



# STOCHASTIC SEARCH PROCESSES AND CHEMICAL REACTIVITY IN HETEROGENEOUS MEDIA

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Intermittent search processes alternate between two different stochastic motions in order to reach a given target. If the faster motion has a lower probability to detect the target, a question arises concerning the efficiency of both processes, and it may be possible to minimize the search time by a convenient choice of the parameters. This argument has been used to interpret observations in molecular biology or to explain the behavior of animals when searching for food. It can also have interesting consequences for the kinetics of reactions in heterogeneous media. In particular, the reaction kinetics in a biological cell can be enhanced when the active molecules occasionally bind to molecular motors that inactivate their reactivity and carry them far away. Here, we present a synthesis of the recent results obtained on these topics, with new perspectives and possible applications of intermittent behavior in reaction kinetics to be soon developed.

*Keywords:* Search processes; intermittency; kinetics; powered reactions.

## 1. Introduction

Search problems have been widely studied in applied cases, such as the search for mines in the Second World War, search for a lost submarine, rescue operations, and many other examples (see [Von Hippel *et al.*, 1989; Cox, 1983; O'Brien *et al.*, 1990; Bell, 1991]). The main question is how to find a given target in the most efficient way. In fact, it is often crucial to find the target as rapidly as possible: thus, we focus here on minimizing the time needed to reach the target. In the case of hidden targets, when they cannot be seen from a large distance and no information enables the definition of a nonuniform target distribution probability, the searcher has to follow an arbitrary trajectory to prospect the territory until a target enters into the action field of the sensors which can detect it. It can be difficult to determine the best trajectory for a systematic, deterministic exploration, and this is a

specific problem, which does not allow for a general solution: thus, for practical reasons, the trajectory is often stochastic.

Examples can be found in many fields and at very different scales. For instance, eagles searching for preys follow a stochastic trajectory (but not any trajectory) as well as many predators whose behavior has been carefully studied by ecologists. People looking for lost, small objects (keys, rings, money...) often seem to walk or run randomly. On the other hand, a person trying to recognize a word or a group of letters in a text generally focuses on a randomly moving point of the page. At a different scale, particles or bacteria that can attach to a specific region of a vessel generally have no proper locomotion and are subject to a random walk or Brownian motion before reaching their target. Similarly, reagents in a solution generally diffuse till they meet and can react (see the theory

of diffusion limited reactions, initiated by Smoluchowski [1916], and many related papers, such as for instance [Noyes, 1961]).

A special, but widely widespread case of stochastic research includes intermittent processes, when the searcher alternates between two search regimes. We now rapidly review the main results of the first model where this behavior was studied [Bénichou *et al.*, 2005], which concerned foraging animals: in fact, with relevant changes, it can be adapted to model some chemical reactions. Then, we summarize recent results on powered chemical reactions in a cell [Loverdo *et al.*, 2008], which are based on extensions of the previous case and show that reaction kinetics can be enhanced by intermittent search.

## 2. Intermittent Search Processes: The Example of Foraging Animals

Imperfect detectors cannot instantaneously recognize the presence of a target in their range of action. Their ability to detect a target decreases when they move rapidly. This is often the case, for instance, for seeing keys on a beach, or finding any hidden target. Then, it may be favorable to adopt a slower motion with higher probability for detecting a target when it enters into the sensors action range. In the simplest case, the searcher may alternate slow displacements with high detection abilities, and fast motions with no possible detection which allow for rapid displacements to new territories. Such an intermittent strategy is in fact observed with many foraging animals: numerous studies of a broad range of animals show that they use an intermittent, or saltatory behavior, when the preys are difficult to find and sparsely distributed. Many examples have been observed among birds, fishes, lizards or insects [Bell, 1991; O'Brien *et al.*, 1990; Anderson *et al.*, 1997].

A few years ago, several of us presented a one-dimensional model of intermittent search [Bénichou *et al.*, 2005]. In this model, the predator  $\mathbf{P}$  follows a one-dimensional motion (in fact, observations show that the turning angle between different phases is usually small) including two phases: (i) the search phase 1 is modeled as a diffusive motion with diffusion coefficient  $D$ , the target being found as soon as the predator reaches it during this phase, and (ii) the motion phase 2 is a ballistic motion at constant velocity  $v$ : during phase 2, the target cannot be found. The durations of each phase  $i$  is

an exponential, stochastic variable  $T_i$

$$P(T_i > t) = \exp(-\lambda_i t)$$

Preys are supposed to be regularly distributed along a straight line, with an inter-distance  $L$ . Let  $t(x, i)$  be the search time (mean first arrival time to a prey) when  $\mathbf{P}$  starts from position  $x$  and phase  $i$ . The search time satisfies the (backward) Chapman–Kolmogorov equations [Gardiner, 1985; Redner, 2001]

$$D \frac{\partial^2 t(x, 1)}{\partial x^2} + \lambda_1 [t(x, 2) - t(x, 1)] = -1$$

$$v \frac{\partial t(x, 2)}{\partial x} + \lambda_2 [t(x, 1) - t(x, 2)] = -1$$

which can be solved easily with relevant, periodic boundary conditions [Bénichou *et al.*, 2005]. The average search time  $\langle T \rangle$  from an initial diffusive state is obtained by averaging  $t(x, 1)$  on uniform distribution of initial position  $x$  in the interval  $(0, L)$ . It is found that in the low target density limit  $L \gg v\tau_2, \sqrt{D\tau_1}, D\tau_1/v\tau_2$  (where  $\tau_i = 1/\lambda_i$  is the mean duration of phase  $i$ ,  $i = 1$  or  $2$ ) the average search time  $\langle T \rangle$  is

$$\langle T \rangle = \frac{L}{2\sqrt{D}} \left( \frac{1}{\lambda_1} + \frac{1}{\lambda_2} \right) \frac{\tau\lambda_2^2 + 2\lambda_1}{\sqrt{\tau\lambda_2^2 + 4\lambda_1}}$$

$\tau$  being the characteristic time  $\tau = D/v^2$ .

Thus, the average search time scales with the distance of the preys as  $L$  instead of  $L^2$  as would be the case for a purely diffusive search. Intermittence is thus favorable for optimizing the search. Furthermore, it can be shown from the expression of  $\langle T \rangle$  that the search strategy is optimal when the mean duration  $\tau_1$  of the search phase 1 is as small as possible, and when the mean duration  $\tau_2$  of the motion phase 2 scales as the power  $3/5$  or  $2/3$  of  $\tau_1$ , depending on the regime. These nonintuitive conclusions agree with experimental observations of a large class of foraging animals [Anderson *et al.*, 1997; Bénichou *et al.*, 2005].

Thus, the previous, elementary model is able to capture some important features of intermittent search processes, which makes it useful for studying many phenomena, provided that they are practically one-dimensional, and that the searcher has spatial memory, i.e. it keeps memories of its velocity in the fast, ballistic phase. Several other models have been presented to improve it and to address the phenomena which do not satisfy the previous conditions [Coppey *et al.*, 2004; Moreau

*et al.*, 2007; Bénichou *et al.*, 2007]. We will now focus on diffusion controlled chemical reactions, when the “searcher” is a particle which has no memory and moves in a medium which can be one-, two- or three-dimensional. The theory of intermittent search is relevant in special cases only, but it covers interesting, complex situations, when one of the reactants can move either slowly with a high reactivity, either rapidly without any probability to react. Such examples are mainly found in heterogeneous media.

### 3. Chemical Reactions at an Interface

If most chemical reactions, the reagent molecules undergo Brownian motions till the moment when they meet and react. In some cases, their motion can be temporarily accelerated by external agents, and intermittent reactivity may occur. We first focus on a specific case which plays an important role in biology and has been studied recently: the active transport in a cell [Loverdo *et al.*, 2008].

#### 3.1. Powered reaction kinetics in a biological cell

Active transport in cellular media can have a very large impact on mechanical and chemical properties of the cell. It has been shown recently [Alberts *et al.*, 2002; Salman *et al.*, 2005] that some tracers can either diffuse freely in the cell and react with specific reactants, or temporarily bind to a motor protein which inhibits its reactivity, but carries it rapidly through the cell. Let us study a recent model [Loverdo *et al.*, 2008] of such powered reaction



We suppose that

- a particle  $\mathbf{B}$  (tracer) with time-dependent position  $x$  diffuses in a  $n$ -dim medium  $X$  containing immobile particles  $\mathbf{A}$  (targets, or receptors), with  $n = 1, 2$  or  $3$ .
- the range of interaction between  $\mathbf{A}$  and  $\mathbf{B}$  is  $a$ :  $\mathbf{A}$  and  $\mathbf{B}$  react as soon as the distance between them is smaller than or equal to  $a$ .
- however,  $\mathbf{B}$  can temporarily bind to other particles (motors) which carry  $\mathbf{B}$  according to their own, independent fast motion, which can be, for instance, a ballistic motion with absolute velocity  $v$ , or consists of a “teleportation” (which restores

random distribution of final location, independently of its initial position). Many other cases can be considered. Later on, we assume that the motors velocity has a constant absolute value  $v$ , and is randomly reoriented as indicated below.

- in  $n$ -dim space, particle  $\mathbf{B}$  (tracer) moves in a sphere ( $b$ ) with center  $\mathbf{A}$  and radius  $b$  which is the average distance between target particles  $\mathbf{A}$  in the actual medium. Sphere ( $b$ ) contains only one target  $\mathbf{A}$ , represented as a concentric sphere ( $a$ ) with radius  $a$  ( $a \ll b$ ).

Then  $\mathbf{B}$  can obey two dynamical regimes: either it diffuses freely with diffusion coefficient  $D$  (regime 1), or it undergoes a ballistic motion with constant absolute velocity  $\mathbf{v}$  (regime 2), randomly reoriented when it touches the external sphere ( $b$ ) or at the beginning of each new phase 2. In regime 1,  $\mathbf{B}$  reacts instantaneously if it is at distance smaller than or equal to  $a$  from particle  $\mathbf{A}$ , whereas it cannot react during regime 2. Again, we assume that the distribution of  $T_i$ , the duration of each regime  $i$ , is exponential:  $P(T_i > t) = \exp(-\lambda_i t)$ . We consider that the outer boundary of sphere ( $b$ ) is reflecting for particle  $\mathbf{B}$ , whereas the boundary of sphere ( $a$ ) is absorbing.

The reactant  $\mathbf{B}$  experiments an intermittent behavior (partially) *without memory*, since it keeps no memory of its velocity orientations during the previous ballistic phases (but it remembers its absolute velocity).

#### 3.2. Equations

Such a model can be solved exactly in one-dim, and approximately in  $d$ -dimensions [Bénichou *et al.*, 2006]. As done previously, we define the stochastic search time  $t(\mathbf{x}, 1)$  for  $\mathbf{B}$  to react with the target  $\mathbf{A}$  at time  $t$ , if starting from position  $\mathbf{x}$  and regime 1, and similar to the stochastic search time  $t(\mathbf{x}, \mathbf{v}, 2)$ , which now depends on the initial velocity  $\mathbf{v}$ . The Chapman–Kolmogorov backward equations for search times read

$$D\nabla_{\mathbf{x}}^2 t(\mathbf{x}, 1) + \frac{1}{\tau_1} [\langle t(\mathbf{x}, \mathbf{v}, 2) \rangle_{\mathbf{v}} - t(\mathbf{x}, 1)] = -1$$

$$\text{with } t(\mathbf{x}, 1) = 0 \text{ if } |\mathbf{x}| \leq a$$

$$\mathbf{v} \cdot \nabla_{\mathbf{x}} t(\mathbf{x}, \mathbf{v}, 2) + \frac{1}{\tau_2} (t(\mathbf{x}, 1) - t(\mathbf{x}, \mathbf{v}, 2)) = -1$$

They cannot be solved, except in very special cases. However, we can define the reduced variables  $s(\mathbf{x}) = \langle t(\mathbf{x}, \mathbf{v}, 2) \rangle_{\mathbf{v}}$  and  $d(\mathbf{x}) = \langle \mathbf{v} t(\mathbf{x}, \mathbf{v}, 2) \rangle_{\mathbf{v}}$ , the averages

being taken on velocities  $\mathbf{v}$  only. With the aid of a decoupling approximation (exact in one-dim)

$$\langle v_i v_j t(\mathbf{x}, \mathbf{v}, 2) \rangle \approx \left( \frac{v^2}{n} \right) \delta_{ij} s(\mathbf{x})$$

and defining the effective diffusion coefficient  $\bar{D} = v^2 \tau_2 / n$ , we obtain the approximate reduced equations

$$D \nabla_{\mathbf{x}}^2 t(\mathbf{x}, 1) + \frac{1}{\tau_1} [s(\mathbf{x}) - t(\mathbf{x}, 1)] = -1$$

$$\bar{D} \nabla_{\mathbf{x}}^2 s(\mathbf{x}) + \frac{1}{\tau_2} [t(\mathbf{x}, 1) - s(\mathbf{x})] = -1$$

which are formally equivalent to two diffusions with coefficients  $D$  and  $\bar{D}$ . They can be solved exactly in spherical geometry [Bénichou et al., 2007].

### 3.3. Two-dimension results

It is found that in two-dim

- if  $a < b \ll D/v$ , intermittence is *not favorable* for minimizing search time
- if  $a \ll D/v \ll b$ , the intermittence is *moderately favorable* and permits to minimize the search time for certain finite values  $\tau_{1 \min}$  and  $\tau_{2 \min}$  of the mean durations of regimes 1 and 2 such that the diffusion length is of the order of the ballistic length, and we have

$$\frac{\langle t(\mathbf{x}, 1) \rangle_{\min}}{\langle t(\mathbf{x}) \rangle_{\text{dif}}} \sim 0.5$$

$\langle t(\mathbf{x}) \rangle_{\text{dif}}$  being the average search time in the pure diffusive regime

- if  $D/v \ll a \ll b$  there is also an optimal intermittent strategy for other values of the average durations  $\tau_{1 \min}$  and  $\tau_{2 \min}$ , but now

$$\frac{\langle t(\mathbf{x}, 1) \rangle_{\min}}{\langle t(\mathbf{x}) \rangle_{\text{dif}}} \rightarrow 0 \quad \text{if } v \rightarrow \infty$$

Thus, in this case, intermittence can be *very efficient* for minimizing the search time. These results can be generalized to  $n$  dimensions as follows.

### 3.4. Enhanced reactivity

We now specify the results [Loverdo et al., 2008] of the previous model for the powered reaction

$\mathbf{A} + \mathbf{B} \rightarrow \mathbf{C}$ :

(i) *In three dimensions*, which is the case of a generic *in vitro* active solution, the reaction rate  $K_{3d}$  can be maximized if  $a \geq a_c \equiv D/v$  by choosing

$$\tau_1 \approx \frac{6D}{v^2}, \quad \tau_2 \approx \frac{\sqrt{3}a}{vx_0} \approx 1.078 \frac{a}{v}$$

It is interesting to notice that  $\tau_2$  is independent of  $D$ .

The optimal rate is then

$$K_{3d}^{\max} \approx \frac{cv}{a} \frac{\sqrt{3}(x_0 - \tanh(x_0))}{(x_0)^2}, \quad \text{where } c = \left( \frac{a}{b} \right)^n$$

corresponds to the concentration of  $\mathbf{A}$ ,  $x_0$  being the solution of  $2 \tanh(x) - 2x + x \tanh(x^2) = 0$ .

The gain  $G$  can be defined by the ratio of the maximum kinetic constant in the intermittent regime to the kinetic constant for pure diffusion

$$G_{3d} = \frac{K_{3d}^{\max}}{K_{3d}^{\text{dif}}} \approx 0.26 \frac{av}{D}$$

In standard cellular conditions, a typical value of the gain is  $G_{3d} \approx 2.5$  so that active transport is (moderately) efficient for large tracers (vesicles) with small  $D$ .

(ii) *In two dimensions*, a typical example is a reaction in a cytoplasmic membrane. The reaction rate  $K_{2d}$  can be maximized if  $D/v \ll a \ll b$  by choosing

$$\tau_1 = \frac{D}{2v^2} \frac{\ln^2\left(\frac{1}{\sqrt{c}}\right)}{2 \ln\left(\frac{1}{\sqrt{c}}\right) - 1}, \quad \tau_2 = \frac{a}{v} \left[ \ln\left(\frac{1}{\sqrt{c}}\right) - \frac{1}{2} \right]^{1/2}$$

Then the gain is

$$G_{2d} = \frac{K_{2d}^{\max}}{K_{2d}^{\text{pas}}} \approx \frac{av}{4D} \sqrt{\ln\left(\frac{1}{\sqrt{c}}\right)}$$

It decreases if  $D$  or the concentration  $c$  of reactant  $\mathbf{A}$  increases. Thus active transport is efficient for large tracers and low concentrations of  $\mathbf{A}$ .

A typical value is  $G_{2d} \sim 8$ : in two-dim, the gain due to intermittency is more significant than in three-dim.

(iii) The one-dim case applies, for instance, to cellular tubes such as axons or dendrites of neuron cells. The model is then exactly solvable. The reaction rate  $K_{1d}$  is maximized if  $D/v \ll a \ll b$  by choosing

$$\tau_1 = \frac{1}{48} \frac{D}{v^2 c}, \quad \tau_2 = \frac{1}{\sqrt{3}} \frac{a}{vc^{1/2}}$$

and the gain is

$$G_{1d} = \frac{K_{1d}^{\max}}{K_{1d}^{\text{pas}}} \approx \left( \frac{1}{2\sqrt{3}} \right) \frac{av}{Dc^{1/2}}$$

It decreases with increasing concentrations  $c$  more rapidly than in two-dim. A typical value is  $G_{1d} \sim 100$  so that *the gain due to intermittency can be very significant* in one-dim, especially for low diffusion coefficients and low concentrations.

### 3.5. Perspectives: Intermittent reactivity and reactions at an interface

It often happens that a chemical reaction can only be completed in a given region of space, in particular, on an interface. This is the case, for instance, for a catalytic reaction, if the catalyst stays on the interface (heterogeneous catalysis), for instance, in the celebrated catalytic oxidation of CO [Ertl *et al.*, 1982]



It is also possible that one of the reacting species lives on the interface, for instance, if one of the reactants is grafted on a surface. This situation can be produced artificially or it can be natural. Many similar examples can be found in biology, for instance in the detection of odorous molecules by sensors anchored on olfactory filaments [Rospars *et al.*, 2003].

If one of the reactants is fixed on the interface, the other one can be dragged by a flow in a contiguous fluid, but it may be temporarily absorbed by the interface and diffuse on it, till either it desorbs, or it meets the interfacial reactant and reacts with it: this is an intermittent search problem and intermittency can again enhance the reactivity in this case, which will be studied elsewhere.

## 4. Conclusion

We have shown that intermittence can be a very efficient strategy for optimizing the search, as to be expected from the observed behavior of many foraging animals and from other natural phenomena. It can also enhance the kinetics of certain reactions in heterogeneous media. In the particular case of powered reactions in cells, the gain due to intermittence has been explicitly calculated in 1, 2 and 3 dimensions. It has been shown that its efficiency is much greater in low dimensions. Since biology offers many examples of restricted geometry and

low dimension phenomena, one can presume that in many examples, intermittence should allow them to obtain optimal conditions: this could explain why it is so frequently observed.

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