-target-density limit ($b\gg a$), the following approximation of the mean first-passage time around its minimum can be obtained:

$$t_m=(\tau_1+\tau_2)b\left(\frac{b}{3V^2\tau_2^2}+\frac{1}{\sqrt{D\tau_1}}\right). \tag{B23}$$

This expression gives a good approximation of t_m in this regime, in particular, around the optimum (see Fig. 37). The simplified t_m expression (B23) is minimized for

$$\tau_1^{\rm opt}=\frac{1}{2}\sqrt[3]{\frac{2b^2D}{9V^4}}, \tag{B24}$$

$$\tau_2^{\rm opt}=\sqrt[3]{\frac{2b^2D}{9V^4}}, \tag{B25}$$

$$t_m^{\rm opt}\simeq\sqrt[3]{\frac{3^5}{2^4}\frac{b^4}{DV^2}}. \tag{B26}$$

This compares to the case without intermittence according to

$$\text{gain}^{\rm opt}=\frac{t_{\rm diff}}{t_m^{\rm opt}}\simeq\sqrt[3]{\frac{2^4}{3^8}}\left(\frac{bV}{D}\right)^{2/3}\simeq 0.13\left(\frac{bV}{D}\right)^{2/3}. \tag{B27}$$

(iii) For $b>D/V$ and $1\gg bD^2/a^3V^2$ intermittence is favorable.

In this regime, the mean search time is given by

$$t_m\simeq\frac{b}{a}(\tau_1+\tau_2)\left(\frac{a}{a+\sqrt{D\tau_1}}+\frac{ab}{3V^2\tau_2^2}\right). \tag{B28}$$

This expression gives a good approximation of t_m, at least around the optimum (see Fig. 38), which is characterized by

$$\tau_1^{\rm opt}=\frac{Db}{48V^2a}, \tag{B29}$$

$$\tau_2^{\rm opt}=\frac{a}{V}\sqrt{\frac{b}{3a}}, \tag{B30}$$

$$t_m^{\rm opt}\simeq\frac{2a}{V\sqrt{3}}\left(\frac{b}{a}\right)^{3/2}, \tag{B31}$$

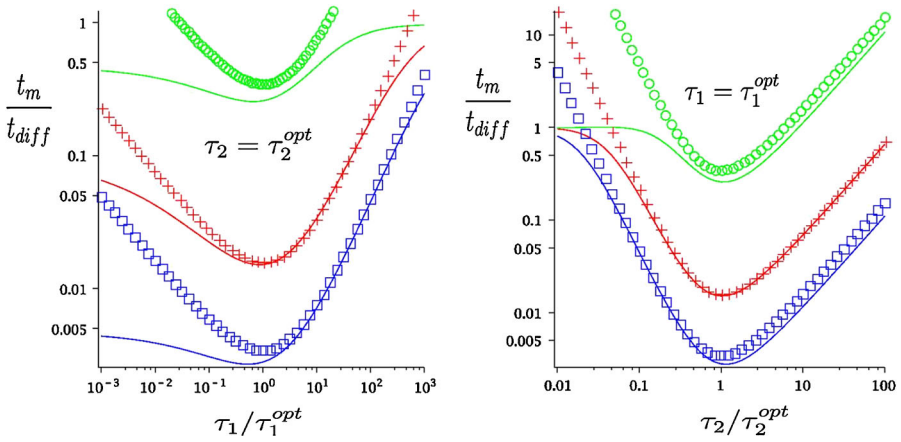


FIG. 37. Diffusive mode in one dimension. $t_m/t_{\rm diff}$, exact expression (line), and approximation in the regime of favorable intermittence and $bD^2/a^3V^2 \gg 1$ (B23) (symbols). $a = 1$, $b = 100$ ($\circ$); $a = 1$, $b = 10^4$ (+); $a = 10$, $b = 10^5$ ($\square$). $D = 1$, $V = 1$. $\tau_1^{\rm opt}$ is from Eq. (B24), and $\tau_2^{\rm opt}$ is obtained from Eq. (B25).

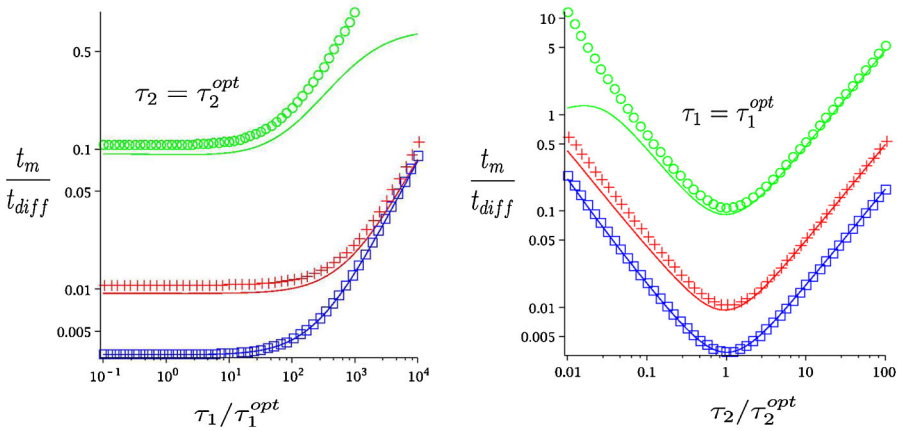


FIG. 38. Diffusive mode in one dimension. $t_m/t_{\rm diff}$, exact expression (line), and approximation in the regime of favorable intermittence and $bD^2/a^3V^2 \ll 1$ (B28) (symbols). $a = 10$, $b = 100$ ($\circ$); $a = 10$, $b = 1000$ (+); $a = 100$, $b = 10^4$ ($\square$). $D = 1$, $V = 1$. $\tau_1^{\rm opt}$ is from Eq. (B29), and $\tau_2^{\rm opt}$ is obtained from Eq. (B30).

$$\text{gain} \simeq \frac{1}{2\sqrt{3}} \frac{aV}{D} \sqrt{\frac{b}{a}}. \tag{B32}$$

Note that the gain can be very large at low target density and that the value obtained for $\tau_2^{\rm opt}$ is the same as in the static mode.

c. Ballistic mode

We now treat the case where the detection phase 1 is modeled by the ballistic mode (see Fig. 21). This model schematically accounts for the general observation that speed often degrades perception abilities. Our model corresponds to the extreme case where only two modes are available: either the motion is slow and the target can be found or the motion is fast and the target cannot be found. Note that this model can be compared to the model of Viswanathan *et al.* (1999), where there is only the detection phase.

i. Equations. The backward equations read outside the target ($x > a$)

$$v_l \frac{dt_1^+}{dx} + \frac{1}{\tau_1}\left(\frac{t_2^+}{2} + \frac{t_2^-}{2} - t_1^+\right) = -1, \tag{B33}$$

$$-v_l \frac{dt_1^-}{dx} + \frac{1}{\tau_1}\left(\frac{t_2^+}{2} + \frac{t_2^-}{2} - t_1^-\right) = -1, \tag{B34}$$

$$V \frac{dt_2^+}{dx} + \frac{1}{\tau_2}\left(\frac{t_1^+}{2} + \frac{t_1^-}{2} - t_2^+\right) = -1, \tag{B35}$$

and

$$-V \frac{dt_2^-}{dx} + \frac{1}{\tau_2}\left(\frac{t_1^+}{2} + \frac{t_1^-}{2} - t_2^-\right) = -1. \tag{B36}$$

Inside the target ($x \le a$), one has $t_1^{+,\rm in}(x) = t_1^{-,\rm in}(x) = 0$, and

$$V \frac{dt_2^{+,\rm in}}{dx} - \frac{1}{\tau_2} t_2^{+,\rm in} = -1, \tag{B37}$$

$$-V \frac{dt_2^{-,\rm in}}{dx} - \frac{1}{\tau_2} t_2^{-,\rm in} = -1. \tag{B38}$$

ii. Results. In the case where phase 1 is modeled by the ballistic mode in one dimension, we have calculated the exact mean first-passage time t_m at the target. t_m can be minimized as a function of τ_1 and τ_2, yielding two possible optimal strategies:

(i) for $v_l > v_l^c = V(\sqrt{3}/2)(\sqrt{a/b})$, intermittence is not favorable: $\tau_1^{\rm opt} \to \infty$, $\tau_2^{\rm opt} \to 0$,

(ii) for $v_l < v_l^c = V(\sqrt{3}/2)(\sqrt{a/b})$, intermittence is favorable, with $\tau_1^{\rm opt} \to 0$ and

$$\tau_2^{\rm opt} \simeq \frac{a}{V}\sqrt{\frac{b}{3a}}.$$

The gain reads

$$\text{gain} \approx \frac{\sqrt{3}}{2}\frac{V}{v_l}\sqrt{\frac{a}{b}}. \tag{B39}$$

This shows that the gain is larger than 1 for $v_l < v_l^c = V\frac{\sqrt{3}}{2}\sqrt{\frac{a}{b}}$, which defines the regime where intermittence is favorable.

Note that the model studied by Viswanathan *et al.* (1999) showed that when targets are not revisitable, the optimal strategy for a single-state searcher is to perform a straight ballistic motion. This strategy corresponds to $\tau_1 \to \infty$ in our model. Our results show that if a faster phase without detection is allowed, this straight line strategy can be outperformed.

d. Conclusion in one dimension

Intermittent search strategies in one dimension share similar features for the static, diffusive, and ballistic detection modes. In particular, all modes show regimes where intermittence is favorable and leads to a minimization of the search time. Strikingly, the optimal duration of the nonreactive relocation phase 2 is quite independent of the modeling of the reactive phase: $\tau_2^{\rm opt} = (a/3V)(\sqrt{b/a})$ for the static mode, for the ballistic mode (in the regime $v_l < v_l^c \simeq (V/2)(\sqrt{3a/b})$), and for the diffusive mode (in the regime $b > D/V$ and $a \gg (D/V)(\sqrt{b/a})$). This shows the robustness of the optimal value $\tau_2^{\rm opt}$.

2. Dimension 2

a. Static mode

We study here the case where the detection phase is modeled by the static mode: The searcher does not move during the detection phase and has a finite reaction rate with the target if it is within its detection radius a (see Fig. 21).

i. Equations and results. The mean first-passage time at a target satisfies the following backward equations (Redner, 2001):

$$\frac{1}{2\pi\tau_1}\int_0^{2\pi}[t_2(\vec{r}) - t_1(\vec{r})]d\theta_{\vec{V}} - kI_a(\vec{r})t_1(\vec{r}) = -1, \tag{B40}$$

$$\vec{V}\cdot\nabla_{\mathbf{r}}t_2(\vec{r}) - \frac{1}{\tau_2}[t_2(\vec{r}) - t_1(\vec{r})] = -1. \tag{B41}$$

The function I_a is defined by $I_a(\vec{r}) = 1$ inside the target (if $|\vec{r}| \le a$) and $I_a(\vec{r}) = 0$ outside the target (if $|\vec{r}| > a$). In the present form, these integro-differential equations (completed with boundary conditions) do not seem to allow for an exact resolution with standard methods. t_2 is the mean first-passage time to the target, starting from $\vec{r}$ in phase 2, with speed $\vec{V}$, of angle $\theta_{\mathbf{V}}$, and with projections on the axes V_x,V_y. i and j can take either x or y as a value. The following decoupling assumption is introduced:

$$\langle V_i V_j t_2\rangle_{\theta_{\mathbf{V}}} \simeq \langle V_i V_j\rangle_{\theta_{\mathbf{V}}}\langle t_2\rangle_{\theta_{\mathbf{V}}} \tag{B42}$$

and leads to the following approximation of the mean search time, which can be checked by numerical simulations (see Fig. 39):

$$t_m = \frac{\tau_1+\tau_2}{2k\tau_1 y^2}\left\{\frac{1}{x}(1+k\tau_1)(y^2-x^2)^2\frac{I_0(x)}{I_1(x)} + \frac{1}{4}\{8y^2 + (1+k\tau_1)[4y^4\ln(y/x) + (y^2-x^2)(x^2-3y^2+8)]\}\right\}, \tag{B43}$$

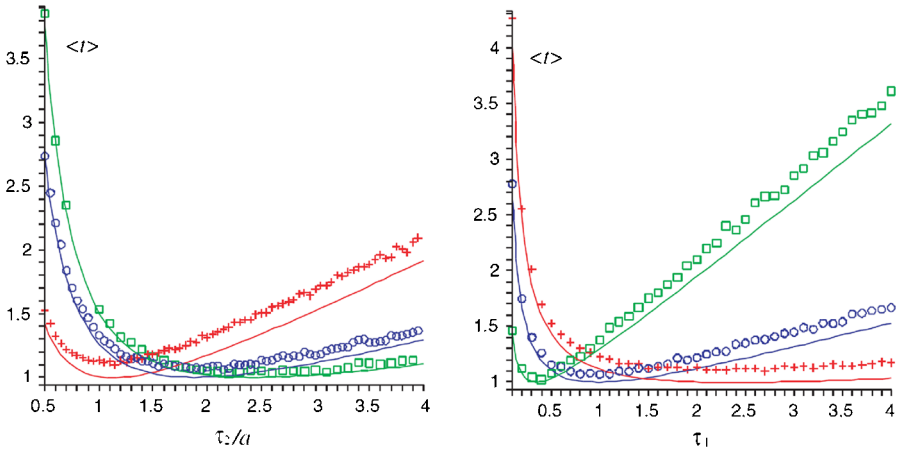


FIG. 39. Static mode in two dimensions. Simulations (symbols) and analytical approximation (B43) (lines). $k = 1$, $V = 1$, $b = 56$; $a = 10$ (+) ($\tau_1^{\rm opt} = 2.41$, $\tau_2^{\rm opt} = 11.2$); $a = 1$ (∘) ($\tau_1^{\rm opt} = 0.969$, $\tau_2^{\rm opt} = 1.88$); $a = 0.1$ (□) ($\tau_1^{\rm opt} = 0.348$, $\tau_2^{\rm opt} = 0.242$). Left: mean search time t_m as a function of τ_2/a, with $\tau_1 = \tau_1^{\rm opt}$. Right: mean search time t_m as a function of τ_1, with $\tau_2 = \tau_2^{\rm opt}$.

where

$$x = \sqrt{\frac{2k\tau_1}{1+k\tau_1}}\frac{a}{V\tau_2} \quad \text{and} \quad y = \sqrt{\frac{2k\tau_1}{1+k\tau_1}}\frac{b}{V\tau_2}. \tag{B44}$$

In that case, intermittence is trivially necessary to find the target. In the regime $b \gg a$, the optimization of the search time (B43) leads to

$$\tau_1^{\text{opt}} = \left(\frac{a}{Vk}\right)^{1/2}\left(\frac{2\ln(b/a)-1}{8}\right)^{1/4}, \tag{B45}$$

$$\tau_2^{\text{opt}} = \frac{a}{V}[\ln(b/a) - 1/2]^{1/2}, \tag{B46}$$

and the minimum search time is given in the large-volume limit by

$$t_m^{\text{opt}} = \frac{b^2}{a^2k} - \frac{2^{1/4}}{\sqrt{Vka^3}}\frac{(a^2-4b^2)\ln(b/a)+2b^2-a^2}{[2\ln(b/a)-1]^{3/2}} - \frac{\sqrt{2}}{48ab^2V} \times \frac{(96a^2b^2-192b^4)\ln^2(b/a)+(192b^4-144a^2b^2)\ln(b/a)+46a^2b^2-47b^4+a^4}{[2\ln(b/a)-1]^{3/2}}. \tag{B47}$$

b. Diffusive mode

We now assume that the searcher diffuses during the detection phase (see Fig. 21). For this process, the mean first-passage time to the target satisfies the following backward equation (Redner, 2001):

$$D\nabla_{\mathbf{r}}^2 t_1(\vec{r}) + \frac{1}{2\pi\tau_1}\int_0^{2\pi}[t_2(\vec{r}) - t_1(\vec{r})]d\theta_{\mathbf{V}} = -1, \tag{B48}$$

$$\vec{V}\cdot\nabla_{\mathbf{r}} t_2(\vec{r}) - \frac{1}{\tau_2}[t_2(\vec{r}) - t_1(\vec{r})] = -1, \tag{B49}$$

with $t_1(\vec{r}) = 0$ inside the target ($r \le a$). The same decoupling assumption as for the static case is used (B42). It eventually leads to the following approximation of the mean search time, which can be checked by numerical simulations (see Fig. 40):

$$t_m = (\tau_1+\tau_2)\frac{1-a^2/b^2}{(\alpha^2 D\tau_1)^2}\left\{a\alpha(b^2/a^2-1)\frac{M}{2L_+} - \frac{L_-}{L_+} - \frac{\alpha^2 D\tau_1}{8\tilde{D}\tau_2}\frac{[3-4\ln(b/a)]b^4 - 4a^2b^2 + a^4}{b^2-a^2}\right\}, \tag{B50}$$

with

$$L_\pm = I_0\left(\frac{a}{\sqrt{\tilde{D}\tau_2}}\right)(I_1(b\alpha)K_1(a\alpha) - I_1(a\alpha)K_1(b\alpha)) \pm \alpha\sqrt{\tilde{D}\tau_2}I_1\left(\frac{a}{\sqrt{\tilde{D}\tau_2}}\right)[I_1(b\alpha)K_0(a\alpha) + I_0(a\alpha)K_1(b\alpha)], \tag{B51}$$

and

$$M = I_0\left(\frac{a}{\sqrt{\tilde{D}\tau_2}}\right)[I_1(b\alpha)K_0(a\alpha) + I_0(a\alpha)K_1(b\alpha)] - 4\frac{a^2\sqrt{\tilde{D}\tau_2}}{\alpha(b^2-a^2)^2}I_1\left(\frac{a}{\sqrt{\tilde{D}\tau_2}}\right)[I_1(b\alpha)K_1(a\alpha) - I_1(a\alpha)K_1(b\alpha)], \tag{B52}$$

where $\alpha = [1/(D\tau_1) + 1/(\tilde{D}\tau_2)]^{1/2}$ and $\tilde{D} = V^2\tau_2$. The minimization as a function of τ_1 and τ_2 is as follows.

i. $a < b \ll D/V$: Intermittence is not favorable. In this regime, intermittence is not favorable. Indeed, the typical time required to explore the whole domain of radius b is of order b^2/D with diffusive motion, which is shorter than the corresponding time b/V with ballistic motion. As a consequence, it is never useful to interrupt the diffusive phases by merely relocating ballistic phases. The mean first-passage time to the target in this optimal regime of diffusion only is obtained using standard methods (Redner, 2001) and reads in the limit $b \gg a$

$$t_{\text{diff}} = \frac{b^2}{8D_{\text{eff}}}\left(-3 + 4\ln\frac{b}{a}\right). \tag{B53}$$

ii. $a \ll D/V \ll b$: First regime of intermittence. In this second regime, one can use the following approximate formula for the search time:

$$t_m = \frac{b^2}{4DV^2\alpha^2}\frac{\tau_1+\tau_2}{\tau_1\tau_2^2}\left\{4\ln(b/a) - 3 - 2\frac{(V\tau_2)^2}{D\tau_1}[\ln(\alpha a) + \gamma - \ln 2]\right\}, \tag{B54}$$

with γ the Euler constant. An approximate criterion to determine whether intermittence is useful can be obtained by expanding t_m in powers of $1/\tau_1$ when $\tau_1 \to \infty$ ($\tau_1 \to \infty$ corresponds to the absence of intermittence), and requiring that the coefficient of the term $1/\tau_1$ is negative for all values of τ_2. Using this criterion, we find that intermittence is useful if

$$\sqrt{2}\exp(-7/4+\gamma)Vb/D - 4\ln(b/a) + 3 > 0. \tag{B55}$$

In this regime, using Eq. (B54), the optimization of the search time leads to

$$\tau_1^{\text{opt}} = \frac{b^2}{D}\frac{4\ln w - 5 + c}{w^2(4\ln w - 7 + c)}, \qquad \tau_2^{\text{opt}} = \frac{b}{V}\frac{\sqrt{4\ln w - 5 + c}}{w}, \tag{B56}$$

where w is the solution of the implicit equation $w = 2Vbf(w)/D$ with

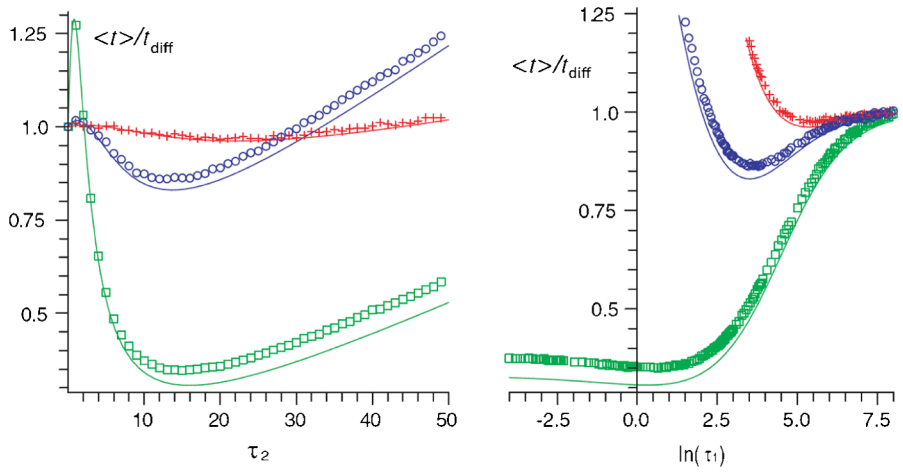


FIG. 40. Diffusive mode in two dimensions. Simulations (symbols) versus analytical approximate (B50) (line) of the search time, rescaled by the value in the absence of intermittence $t_{\rm diff}$ as a function of τ_2 (left) and $\ln(\tau_1)$ = (right), for $D = 1$, $V = 1$, $b = 226$. Left: $a = 10$, $\tau_1 = 1.37$ (□); $a = 1$, $\tau_1 = 33.6$ (∘); $a = 0.1$, $\tau_1 = 213$ (+). Right: $a = 10$, $\tau_2 = 15.9$ (□); $a = 1$, $\tau_2 = 13.7$ (∘); $a = 0.1$, $\tau_2 = 22$ (+).

$$\frac{\sqrt{4\ln w - 5 + c}}{f(w)} = -8(\ln w)^2 + [6 + 8\ln(b/a)]\ln w - 10\ln(b/a) + 11 - c[c/2 + 2\ln(a/b) - 3/2] \quad \text{(B57)}$$

and $c = 4[\gamma - \ln(2)]$, with γ the Euler constant. A useful approximation for w is given by

$$w \simeq \frac{2Vb}{D} f\left(\frac{Vb}{2D\ln(b/a)}\right). \quad \text{(B58)}$$

The gain for this optimal strategy reads

$$\text{gain} = \frac{t_{\rm diff}}{t_m^{\rm opt}} \simeq \frac{1}{2}\frac{4\ln b/a - 3 + 4a^2/b^2 - a^4/b^4}{4\ln b/a - 3 + 2(4\ln w)\ln(b/aw)} \times \left(\frac{1}{4\ln w - 5} + \frac{wD}{bV}\frac{4\ln w - 7}{(4\ln w - 5)^{3/2}}\right)^{-1}. \quad \text{(B59)}$$

If intermittence significantly speeds up the search in this regime (typically by a factor of 2), it does not change the order of magnitude of the search time.

iii. $D/V \ll a \ll b$: "Universal" regime of intermittence. In the last regime $D/V \ll a \ll b$, the optimal strategy is obtained for

$$\tau_1^{\rm opt} \simeq \frac{D}{2V^2}\frac{\ln^2(b/a)}{2\ln(b/a) - 1}, \qquad \tau_2^{\rm opt} \simeq \frac{a}{V}[\ln(b/a) - 1/2]^{1/2}, \quad \text{(B60)}$$

and the gain reads

$$\text{gain} = \frac{t_{\rm diff}}{t_m^{\rm opt}} \simeq \frac{\sqrt{2}aV}{8D}\left(\frac{1}{4\ln(b/a) - 3} \times \frac{I_0(2/\sqrt{2\ln(b/a) - 1})}{I_1(2/\sqrt{2\ln(b/a) - 1})} + \frac{1}{2\sqrt{2\ln(b/a) - 1}}\right)^{-1}. \quad \text{(B61)}$$

Here the optimal strategy leads to a significant decrease of the search time, which can be rendered arbitrarily smaller than the search time in the absence of intermittence.

c. Ballistic mode

In this case, the searcher has access to two different speeds: One (V) is fast but prevents the searcher from finding its target, and the other (v_l) is slower but enables the searcher to detect the target (see Fig. 21).

i. Simulations. Since an explicit expression of the mean search time is not available, a numerical study is performed. Exploring the parameter space numerically allows identification of the regimes where the mean search time is minimized. Then, for each regime, approximation schemes are developed to provide analytical expressions for the mean search time. The numerical results presented in Fig. 41 suggest two regimes defined according to a threshold value v_l^c of v_l to be determined later on:

(i) for $v_l > v_l^c$, t_m is minimized for $\tau_2 \to 0$,
(ii) for $v_l < v_l^c$, t_m is minimized for $\tau_1 \to 0$.

ii. Regime without intermittence ($\tau_2 \to 0$, $\tau_1 \to \infty$). Qualitatively, it is rather intuitive that for v_l large enough (the precise threshold value v_l^c will be determined next), phase 2 is inefficient since it does not allow for target detection. The optimal strategy is therefore $\tau_2 \to 0$ in this case. In this regime, the searcher performs a ballistic motion, which is randomly reoriented with frequency $1/\tau_1$. Along the same lines as in Viswanathan *et al.* (1999) (where, however, the times between successive reorientations are Lévy distributed), it can be shown that the optimal strategy to find a target (which is assumed to disappear after the first encounter) is to minimize oversampling and therefore to perform a purely ballistic motion. In our case this means that in the regime $\tau_2 \to 0$, the optimal τ_1 is given by $\tau_1^{\rm opt} \to \infty$.

In this regime, we can propose an estimate of the optimal search time $t_{\rm bal}$. The surface scanned during δt is $2av_l\delta t$. $p(t)$ is the proportion of the total area that has not yet been scanned at t. If we neglect correlations in the trajectory, $p(t)$ is the solution of

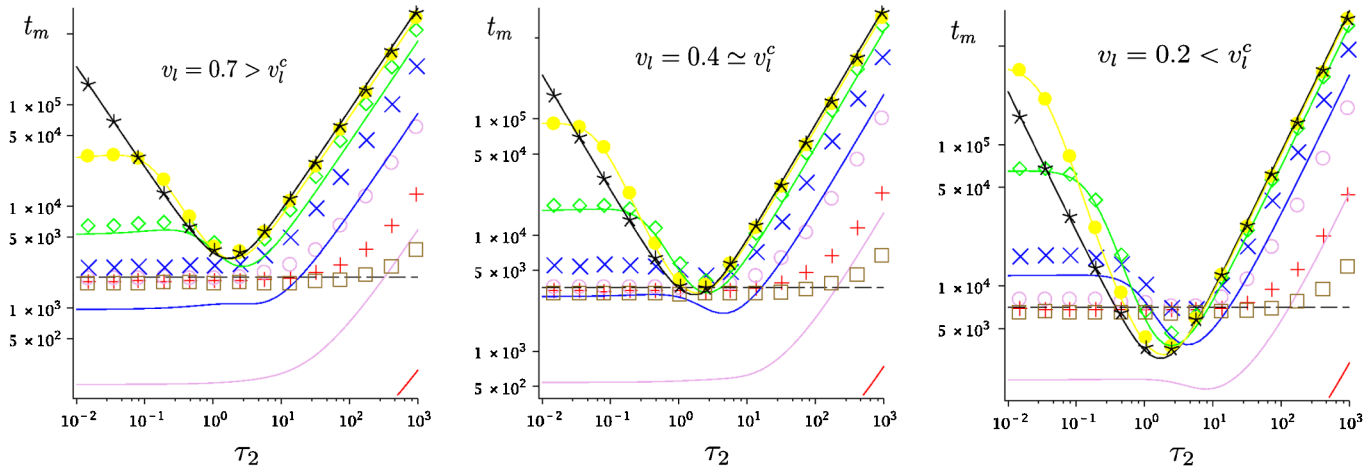


FIG. 41. Ballistic mode in two dimensions. $\ln(t_m)$ as a function of $\ln(\tau_2)$. Simulations (symbols), diffusive-diffusive approximation (B50) with (B65) (lines), $\tau_1 \to 0$ limit (B66) (line), $\tau_1 \to \infty$ (no intermittence) (B64) (dotted line). $b = 30$, $a = 1$, $V = 1$. $\tau_1 = 0$ ($\star$), $\tau_1 = 0.17$ ($\bullet$), $\tau_1 = 0.92$ ($\diamond$), $\tau_1 = 5.0$ ($\times$), $\tau_1 = 28$ ($\circ$), $\tau_1 = 150$ ($+$), $\tau_1 = 820$ ($\square$).

$$\frac{dp}{dt} = -\frac{2av_l p(t)}{\pi b^2}. \tag{B62}$$

Then, given that $p(t=0) = 1$, we obtain

$$p(t) = \exp\left(-\frac{2av_l}{\pi b^2}\right), \tag{B63}$$

and the mean first-passage time to the target in these conditions is

$$t_{\rm bal} = -\int_0^\infty t\frac{dp}{dt}dt = \frac{\pi b^2}{2av_l}. \tag{B64}$$

This expression yields good agreement with numerical simulations. Note, in particular, that $t_{\rm bal} \propto 1/v_l$.

iii. Regime with intermittence ($\tau_1 \to 0$). In this regime where $v_l < v_l^c$, the numerical study shows that the search time is minimized for $\tau_1 \to 0$ (see Fig. 41). We determine here the optimal value of τ_2 in this regime. To proceed, we approximate the problem by the case of a diffusive mode previously studied (B50), with an effective diffusion coefficient

$$D = \frac{v_l^2\tau_1}{2}. \tag{B65}$$

This approximation is very satisfactory in the regime $\tau_1 \to 0$ (see Fig. 41).

We can then use the results of the previous section for the diffusive mode in the $\tau_1 \to 0$ regime and obtain

$$t_m = \tau_2\left(1-\frac{a^2}{b^2}\right)\left[1-\frac{1}{4}\frac{[3+4\ln(a/b)]b^4-4a^2b^2+a^4}{\tau_2^2V^2(b^2-a^2)} + \frac{a}{V\tau_2\sqrt{2}}\left(\frac{b^2}{a^2}-1\right)\frac{I_0(a\sqrt{2}/\tau_2 V)}{I_1(a\sqrt{2}/\tau_2 V)}\right]. \tag{B66}$$

The calculation of $\tau_2^{\rm opt}$ minimizing t_m then gives

$$\tau_2^{\rm opt} = \frac{a}{V}\sqrt{\ln\left(\frac{b}{a}\right)-\frac{1}{2}}. \tag{B67}$$

Finally the gain reads

$$\text{gain} = \frac{t_{\rm bal}}{t_m^{\rm opt}} \simeq \frac{\pi V}{4v_l}\left[\ln\left(\frac{b}{a}\right)\right]^{-0.5}. \tag{B68}$$

iv. Determination of v_l^c. Note that an estimate of v_l^c can be obtained from (B68) as the value of v_l for which gain $= 1$:

$$v_l^c \simeq \frac{\pi V}{4}\left[\ln\left(\frac{b}{a}\right)\right]^{-0.5} \propto \frac{V}{\sqrt{\ln(b/a)}}. \tag{B69}$$

It is noteworthy that intermittence becomes less favorable with increasing b. This effect is similar to the one-dimensional case, even though it is less important here. It can be understood as follows: at very large scales the intermittent trajectory is reoriented many times and therefore scales as diffusion, which is less favorable than the non-intermittent ballistic motion.

d. Conclusion in dimension 2

Remarkably, for the three different modes of detection (static, diffusive, and ballistic), we find a regime where intermittence minimizes the search time for one and the same $\tau_2^{\rm opt}$, given by $\tau_2^{\rm opt} = (a/V)\sqrt{\ln(b/a)-\frac{1}{2}}$. As in one dimension, this indicates that optimal intermittent strategies are robust and widely independent of the details of the description of the detection mechanism.

3. Dimension 3

a. Static mode

We study in this section the case where the detection phase is modeled by the static mode, for which the searcher does not move during the detection phase, and has a finite reaction rate with the target if it is within a detection radius a (see Fig. 21).

i. Equations. Denoting by $t_1(r)$ the mean first-passage time to the target starting from a distance r from the target in phase 1 (detection phase), and by $t_{2,\theta,\phi}(r)$ the mean first-passage time to the target starting from a distance r from the

target in phase 2 (relocation phase) with a ballistic motion in a direction characterized by θ and ϕ, we obtain

$$\vec{V}\cdot\vec{\nabla}t_{2,\theta,\phi}+\frac{1}{\tau_2}(t_1-t_{2,\theta,\phi})=-1. \tag{B70}$$

Then outside the target ($r>a$)

$$\frac{1}{\tau_1}\left(\frac{1}{4\pi}\int_0^{\pi}d\theta\sin\theta\int_0^{2\pi}d\phi t_{2,\theta,\phi}-t_1\right)=-1, \tag{B71}$$

and inside the target ($r\le a$)

$$\frac{1}{\tau_1}\frac{1}{4\pi}\int_0^{\pi}d\theta\sin\theta\int_0^{2\pi}d\phi t_{2,\theta,\phi}-\left(\frac{1}{\tau_1}+k\right)t_1=-1. \tag{B72}$$

Defining $t_2=\frac{1}{4\pi}\int_0^{\pi}d\theta\sin\theta\int_0^{2\pi}d\phi t_{2,\theta,\phi}$, one obtains outside the target ($r>a$)

$$\frac{1}{\tau_1}(t_2-t_1)=-1, \tag{B73}$$

and inside the target ($r<a$)

$$\frac{1}{\tau_1}t_2-\left(\frac{1}{\tau_1}+k\right)t_1=-1. \tag{B74}$$

Making a similar decoupling approximation as in two dimensions leads finally to

$$\frac{V^2\tau_2}{3}\Delta t_2-\frac{1}{\tau_2}(t_1-t_2)=-1. \tag{B75}$$

These equations are solved inside and outside the target, using the following boundary conditions:

$$\left.\frac{dt_2^{\text{out}}}{dr}\right|_{r=b}=0, \tag{B76}$$

$$t_2^{\text{out}}(a)=t_2^{\text{in}}(a), \tag{B77}$$

$$\left.\frac{dt_2^{\text{out}}}{dr}\right|_{r=a}=\left.\frac{dt_2^{\text{in}}}{dr}\right|_{r=a}, \tag{B78}$$

and the condition that $t_2^{\text{in}}(0)$ should be finite.

ii. Results. The following approximate expression of the mean search time is found in the low-density limit:

$$t_m=\frac{b^3(\tau_2+\tau_1)}{a}\left(\frac{(1+k\tau_1)}{\tau_1 ka^2}+\frac{6}{5\tau_2^2V^2}\right). \tag{B79}$$

This expression of t_m can be minimized for

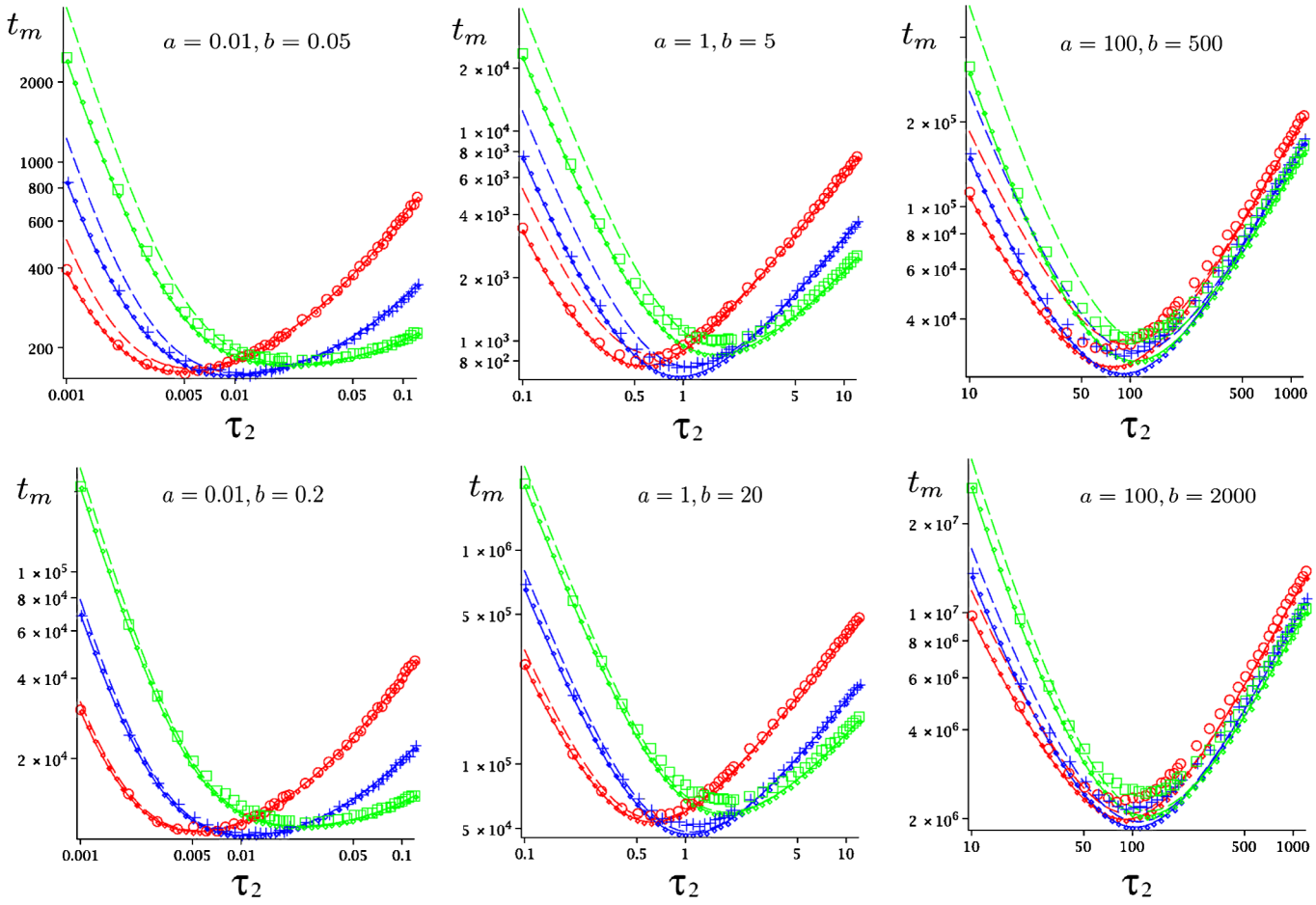


FIG. 42. Static mode in three dimensions. $\ln(t_m)$ as a function of $\ln(\tau_2)$ for different values of τ_1, a, and b/a. Comparison among simulations (symbols), analytical expression (line), and its asymptotics for $b\gg a$ obtained by Loverdo *et al.* (2009b) (small dots), and simple expression for $b\gg a$ and small α (B79) (dashed line). $\tau_1\simeq\tau_1^{\text{opt}}\simeq 0.74\sqrt{aV/k}$ (B80) (+), $\tau_1=0.25\sqrt{aV/k}$ (∘), $\tau_1=2.5\sqrt{aV/k}$ (□). $V=1$, $k=1$.

$$\tau_1^{\rm opt} = \left(\frac{3}{10}\right)^{1/4}\sqrt{\frac{a}{Vk}}, \tag{B80}$$

$$\tau_2^{\rm opt} = \sqrt{1.2}\,\frac{a}{V}, \tag{B81}$$

and the minimum mean search time finally reads

$$t_m^{\rm opt} = \frac{1}{\sqrt{5}}\,\frac{1}{k}\,\frac{b^3}{a^3}\left(\sqrt{\frac{ak}{V}}24^{1/4} + 5^{1/4}\right)^2. \tag{B82}$$

Data obtained by numerical simulations (Fig. 42) are in good agreement with the analytical expression (B79) except for small τ_2 or small b, where a refined analytical expression can be obtained [see Loverdo *et al.* (2009b)]. In particular, the position of the minimum is very well approximated, and the error on the value of the mean search time at the minimum is close to 10%.

With the static detection mode, intermittence is always favorable and leads to a single optimal intermittent strategy. As in one and two dimensions, the optimal duration of the relocation phase does not depend on k, i.e., on the description of the detection phase. In addition, this optimal strategy does not depend on the typical distance between targets b.

Note that for the static mode in the three cases studied (1, 2, and 3 dimensions), we have $\tau_1^{\rm opt} = \sqrt{\tau_2^{\rm opt}/(2k)}$. This relation between the optimal durations of the two phases is independent of the dimension.

b. Diffusive mode

We now study the case where the detection phase is modeled by a diffusive mode. During the detection phase, the searcher diffuses and detects the target as soon as its respective distance is less than a (see Fig. 21).

i. Equations. Outside the target ($r > a$), one has

$$\vec{V}\cdot\vec{\nabla}t_{2,\theta,\phi} + \frac{1}{\tau_2}(t_1 - t_{2,\theta,\phi}) = -1, \tag{B83}$$

$$D\Delta t_1 + \frac{1}{\tau_1}\left(\frac{1}{4\pi}\int_0^{\pi} d\theta\sin\theta\int_0^{2\pi} d\phi\, t_{2,\theta,\phi} - t_1\right) = -1, \tag{B84}$$

and inside the target ($r \le a$)

$$\vec{V}\cdot\vec{\nabla}t_{2,\theta,\phi} - \frac{1}{\tau_2}t_{2,\theta,\phi} = -1, \tag{B85}$$

$$t_1 = 0. \tag{B86}$$

With $t_2 = \frac{1}{4\pi}\int_0^{\pi} d\theta\sin\theta\int_0^{2\pi} d\phi\, t_{2,\theta,\phi}$, one obtains outside the target ($r > a$)

$$D\Delta t_1^{\rm out} + \frac{1}{\tau_1}(t_2^{\rm out} - t_1^{\rm out}) = -1. \tag{B87}$$

The decoupling approximation described previously then yields outside the target

$$\frac{V^2\tau_2}{3}\Delta t_2^{\rm out} + \frac{1}{\tau_2}(t_1^{\rm out} - t_2^{\rm out}) = -1, \tag{B88}$$

and inside the target ($r \le a$)

$$\frac{V^2\tau_2}{3}\Delta t_2^{\rm int} - \frac{1}{\tau_2}t_2^{\rm int} = -1. \tag{B89}$$

These equations are completed by the following boundary conditions:

$$\left.\frac{dt_2^{\rm out}}{dr}\right|_{r=b} = 0, \tag{B90}$$

$$t_2^{\rm out}(a) = t_2^{\rm int}(a), \tag{B91}$$

$$\left.\frac{dt_2^{\rm out}}{dr}\right|_{r=a} = \left.\frac{dt_2^{\rm int}}{dr}\right|_{r=a}. \tag{B92}$$

ii. Results in the general case. Through standard but lengthy calculations the above system can be solved and leads to an analytical approximation of t_m [see Loverdo *et al.* (2009b)]. In the regime $b \gg a$ and $b\sqrt{(\tau_1 D)^{-1} + 3(\tau_2 v)^{-2}} \gg 1$, one obtains

$$t_m = \frac{b^3\kappa_2^4(\tau_1+\tau_2)}{\kappa_1} \times \frac{\tanh(\kappa_2 a) + \kappa_1/\kappa_2}{\kappa_1\kappa_2^2\tau_1 Da[\tanh(\kappa_2 a) + \kappa_1/\kappa_2] - \tanh(\kappa_2 a)} \tag{B93}$$

with $\kappa_1 = \sqrt{\tau_2^2V^2 + 3\tau_1 D}/\tau_2 V\sqrt{D\tau_1}$ and $\kappa_2 = \sqrt{3}/V\tau_2$. It can be shown that t_m only weakly depends on τ_1, which indicates that this variable will be less important than τ_2 in the minimization of the search time. The relevant order of magnitude for $\tau_1^{\rm opt}$ can be evaluated by comparing the typical diffusion length $L_{\rm diff} = \sqrt{6Dt}$ and the typical ballistic length $L_{\rm bal} = Vt$. An estimate of the optimal time $\tau_1^{\rm opt}$ can be given by the time scale for which those lengths are of the same order, which gives

$$\tau_1^{\rm opt} \sim \frac{6D}{V^2}. \tag{B94}$$

In turn, the minimization of t_m leads to

$$\tau_2^{\rm opt} = \frac{\sqrt{3}a}{Vx}, \tag{B95}$$

with x the solution of

$$2\tanh(x) - 2x + x\tanh(x)^2 = 0. \tag{B96}$$

This finally yields

$$\tau_2^{\rm opt} \simeq 1.078\,\frac{a}{V}. \tag{B97}$$

It is important that this approximate expression is very close to the expression obtained for the static mode ($\tau_2^{\rm opt} = (\sqrt{6/5})(a/V) \simeq 1.095(a/V)$) (B81), and there is no dependence on the typical distance between targets b. The simplified expression for the minimal t_m can then be obtained as

$$t_m^{\rm opt} = \frac{b^3x^2}{\sqrt{3}a^2V}[x - \tanh(x)]^{-1} \simeq 2.18\,\frac{b^3}{a^2V}, \tag{B98}$$

and the gain reads

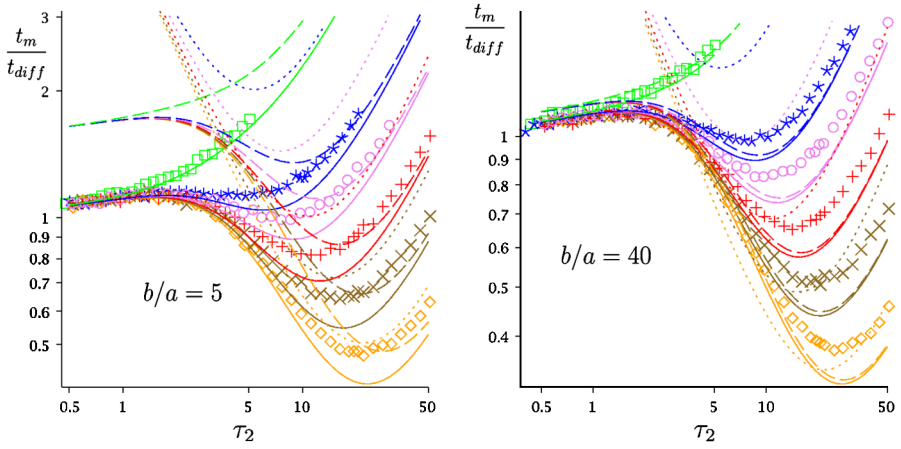


FIG. 43. Diffusive mode in three dimensions. $t_m/t_{\rm diff}$ as a function of τ_2 for different values of the ratio b/a (logarithmic scale). The full analytical form given in Loverdo *et al.* (2009b) (plain lines) is plotted against the simplified expression (B93) (dashed lines), the simplified expression with $\tau_1 = 0$ (dotted line), and numerical simulations (symbols) for the following values of the parameters (arbitrary units): $a = 1$ (□); $a = 5$ (⋆); $a = 7$ (∘); $a = 10$ (+); $a = 14$ (×); $a = 20$ (◇). $\tau_1 = 6$ everywhere except for the small dots, $V = 1$, $D = 1$. $t_m/t_{\rm diff}$ presents a minimum only for $a > a_c \simeq 4$.

$$\text{gain} = \frac{t_{\rm diff}}{t_m^{\rm opt}} \simeq 0.15\frac{aV}{D}, \tag{B99}$$

where the search time without intermittence is given by $t_{\rm diff} \simeq b^3/3Da$ for $b \gg a$ (Redner, 2001).

There is a range of parameters for which intermittence is favorable, as indicated by Fig. 43. Both the analytical expression for $t_m^{\rm opt}$ in the regimes without intermittence and with intermittence (B98) scale as b^3. However, the dependence on a is different. In the diffusive regime $t_m \propto a^{-1}$, whereas in the intermittent regime $t_m \propto a^{-2}$. This enables us to define a critical a_c, such that when $a > a_c$, intermittence is favorable: $a_c \simeq 6.5D/V$ is the value for which the gain (B99) is 1.

c. Ballistic mode

We now discuss the last case, where the detection phase 1 is modeled by a ballistic mode (see Fig. 21). Since an explicit analytical determination of the search time seems out of reach, a numerical exploration of the parameter space is needed to identify the regimes where the search time can be minimized. Approximation schemes are then developed in each regime to obtain analytical expressions [more details are given in Loverdo *et al.* (2009b)].

i. Numerical study. The numerical analysis performed by Loverdo *et al.* (2009b) puts forward two strategies minimizing the search time, depending on a critical value v_l^c to be determined later on:

(i) When $v_l > v_l^c$, $\tau_1^{\rm opt} \to \infty$ and $\tau_2^{\rm opt} \to 0$. In this regime intermittence is not favorable.

(ii) When $v_l < v_l^c$, $\tau_1^{\rm opt} \to 0$ and $\tau_2^{\rm opt}$ is finite. In this regime the optimal strategy is intermittent.

ii. Regime without intermittence (single-state ballistic searcher): $\tau_2 \to 0$. Following the same argument as in two dimensions, without intermittence the best strategy is obtained in the limit $\tau_1 \to \infty$ in order to minimize oversampling of the search space. Following the derivation of (B64) [see Loverdo *et al.* (2009b) for details], it is found that the search time reads

$$t_{\rm bal} = \frac{4b^3}{3a^2 v_l}. \tag{B100}$$

iii. Regime with intermittence. In the regime of favorable intermittence, the numerical study suggests that the best strategy is realized for $\tau_1 \to 0$. In this regime $\tau_1 \to 0$, phase 1 can be well approximated by diffusion with an effective diffusion coefficient $D_{\rm eff} = v_l^2\tau_1/3$. The analytical expression t_m derived in (B93) can then be used and yields for $\tau_1 = 0$ and $b \gg a$

$$t_m = \frac{b^3\sqrt{3}}{V^2\tau_2^2}\left[\frac{\sqrt{3}a}{V\tau_2} - \tanh\left(\frac{\sqrt{3}a}{V\tau_2}\right)\right]^{-1}. \tag{B101}$$

Then one finds straightforwardly that $\tau_2^{\rm opt} = \sqrt{3}a/Vx$, where x is the solution of $x\tanh(x)^2 + 2\tanh(x) - 2x = 0$, that is, $x \simeq 1.606$. Using this optimal value of τ_2 in the expression of t_m, one finally obtains

$$t_m^{\rm opt} = \frac{2}{\sqrt{3}}\frac{x}{\tanh(x)^2}\frac{b^3}{a^2V} \simeq 2.18\frac{b^3}{a^2V}. \tag{B102}$$

These expressions show good agreement with numerical simulations [see Loverdo *et al.* (2009b)].

iv. Discussion of the critical value v_l^c. The gain is given by

$$\text{gain} = \frac{t_{\rm bal}}{t_m^{\rm opt}} \simeq 0.61\frac{V}{v_l}. \tag{B103}$$

As in two dimensions, it is trivial that $v_l^c < V$, and the critical value v_l^c can be defined as the value of v_l such that gain $= 1$. This yields

$$v_l^c \simeq 0.6V. \tag{B104}$$

Importantly, v_l^c depends on neither b nor a. Simulations are in good agreement with this result, except for a small numerical shift.

d. Conclusion in dimension 3

For the three possible modelings of the detection mode (static, diffusive, and ballistic) in three dimensions, there is a regime where the optimal strategy is intermittent. Remarkably, and as was the case in one and two dimensions, the optimal time to spend in the fast nonreactive phase 2 is independent of the modeling of the detection mode and reads $\tau_2^{\mathrm{opt}} \simeq 1.1a/V$. Additionally, while the mean first-passage time to the target scales as b^3, the optimal values of the durations of the two phases do not depend on the target density a/b.

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