LABORPROJEKT

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Active Motion and Random Search Problems In Biological Systems

CONTENTS

ACRONYMS

SRW   simple isotropic random walk

MSD   mean squared displacement

BRW   biased random walk

PRW   persistent random walk

MFPT   mean first-passage time

INTRODUCTION

What is the common denominator between a human looking for its keys, an animal seeking for food, a T-killer cell on the hunt for cancer cells, and a bacterium trying to find glucose to feast on? No matter how advanced the life form, they are all facing different types of search problems.

As above examples show, search problems are an essential part of life. The efficiency of search strategies – or in some cases equivalently the time needed to successfully finish a search – is quite often crucial in survival. Obviously, depending on the life form, different capabilities are available to go about a search problem and thus, different strategies have evolved over the course of evolution. However, as a general prerequisite, all searchers need to be able to move and explore their environment, or more specifically, the search vicinity.

Albeit many reasons for motion are related to search problems and equivalent problems, motion in general is a more essential phenomenon in nature and has been the focus of much research, such as in ancient human migration [15], movement of marine species [38], and bacterial migration [17].

Quite often the goal of such research is to identify certain properties of motion or movement patterns. For this purpose, mathematical models provide many useful tools. Especially the theory around random walk models has proven to be of invaluable worth when it comes to modeling random motion.

However, the main interest of this work lies in search problems and related search strategies. With motion models provided by the random walk theory, the next step is to analyze such random search problems. Therefore, the first-passage theory serves as an adequate tool to calculate search times and compare different search strategies.

In addition, random search problems can be expanded with hints in the environment that help the searcher find the target. This corresponds to real biological systems, in which e.g. traces, odor, or chemicals are detected by the searcher to obtain information about the whereabouts of the target.

In this work we want to focus on random search problems, which often appear in microscopic systems, i.e. for cells and other microorganisms such as bacteria. We will start with an introduction to active motion in biological systems of any size in Chapter 2. There, we will also give an overview of related research in different fields. In Chapter 3 we will introduce some random walk models and the corresponding mathematical background. Following this, in Chapter 4 we

will talk about random search strategies as well as the first-passage time theory. We will also briefly review the work of Tejedor, Voituriez, and Bénichou (2012) [44] on optimizing persistent random walk searches. Finally, we will give a brief introduction of search problems with hints in the environment in Chapter 5. For this purpose, among others, we will also take a look at the works of Celani and Vergassola (2010) [8] and Novikova et al. (2017) [34] on bacterial chemotaxis and durotactic motion of cells.

ACTIVE MOTION

Active motion describes the process of converting energy resources into directed motion. Living beings performing active motion are e. g. humans, animals, migrating cells, and microorganisms such as bacteria.

While it is everyday experience that animals and humans are able to move directed, it is a nontrivial fact for microorganisms. Especially considering cells and bacteria which are often surrounded by fluids and therefore experience thermal *diffusion*. The diffusion alone would lead to the so called *Brownian motion*, a purely random motion named after its famous discoverer Brown and his studies on the motion of pollen particles [7]. However, non-diffusive motion patterns have been observed for microorganisms in many experiments. Figure 2.1 shows two examples of cells and bacteria for which directed and persistent motion has been recorded.

The motion of a human floating in a sea is only subject to the current, however, by using energy and muscle power the human can swim and therefore move directed.

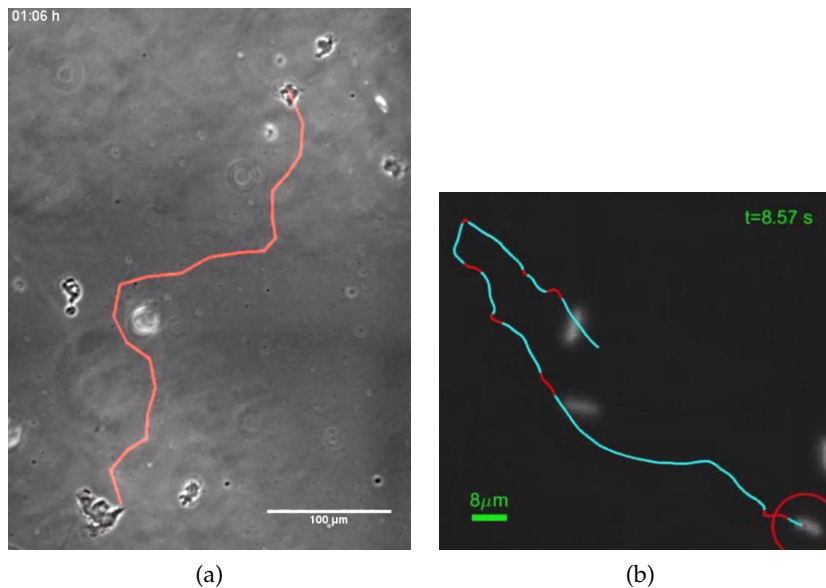Figure 2.1: Directed and piecewise persistent migration paths for (a) an immature bone marrow-derived mice dendritic cell [30], and (b) a Bacillus subtilis bacterium [33].

In the following, the main reasons and applications of active motion in biological environments are discussed, an overview of the related current research in different fields is presented, and the *search problem* aspects are briefly introduced.

2.1   MOTIVATION AND EXAMPLES

The reasons for active motion are manifold and depend among others on the species and environmental conditions. They include, for example:

A mouse might need to hide or run from a fox while a human might be looking for lost keys.

- *Survival*: evading predators, escaping hazardous locations, finding shelter.

- *Foraging*: finding food or nutrients, hunting prey.

- *Reproduction*: finding mates.

- *Search*: searching for objects or locations of interest.

- *Migration*: finding and exploring new habitats and environments.

- *Biological tasks*: e. g. morphogenesis, wound healing, immune response, etc.

From this list one can infer that most of the time a specific *search problem* is the cause of active motion. Furthermore, it is reasonable to assume that, depending on the motivation, also the movement patterns of active motion vary. To stick with the example of the mouse and the human: the movement pattern of a mouse running for its life certainly looks different from that of a human looking for its lost keys. Therefore, there is a lot of ongoing research with the goal of obtaining a qualitative and quantitative understanding of the many kinds of active motion. Considering the tasks and functions of cells and bacteria, understanding their migrational properties is especially relevant in the fields of biology and medicine.

To give an impression of the current research on search related problems, a few examples are presented below.

Humans

For humans almost any activity in everyday life is connected to active motion (e. g. doing groceries, sports, work, ...). However, on a macroscopic scale ancient migration and colonization can be also analyzed as active motion. In this sense, the colonization of America and the Neanderthal replacement in Europe has been studied [15]. The total dispersal times as well as the effective velocity of dispersal, which have been derived within this study, are in good agreement with archeological data and the given reference values.

Animals

Here, the term animals includes all kinds of terrestrial animals, birds, fishes and insects.

There is quite a lot of literature on active motion of animals such as the "*Encyclopedia of Animal Behavior*" [5] and the book "*Animal Behav-*

ior" [6] which cover many interesting aspects such as *search, naviga-tion, migration, dispersal, foraging, self-defense, mating*, and many more in great generality. However, a wide range of research also focuses on very specific topics with most of them being focused on foraging behavior or other search problems requiring active motion or reloca-tion.

Based on the foraging behavior of animals, people first categorized them into *cruise* and *ambush* types [16]. The animals of cruise type, such as tuna and soaring hawks, move around the environment and simultaneously search for food or prey. On the contrary, the animals of ambush type stay immobile for a long time until the prey ap-proaches and enters their strike zone. Examples of animals of this type include herons and rattlesnakes.

First animals were categorized into cruise and ambush searchers...

Nonetheless, in a theoretical approach, Andersson (1981) [2] com-pared continuous travel to a search mode of alternating pause-and-travel in regard of energy consumption and prey detection efficiency. The results propose that, under given circumstances (prey density and detectability, energy expenditure during travel, etc.) a pause-travel tactic may become superior.

The studies of foraging in planktivorous fish [23] revealed that the searching behavior follows a pause-and-travel type of dynamics rather than a cruise or ambush strategy. This search pattern, called *saltatory search* by Evans and O'Brien (1988) [14], has been observed in many foraging species. Even the movement of the human eye dur-ing the process of reading, as the eye shifts focus along a line of type [21] or finding a specific letter sequence [9], can be described in such a saltatory manner. It is even possible to assign a kind of saltatory search to the animals such as soaring hawks, which are traditionally categorized as cruise searchers. The reason is that their eye move-ments can be locked in to scan an area for preys before switching to a new region. Therefore, the saltatory search serves as an explanatory tool and supposedly all search behavior can be placed on a saltatory continuum with the extremes being the cruise and the ambush search [23].

... whereas later on they were classified using a continuum in-between both extremes.

Indeed, the saltatory motion has given rise to a lot of research up to today. Observations of white crappie revealed alterations in speed, travel distance and pause times when feeding on prey of different sizes [24]. These adaptions were analyzed with regard to efficiency using a net energy gain simulation model and the results are believed to have considerable generality for other saltatory animals.

Kramer and McLaughlin (2001) [26] propose the term *intermittent locomotion* to describe the observed stop-and-go motion. They showed that despite the fact that pausing adds acceleration and deceleration phases to locomotion, which are costly in terms of energy usage, it is still widespread among diverse species and can have benefits such

The mentioned movement pattern has had many names in biophysics literature, namely saltatory search, intermittent locomotion, intermittent search, stop-go running, stop-and-go swimming, pause-travel locomotion, ...

as recovery from fatigue, improved detection of prey, predators and travel routes, and reduced detection by other organisms.

Juvenile plaice (*Pleuronectes platessa*) change their predatory behavior and motion upon the discovery of a potential prey during search [18]. Performing several moves before an attack, while the distance of moves is decreased, gives rise to the assumption that plaices detect their prey more efficiently when stationary than while moving. Furthermore, the pauses between moves are shortened and the rate of turning per unit distance is increased.

Naturally, mathematical approaches and models describing saltatory or intermittent motion of animals have also emerged over the years, which will be briefly discussed in Chapter 4 (also see e. g. [4, 39]).

Besides the saltatory search research, which is a topic to fill a whole book alone, there have been further relevant studies, e. g. along the following lines:

- A study on the depth vision and perception of the three-dimensional environment of a toad [29] revealed that in presence of a prey, the toad plans its route before starting to move and that the route is preprogrammed, meaning that once the toad has started moving, it does not correct its path even if the prey has relocated.

- Life cycle specific movements are a widespread phenomenon among many marine species [38] such as fish and decapod crustaceans and happen at a broad range of spatial and temporal scales. Because these scales are not considered in many traditional studies of animal-environment relationships they underlie scale-related limitations. The authors therefore argue that this needs to be considered in the process of designing sampling strategies. Furthermore, they offer a conceptual framework which addresses scale and environmental heterogeneity. The awareness of these concepts may not only help in improving studies but also in counteracting the overexploitation of marine animals, which is a severe global threat to marine life and environment with no foreseeable solution in the near future.

- The control and function of counterturning (succession of alternating left and right turns), a feature in the flight of insects following a wind-borne odor, was discussed [25] as there was unambiguous evidence only for the findings concerning a certain flying male moth. Furthermore, the main function of counterturning appeared to be the redetection of an already perceived elusive odor.

- Radiotagged red squirrels (*Sciurus vulgaris*) have been observed in coniferous and deciduous habitats in regard to activity pat-

tern, activity budget and foraging behavior [47]. Food availability, food choice and feeding rate are then used to explain differences between habitats.

- The prey-capture techniques and prey preferences of six different ant-eating jumping spiders (*Saliticidae*) have been studied in the laboratory [22]. The results on the predatory behavior as well as the preference for ants are discussed in consideration of the findings on other ant-eating spiders.

The observed motility patterns in biological environments are not limited to macroscopic scales. As we will discuss below, similar dynamical behavior is frequently observed on microscopic scales as well.

Microorganisms

Directed and persistent motion has also been observed for microorganisms as it was stated before and shown in Figure 2.1. Considering the diverse tasks and functions of different microorganisms, this is not surprising as diffusive Brownian motion is highly inefficient in most (search) applications.

Understanding cell migration is of utmost importance as it has essential functions (not only) in the human body in regard to diverse health concerns. This importance is emphasized in many of the mentioned references below. Therefore, in the past 30 years there has been a focus on understanding migrational processes of cells and bacteria, the underlying mechanics and their properties, of which some excerpts are presented here.

- The migration of different *E. coli* strains on glass and solid surfaces differing in charge and hydrophobicity was studied in an *in vitro* system in order to gain insight on catheter-associated bacteriuria [17]. The findings propose that prevention strategies should be based on inhibition of bacterial growth rather than on modifying the physicochemical properties of the catheter surface.

- There are many articles around which focus on explaining the mechanics, molecular processes and dynamics involved in cellular motion [19, 20, 28, 32]. Some topics covered include contractile forces and adhesion, the role of actin filaments and the cytoskeleton, polarization of the cell, molecular stimulation, membrane extension, and many others.

- In a study on the directional sensing of *Dictyostelium discoideum* amoebae it is concluded that the cell senses direction by spatial regulation of the activity of the signal transduction pathway [35].

- The specific mechanisms and factors that promote directionally persistent as opposed to random cell migration are identified and examined [37].

- In a study of cell motility a mathematical model is developed, which makes use of the analysis of live cell image sequences in order to gain information about collective biomechanical and molecular mechanisms of cell motion, such as e.g. molecular structures, dynamics, processes within the cell, and many more [11]. Therefore, this model is supposed to allow drawing conclusions from the analysis of the cell motion alone.

- In regard to the medical issue of removing infected prostheses from patients, bacterial cell migration has been observed and studied [43]. For the migration from a colonized to a sterile plate, yeast and *Staphylococcus aureus*, which belongs to the bacteria that are responsible for most hospital infections, have been used. They believe that infected prostheses in patients can be completely cleaned by this method in the near future.

- The coherence of cell migration speed and cell persistence is shown based on experimental data *in vitro* and *in vivo* [30]. Additionally, using a theoretical model a generic phase diagram of cell trajectories is obtained which represents the whole range of observed migration patterns.

- In a preview, the distinct motility modes exhibited by migrating cells and their ability to switch between modes according to physical or chemical cues is discussed [48].

- It is physiologically reasonable that cells move through crowded and complex environments, typically in three-dimensional fibrillar networks [31]. A review on the progress of understanding single-cell migration through such environments is given.

We will take a brief look at search-related studies in nonliving systems in the following.

Artificial particles

Inspired by microorganisms researchers have developed artificial self-propelled active particles with similar properties and behavior in regard to motility. These could turn out to be very useful in many fields such as e.g. health care, sustainability, and security.

In a review, the development of artificial self-propelled micro- and nanoparticles, their application to the study of nonequilibrium phenomena, and open challenges are discussed [3]. While doing so the focus lies on the basic physical features of the interactions with crowded and complex environments.

At this point it is worth emphasizing again that many of the given examples for active motion deal with search problems and in the course of evolution, as an answer, the creativeness of Mother Nature has yielded many different search types and strategies which will be partly addressed later on. Hence, understanding their main qualitative and quantitative properties is beneficial to many fields of research and will be a main focus of this work.

3

MODELING STOCHASTIC DYNAMICS OF ACTIVE MATTER

The importance and relevance of understanding migration, motion and search strategies in many different fields has been outlined in Chapter 2. In order to understand and analyze such processes mathematical modeling is a commonly used tool. A broad range of possible modeling approaches is based on the theory of the so called *Random Walk* and different extensions on it.

Generally, the random walk is a stochastic process that describes successive random steps on a mathematical space such as a hypothetical particle that walks on the integers. The most basic version of the random walk is the *simple isotropic random walk* (SRW). It is unbiased (isotropic), meaning that the walker has no preference for one specific direction, and uncorrelated in direction, meaning that the history of previous steps' directions has no influence on the step direction at a given time. More complex random walk versions are built on the SRW to extend it.

3.1 MATHEMATICAL FRAMEWORK AND CONVENTIONS

In order to describe random walks by means of a proper mathematical framework, at least a minimum of terminology and conventions are required. Thereby, the terminology and conventions remain the same throughout the following chapters, unless otherwise specified.

First of all, Ω refers to the mathematical space in which the random walk takes place, i. e. Ω gives the set of values that the walk can attain. For our purposes it is sufficient to consider only such Ω which define a d-dimensional lattice $\Omega \subseteq \mathbb{Z}^d$ or a topological real domain $\Omega \subseteq \mathbb{R}^d$. We will therefore refer to them as discrete or continuous d-dimensional random walks, respectively. Furthermore, the time domain is denoted by $\mathcal{T}$ and can be discrete $\mathcal{T} \subseteq \mathbb{N}$ or continuous $\mathcal{T} \subseteq \mathbb{R}_0^+$ as well.

Further useful quantities and conventions, which we use in this and the following chapters, are listed in Table 3.1.

The discussion of the following different types of random walks as well as the derivation of results is kept rather brief at some points as the theory on random walks is readily available and we do not want to reinvent the wheel.

Note: More abstract spaces include e. g. graphs, Riemannian manifolds, and finite, finitely generated or Lie groups.

DEFINITIONS	
Ω	space $\subseteq \mathbb{Z}^d, \mathbb{R}^d$
$\partial\Omega$	boundary of the domain Ω
$\overline{\Omega}$	closure of the domain Ω, i.e. $\Omega \cup \partial\Omega$
$\mathcal{T}$	time domain $\subseteq \mathbb{N}, \mathbb{R}_0^+$

QUANTITIES	
$\mathbf{E}[\cdot]$	expectation value
$\langle\cdot\rangle$	average
$\mathcal{P}$	occupation probability: $\Omega \times \mathcal{T} \to [0,1]$
$\mathcal{F}$	first-passage probability: $\Omega \times \mathcal{T} \to [0,1]$
p	persistency parameter or stepping probability
$\langle\tau\rangle$	mean first-passage time

CONVENTIONS	
x	scalar-valued variable
$\mathbf{x}$	vector-valued variable
$\mathbf{n}, \mathfrak{m}$	discrete space and time variables
$\mathbf{x}, t$	continuous space and time variables

Table 3.1: Definitions and conventions for mathematical notation.

3.2   SIMPLE ISOTROPIC RANDOM WALK

Consider a one-dimensional random walk in discrete time and space, i.e. $\Omega = \mathbb{Z}$ and $\mathcal{T} = \mathbb{N}$. One can visualize this process by a lattice with discrete sites, on which a hypothetical particle (the *walker*) jumps from its current site to one of the neighboring sites in each time step (see Figure 3.1). The isotropic property is achieved by symmetric hopping probabilities to the right p and left q, i.e. $p = q = 1/2$. We describe the state of the walker by its position at a given time, i.e. (n, m) or short n_m.
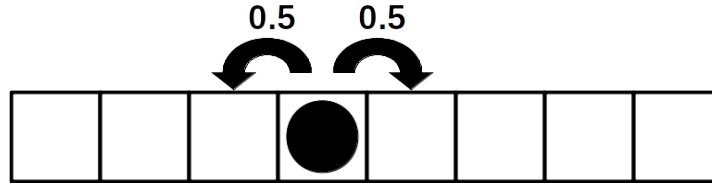
Figure 3.1: SRW on a one-dimensional lattice. Black arrows indicate the possible sites in the next step with the given probabilities.

As an example, imagine the walker starting at the origin $n_0 = 0$. After one time step, its state will be $n_1 = \pm 1$ with equal probability $1/2$. After another time step, accordingly, the walker can be at $n_2 = \pm 2$,

which corresponds to two consecutive steps in the same direction and has probability 1/4, or it can be at $n_2 = 0$, which corresponds to two oppositely directed steps and has probability 1/2. We can continue in this manner and decompose the number of steps m into the number of steps to the right r and the number of steps to the left $m - r$. Then one can argue, that the occupation probability to be at $n = 2r - m$ is given by

$$\mathcal{P}(n, m) = \begin{cases} \binom{m}{r} \left(\frac{1}{2}\right)^m & \text{if } n \leqslant m \text{ and } n + m \text{ is even,} \\ 0 & \text{else.} \end{cases}$$

Note that the second line follows from the condition $n + m = 2r$. It is always handy to know the occupation probability, however, we do not explicitly need it in order to derive other meaningful quantities of the SRW.

Consider, for example, the *mean displacement*

$$\langle n_m \rangle = \mathbf{E}\left[n_m\right] \equiv \sum_{n=-\infty}^{\infty} n\mathcal{P}(n, m),$$

Note: We implicitly use $n_0 = 0$ and $\mathcal{P}(n, 0) = \delta_{n,0}$ here.

and the *mean squared displacement* (MSD)

$$\langle n_m^2 \rangle = \mathbf{E}\left[n_m^2\right] \equiv \sum_{n=-\infty}^{\infty} n^2\mathcal{P}(n, m).$$

As the single steps of the walk are independent of each other, both quantities can be easily derived as $\langle n_m \rangle = 0$, which illustrates the isotropy or absence of a bias, and $\langle n_m^2 \rangle = m$, which is the typical property of diffusion (MSD linear in time). Indeed, the SRW is used to model diffusive motion [10] and therefore cannot be used to model active, directed motion. However, it still serves as a good starting point for extended models.

Transition to continuous time and space

Here, we want to show simple but powerful methods to derive a few properties and the occupation probability $\mathcal{P}(x, t)$ for the one-dimensional random walk in continuous time and space. Therefore, we first need to derive the diffusion equation, however, we only outline the derivation here. We introduce the time step δt and the step size δx. With that we can define

$$x = n \cdot \delta x,$$
$$t = m \cdot \delta t.$$

We then interpret the discrete master equation

$$\mathcal{P}(n, m + 1) = \frac{1}{2}\mathcal{P}(n - 1, m) + \frac{1}{2}\mathcal{P}(n + 1, m),$$

accordingly to

$$\mathcal{P}(x, t + \delta t) = \frac{1}{2}\mathcal{P}(x - \delta x, t) + \frac{1}{2}\mathcal{P}(x + \delta x, t),$$

which we extend to the first non-vanishing orders of δt and δx and after rearranging we obtain

$$\frac{\partial \mathcal{P}(x, t)}{\partial t} = \frac{(\delta x)^2}{2\delta t} \frac{\partial^2 \mathcal{P}(x, t)}{\partial x^2}.$$

As a last step we then take the limit $\delta x, \delta t \to 0$ in such a manner that $(\delta x)^2 / 2\delta t = D$, where D is the diffusion coefficient, to obtain the diffusion equation

$$\frac{\partial \mathcal{P}(x, t)}{\partial t} = D \frac{\partial^2 \mathcal{P}(x, t)}{\partial x^2}. \tag{3.1}$$

We can then try to directly solve Equation 3.1 or we can alternatively try to understand the behavior of the walker.

Consider again the mean displacement. The transition to continuous time and space did not affect the isotropy and therefore there is still no bias. Thus, we can simply write

$$\langle x \rangle = \int_{-\infty}^{\infty} x \mathcal{P}(x, t) \, dx = 0.$$

without further knowledge of $\mathcal{P}(x, t)$. The MSD

$$\langle x^2 \rangle = \int_{-\infty}^{\infty} x^2 \mathcal{P}(x, t) \, dx$$

on the other hand is non-trivial. However, we can use dimensional analysis here in order to quickly derive a result. We can argue that the MSD should depend on the diffusion coefficient D and the time t. If the abstract unit of length is L and T the time unit, then Equation 3.1 gives the dimensions:

$$[\langle x^2 \rangle] = L^2, \quad [D] = \frac{L^2}{T}, \quad [t] = T.$$

The only way to form a dimensional correct relation from this is

$$\langle x^2 \rangle \propto Dt,$$

which again is typical for diffusion. In order to derive the proportional factor one needs to put in a little more work. The correct equation reads

$$\langle x^2 \rangle = 2Dt.$$

We can furthermore apply the powerful tool of dimensional analysis to the occupation probability $\mathcal{P}(x, t)$. It is $[\mathcal{P}(x, t)] = 1/L$ and therefore the quantity $\sqrt{Dt}\,\mathcal{P}(x, t)$ is dimensionless. Thus, we can write

$$\sqrt{Dt}\,\mathcal{P}(x, t) = \mathcal{P}(\lambda),$$

where λ needs to be a dimensionless quantity. The only dimensionless quantity that we can derive from x, t and D is the scaling variable $\lambda = x/\sqrt{Dt}$. Hence, we can write the ansatz

$$\mathcal{P}(x, t) = \frac{1}{\sqrt{Dt}}\mathcal{P}\left(\frac{x}{\sqrt{Dt}}\right),$$

which is often referred to as the *scaling ansatz*. We insert this in the diffusion equation 3.1 in order to reduce the problem to an ordinary differential equation of the form

$$2\mathcal{P}'' + \lambda\mathcal{P}' + \mathcal{P} = 0.$$

This ODE is easier to solve and we obtain as the final result

$$\mathcal{P}(x, t) = \frac{1}{\sqrt{4\pi Dt}}\exp\left(-\frac{x^2}{4Dt}\right), \tag{3.2}$$

a Gaussian probability distribution for the occupation probability of a one-dimensional random walk in continuous time and space. We will seize on this result in Chapter 4.

Note: In order to derive Equation 3.2 we use both the symmetry condition $\mathcal{P}'(0) = 0$ and normalization.

3.3 BIASED RANDOM WALK

For the discrete *biased random walk* (BRW) we have the same situation as in the discrete SRW but we omit the isotropic property, i. e. instead of symmetric hopping probabilities $p = q = 1/2$ we now allow asymmetric $p, q \in [0, 1]$ such that they satisfy the condition $p + q = 1$ (see Figure 3.2).

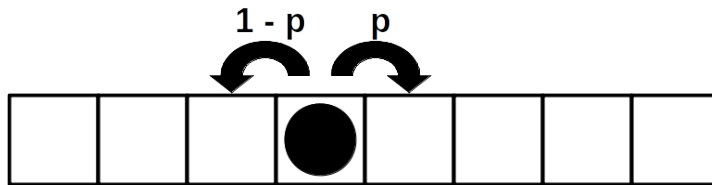*The SRW is a special case of the BRW for $p = 1/2$.*

Figure 3.2: BRW on a one-dimensional lattice. Black arrows indicate the possible sites in the next step with the given probabilities.

In order to compare the BRW to the SRW we again derive the mean displacement as well as the MSD as

$$\langle n_m \rangle = m(2p - 1),$$
$$\langle n_m^2 \rangle = m^2(4p^2 - 4p + 1) + 4mp(1 - p).$$

Note: If we set $p = 1/2$, i. e. the BRW is equivalent to a SRW, we obtain the same results as for the SRW.

Thus, the walker essentially drifts to one direction, which illustrates its preference for this direction (the bias).

Furthermore, the MSD is proportional to the squared time, which is typical for *ballistic motion*. However, since the mean displacement is nonzero, one can also take a look at the mean dispersal around the mean displacement, which is defined as

$$\sigma_m^2 = \sum_{n=-\infty}^{\infty} (n - \langle n_m \rangle)^2 \mathcal{P}(n, m).$$

We obtain

$$\sigma_m^2 = 4mp(1-p),$$

which is linear in time. In other words: in the frame which moves with the drift velocity of the walker, the motion is diffusive and not ballistic.

As we do not use the BRW in our studies, we omit the further analysis of the same. However, we want to remark that because of its drift component, the BRW finds application in modeling search problems in which the walker has some kind of information about the direction in which it needs to move. We will consider and explain this situation in more detail later.

3.4 PERSISTENT RANDOM WALK

So far both the introduced random walk models have been uncorrelated and steps were independent of each other. In the *persistent random walk* (PRW) this is not the case. Instead, at a given time the hopping probabilities for the next step are dependent on the direction of the very previous step. In other words: it matters from which direction the walker came from in the previous step, i. e. the walker has some kind of short memory.

In the one-dimensional discrete PRW we define a *persistency* parameter $p \in [0, 1]$ which represents the probability of preserving the hopping direction. Accordingly, the probability of reversing the hopping direction is $q = 1 - p$. In Figure 3.3 we outline the PRW again with the aid of a lattice representation, however, in opposite to the other random walks presented, here we have two possible scenarios depending on the direction of the previous step.

A PRW with persistency parameter $p = 1/2$ is equivalent to the SRW.

Consequently, walking with $p < 1/2$ tends to reverse the direction of motion in each step leading to *anti-persistent motion*, while walking with $p > 1/2$ tends to preserve the direction of motion leading to *persistent motion*. The trivial cases $p = 0$ and $p = 1$ lead to back-and-forth hopping and a straight trajectory, respectively.

Again we are interested in the mean displacement and MSD. Despite the fact that the hopping probabilities depend on the previous
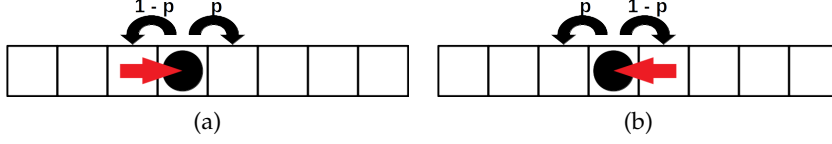
Figure 3.3: During the one-dimensional discrete PRW the walker can step on a lattice site either by arriving from the left (a) or the right site (b). The hopping probabilities for the next step depend on the arrival direction. Red arrows indicate the arrival direction, black arrows indicate the possible sites in the next step with the given probabilities.

step, in PRWs, there is no bias, i.e. preferred direction of motion, in the system. Thus, the dynamics is completely different from BRWs. By means of geometrical arguments [45] or a z-Fourier-transform technique, one obtains [12, 42]

$$\langle n_m \rangle = 0,$$
$$\langle n_m^2 \rangle = \frac{p}{1-p} m + \frac{2p-1}{2(1-p)^2}((2p-1)^m - 1).$$

(3.3)

The mean displacement is as expected, however, the result for the MSD needs to be discussed. Therefore, we take a look at the short and long term behavior.

For short times one obtains

$$\langle n_m^2 \rangle \propto m^\alpha,$$

where $\alpha = 2 + \ln(p)/\ln 2$ [42], which leads to

$$\begin{cases} \alpha = -\infty & \text{(localized)} & \text{if } p = 0, \\ -\infty < \alpha < 1 & \text{(subdiffusive)} & \text{if } 0 < p < 0.5, \\ \alpha = 1 & \text{(diffusive)} & \text{if } p = 0.5, \\ 1 < \alpha < 2 & \text{(superdiffusive)} & \text{if } 0.5 < p < 1, \\ \alpha = 2 & \text{(ballistic)} & \text{if } p = 1. \end{cases}$$

Thus, on short time scales, persistent motion, i.e. $1/2 < p < 1$, is superdiffusive.

For long times, i.e. $m \to \infty$, the second part of the right-hand side of Equation 3.3 becomes a constant and only the first part determines the behavior. This means that the MSD is linear in time and the motion becomes diffusive.

Therefore, the PRW in the persistent regime shows a transition from superdiffusive to diffusive motion, which classifies as a possible model to describe not only active, persistent motion but also efficient search strategies, as superdiffusive motion is usually considered an efficient way of exploring space.

We will use the PRW model throughout the next chapters in order to study different aspects of active motion. For this purpose, we briefly introduce the extensions of the model to discrete and continuous two-dimensional space.

3.4.1   *Persistent random walk on a two-dimensional lattice*

On a two-dimensional lattice, i. e. $\Omega = \mathbb{Z}^2$, the persistency parameter p again gives the probability to preserve the hopping direction. However, additionally to the probability to reverse the hopping direction, which we denote by p_b here, we introduce two turning probabilities p_l and p_r, which define the probabilities to step to the left and right, respectively, with respect to the direction of motion. Obviously, they need to satisfy the condition $p + p_b + p_l + p_r = 1$. Analogously to the one-dimensional case we obtain four possible scenarios depending on the direction of motion, as shown in Figure 3.4.

If all four directions are equally probable, i. e. $p = p_b = p_l = p_r = 1/4$, the two-dimensional discrete PRW describes diffusion.
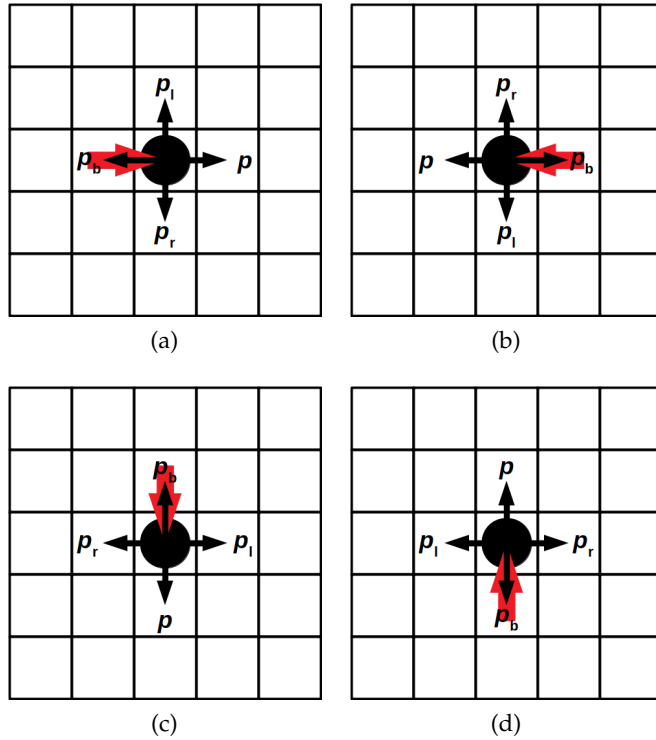

Figure 3.4: During the two-dimensional discrete PRW the walker can step on a lattice site either by arriving from the left (a), the right (b), the upper (c) or the lower site (d). The hopping probabilities for the next step depend on the arrival direction. Red arrows indicate the arrival direction, black arrows indicate the possible sites in the next step with the given probability.

Here, the analytical derivation of the mean displacement and the MSD is more lengthy than in the one-dimensional case. From the results for the one-dimensional case, however, we can assume that the

mean displacement is zero and that there is a superdiffusive motion regime. For our purposes this is sufficient and we do not need to derive the explicit forms.

We return to PRWs on two-dimensional lattices when the search efficiency of persistent walkers on lattices is discussed later.

3.4.2 *Persistent random walk in two-dimensional continuous space*

In two-dimensional continuous space, i.e. $\Omega = \mathbb{R}^2$, instead of hopping probabilities, we deal with a continuous turning angle distribution in order to determine the direction of movement. Additionally, the step-length can be chosen from a step-length distribution.
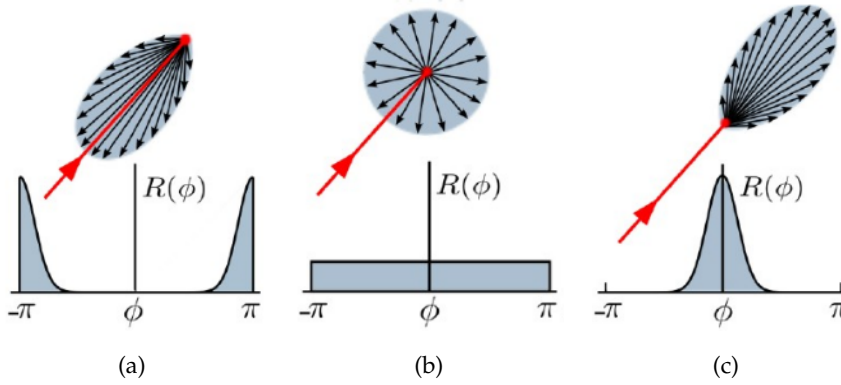

Figure 3.5: Exemplary turning angle distributions and directions of movement in the context of the two-dimensional continuous PRW for anti-persistent (a), diffusive (b) and persistent motion (c). Red arrows indicate the arrival direction, black arrows indicate possible directions in the next step, with length being proportional to the probability [42].

We consider the turning angle distribution $R(\phi)$ and define the mean cosine c and mean sine s of the turning angle as

$$c = \mathbf{E}\left[\cos\phi\right] = \int_{-\pi}^{\pi} \cos\left(\phi\right) R(\phi)\,\mathrm{d}\phi,$$

$$s = \mathbf{E}\left[\sin\phi\right] = \int_{-\pi}^{\pi} \sin\left(\phi\right) R(\phi)\,\mathrm{d}\phi.$$

These quantities hold information about the persistency of the active particle. The mean sine measures the relative probability of clockwise and anticlockwise turns. For most applications, however, the turning angle distributions are symmetric and, hence, the mean turning angle ϕ_{mean} as well as the mean sine s are zero. In this case, we can use the mean cosine c, which measures the correlation or persistency, to define a persistency parameter $p \equiv c$. Note that, in contrast to the

discrete PRW, $p \in [-1, 1]$ can be negative and depending on its value, the motion is either anti-persistent (when $-1 \leqslant p < 0$), diffusive ($p = 0$), or persistent ($0 < p \leqslant 1$). Figure 3.5 shows example distributions for each regime.

As a final remark, the PRW can be generalized to three dimensions as well. Although, the mathematical handling of a three-dimensional PRW can be complicated in general, if the walk is symmetric with respect to the arrival direction, the dynamics can still be described via a single persistency parameter [41].

4

RANDOM SEARCH STRATEGIES

The term *search problem* has been mentioned several times throughout the preceding chapters, but what does it actually describe? A very simple and intuitive form requires a searcher – such as a human, an animal, an organism, or any kind of particle or abstract object, which is able to move and explore the search realm – and at least one target.

Even though this seems to be a very basic problem to which most likely everyone can relate ("Where are those keys again!") it occurs in many fields, at all scales, and can take very complex forms. Examples range from the hunt for hostile submarines during World War II, castaway rescue operations, the recovery of an atomic bomb in the Mediterranean Sea near Palomares in 1966, and the rescue of the lost nuclear submarine Scorpion near the Azores in 1968, over animals searching for food, mates, or shelter and microorganisms (see Chapter 2), to chemical reactions and genomic transcription [4].

Despite the diversity of all these different search problems they have one more thing in common: the *search time* – the time it takes the searcher to find the target – is a limiting factor. The consequences of long search times depend on the situation and are as diverse as the search problems themselves. They can range from just being annoying, as in the case of being late due to the search for keys, to being crucial in living or dying, if e. g. the search burns more energy than the target food can provide, which will eventually lead to starvation and end in death. Therefore, the minimization of the search time is an essential and non-trivial task in most cases.

4.1 CLASSIFICATION OF SEARCH STRATEGIES

Naturally, evolution has yielded many different *search strategies* as efficient species were able to surpass their rivals and thus evade extinction. Also there is abundant scientific and academic interest in search strategies, which has led to the categorization of search strategies into *systematic* versus *random* search.

Systematic search requires the searcher to be able to keep at least a short memory of its past explorations in the search domain. Humans, for instance, are able to draw a (mental) map of the surrounding space and thus perform highly systematic searches (see Figure 4.1). On the other hand, a searcher with very low or no spatial memory at all has no choice but to follow a random trajectory.

In the latter case, the random walk theory introduced in Chapter 3 provides powerful tools for the modeling and analysis of such search processes.
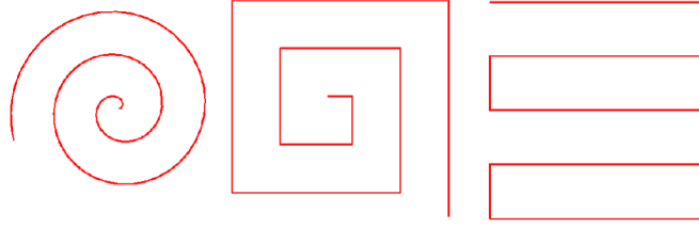

Figure 4.1: Examples of patterns for systematic exploration of space – from left to right: spiral, expanding square, lawn-mower [4].

Additionally, one can distinguish between search with or without cues. Although the target is usually hidden, in practical cases there are often cues in the environment that provide the searcher with information of the whereabouts. Such information can be provided by e. g. odor, sounds, and chemical concentrations or gradients. In this work, we focus on random search problems with and without cues.

4.2 FIRST-PASSAGE PROPERTIES

The search time is a limiting quantity in random search problems and thus it is essential to use search strategies which minimize it. In this work, we quantitatively measure and compare the efficiency of different strategies based solely on their search time, even though there are other measures available such as e. g. energy expenditure or risk factors. For this purpose, the *first-passage* theory provides adequate tools.

In first-passage problems we are not interested in how trajectories look like but rather when a specific point is reached for the first time.

Especially in the context of random walks there is a vast literature available on first-passage phenomena. There, the fundamental issue is to determine the time dependence of the *first-passage probability* $\mathcal{F}(\mathbf{x}, t)$. This is the probability that at time t a random walk hits $\mathbf{x}$ for the very first time. Note that we are *not* concerned with explicit forms of trajectories of walks.

Another fundamental and related issue is to evaluate the *first-passage time* τ. This is the time it takes the random walker to reach a specified location $\mathbf{x}_{\text{tar}}$ for the first time. Or in a more precise way: given a fixed starting location $\mathbf{x_0}$, how long does it take for the walker to reach the specified location $\mathbf{x}_{\text{tar}}$ for the first time *on average*. This quantity is called the *mean first-passage time* (MFPT). Consequently, the MFPT $\langle \tau \rangle$ corresponds to the average search time in an ensemble of similar problems with the same initial and boundary conditions.

Prior to the question of the mean time required to reach a certain target destination, however, we can also ask for the *hitting probability* (sometimes *exit probability*). That is the probability of hitting $\mathbf{x}_{\text{tar}}$

given enough time ($t \to \infty$). In particular one can show that under certain conditions the hitting probability can be zero, meaning that the walker will never reach its target and thus making the question for the MFPT trivially irrelevant.

As a last remark, before moving onto actual first-passage problems, we want to emphasize that first-passage phenomena are not limited to spatial problems, although the text and the terminology around search problems may lead to a different perception. The vector $\mathbf{x}_{tar}$ may represent not only locations but any abstract object or value for which it is interesting to know when it reaches a certain threshold for the first time. Some practical examples are the value of stocks or market prices, the firing of neurons in the brain [1], and the evolution of the number of individuals in a population.

In the following, we will start with a basic and simple first-passage problem to get acquainted with first-passage properties. Afterwards, we will introduce a few general approaches that are applicable to more complex problems.

4.2.1 *An intuitive approach to first-passage properties*

To get started with first-passage properties, we will introduce a very simple first-passage problem for which we will derive the hitting probability and the MFPT in a straightforward and intuitive way.

Let us consider the SRW on a one-dimensional lattice as introduced in Section 3.2. Starting from the origin $n = 0$ at time $m = 0$, we are interested in the probability of reaching site $n = 2$ before $n = -2$. In order to answer this question, it is convenient to calculate the probability for any starting position $n_0 \in [-2, 2] \subset \mathbb{Z}$ in a set of coupled equations. Of course, the desired probability would be 1 (0) if $2 < n_0$ ($n_0 < -2$). We introduce the hitting probability q_i for $i \in [-2, 2] \subset \mathbb{Z}$ as follows:

$$q_i \quad \equiv \quad \text{probability of visiting site } n = 2 \text{ before } n = -2 \text{ starting}$$
$$\text{from } n_0 = i.$$

With this, one can write the set of coupled equations by shifting the problem of obtaining the probability q_i to the problem of obtaining the probabilities of the neighboring sites q_{i-1} and q_{i+1} for all inner

sites $i \in \{-1, 0, 1\}$. Together with the boundary conditions $q_{-2} = 0$ and $q_2 = 1$ one can then easily derive the solution:

$$
\left\{
\begin{array}{l}
q_{-2} = 0 \\[4pt]
q_{-1} = \dfrac{1}{2} q_{-2} + \dfrac{1}{2} q_0 \\[4pt]
q_0 = \dfrac{1}{2} q_{-1} + \dfrac{1}{2} q_1 \\[4pt]
q_1 = \dfrac{1}{2} q_0 + \dfrac{1}{2} q_2 \\[4pt]
q_2 = 1
\end{array}
\right\}
\xrightarrow[\text{equations}]{\text{solve}}
\left\{
\begin{array}{l}
q_{-2} = 0 \\[4pt]
q_{-1} = \dfrac{1}{4} \\[4pt]
q_0 = \dfrac{1}{2} \\[4pt]
q_1 = \dfrac{3}{4} \\[4pt]
q_2 = 1
\end{array}
\right\}.
$$

Analogously, one can derive the MFPTs – which on the lattice are equivalent to the number of steps – for the different starting positions by introducing

$$\langle \tau \rangle_i \quad \equiv \quad \text{MFPT for visiting site } n = 2 \text{ starting from } n_0 = i,$$

and assuming that the left boundary at $n = -2$ is reflective. Then one finds:

$$
\left\{
\begin{array}{l}
\langle \tau \rangle_{-2} = \langle \tau \rangle_{-1} + 1 \\[4pt]
\langle \tau \rangle_{-1} = \dfrac{1}{2} \langle \tau \rangle_{-2} + \dfrac{1}{2} \langle \tau \rangle_0 + 1 \\[4pt]
\langle \tau \rangle_0 = \dfrac{1}{2} \langle \tau \rangle_{-1} + \dfrac{1}{2} \langle \tau \rangle_1 + 1 \\[4pt]
\langle \tau \rangle_1 = \dfrac{1}{2} \langle \tau \rangle_0 + \dfrac{1}{2} \langle \tau \rangle_2 + 1 \\[4pt]
\langle \tau \rangle_2 = 0
\end{array}
\right\}
\xrightarrow[\text{equations}]{\text{solve}}
\left\{
\begin{array}{l}
\langle \tau \rangle_{-2} = 16 \\[4pt]
\langle \tau \rangle_{-1} = 15 \\[4pt]
\langle \tau \rangle_0 = 12 \\[4pt]
\langle \tau \rangle_1 = 7 \\[4pt]
\langle \tau \rangle_2 = 0
\end{array}
\right\}.
$$

As one can see, in this example the derivation of the hitting probability as well as the MFPT is very easy. However, in most situations this intuitive approach is not useful and therefore a general framework is needed.

4.2.2 *Electrostatics approach*

Although the approach in Section 4.2.1 was used for an easy and very specific problem, the generalization of this problem already leads to an interesting analogy to electrostatics, which then again yields some interesting results. Therefore, we want to be more general here and set $\Omega \subseteq \mathbb{R}^d$, i.e. we deal with a d-dimensional continuous random walk. Note that the derivations in this section partly follow the derivations presented in the book "*A Kinetic View of Statistical Physics*" [27].

4.2.2.1 *Hitting probability*

In analogy to 4.2.1 we divide the boundary $\partial \Omega$ into two disjoint subsets $\partial \Omega_1$ and $\partial \Omega_2$. This means, $\partial \Omega_1 \cup \partial \Omega_2 = \partial \Omega$ and $\partial \Omega_1 \cap \partial \Omega_2 = \emptyset$. We can then ask for the hitting probability $q(\mathbf{x})$, $\mathbf{x} \in \Omega$, i.e. that the

random walker hits $\partial\Omega_1$ before $\partial\Omega_2$ starting from $\mathbf{x}$. Even though one could have more complex boundaries, this is sufficient for our purposes.

However, firstly we go back to the one-dimensional discrete and finite case as in 4.2.1 and set $\Omega \subset \mathbb{N}$, $\Omega = (0, N)$. Then, it is $\partial\Omega_1 = \{N\}$, $\partial\Omega_2 = \{0\}$, and $q(\mathbf{x}) = q(x) \equiv q_n$. We can then define the boundary value problem as

$$q_n = \begin{cases} \frac{1}{2}(q_{n-1} + q_{n+1}), & \text{if } n \in \Omega, \\ 1, & \text{if } n \in \partial\Omega_1, \\ 0, & \text{if } n \in \partial\Omega_2. \end{cases}$$

The term boundary value problem is explicitly used here as this problem corresponds to the discrete *Laplace* equation. We know that the solution for this type of equation must be of the linear form $A + Bn$ and invoking the boundary conditions yields

$$q_n = \frac{n}{N}.$$

We can check that this result is in agreement with our findings in Section 4.2.1. However, so far we only generalized the problem of the simple type in 4.2.1. Yet, the observation that this problem is based on solving the Laplace equation leads to the following approach.

We consider the d-dimensional discrete random walk with the above definitions. Taking the continuum limit, the hitting probability then satisfies the Laplace equation

$$\triangle q(\mathbf{x}) = 0, \quad \forall \mathbf{x} \in \Omega,$$

and together with the boundary conditions we can define the boundary value problem

$$\begin{cases} \triangle q(\mathbf{x}) = 0, & \forall \mathbf{x} \in \Omega, \\ q(\mathbf{x}) = 1, & \forall \mathbf{x} \in \partial\Omega_1, \\ q(\mathbf{x}) = 0, & \forall \mathbf{x} \in \partial\Omega_2, \end{cases} \tag{4.1}$$

which is equivalent to the boundary value problem for the electrostatic potential. Therefore, all known results from electrostatics can be used to deduce results for the hitting probability $q(\mathbf{x})$ in arbitrary domains Ω.

As an example, consider a random walker in $\mathbb{R}^d$ (see Figure 4.2) at a distance $x = \|\mathbf{x}\|_2$ from the origin, with $\|\cdots\|_2$ denoting the *Euclidean* norm in $\mathbb{R}^d$. The walker is located between two hyperspheres of radius $R < x \ll R_\infty$, i.e. the domain $\Omega = [\mathbb{R}^d - \mathcal{B}_R^d(0)] \cap \mathcal{B}_{R_\infty}^d(0)$, where $\mathcal{B}_R^d(\mathbf{x_0})$ is the d-dimensional hypersphere with radius $R \in \mathbb{R}$
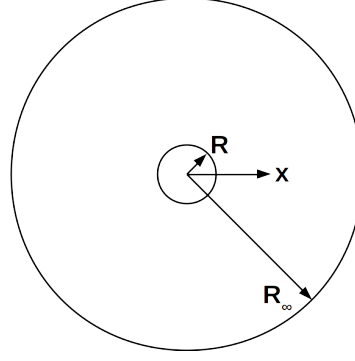
Figure 4.2: Schematic sketch of the relation between the radii of the d-dimensional hyperspheres.

and center $\mathbf{x_0} \in \mathbb{R}^d$, i.e. $\mathcal{B}_R^d(\mathbf{x_0}) = \{\mathbf{r} \in \mathbb{R}^d; \|\mathbf{r} - \mathbf{x_0}\|_2 \leqslant R\}$. Then it reads $\partial\Omega_1 = \partial\mathcal{B}_R^d(0)$ and $\partial\Omega_2 = \partial\mathcal{B}_{R_\infty}^d(0)$.

For the outer sphere the index suggests that we want to take the limit $R_\infty \to \infty$ later on. Therefore, the interesting question is: what is the probability that the walker hits the inner sphere before it hits the outer sphere, namely vanishes into space. To answer this, we have to solve Equation 4.1 and from electrostatics we know that the result depends heavily on the dimension d:

$d = 1$: This corresponds to the case that we have already considered. The solution is of the form $q(x) = A + Bx$. Since $q(x)$ is a probability and we take the limit $R_\infty \to \infty$, B needs to be zero in order to keep $q(x) \in [0, 1]$ as $x \to \infty$. The boundary condition on $\partial\Omega_1$ then leads to the trivial hitting probability $q(x) = 1$ which is in contradiction to the boundary condition on $\partial\Omega_2$, however, since we take the limit $R_\infty \to \infty$ the second boundary condition becomes obsolete, i.e. $\partial\Omega_2 = \emptyset$ and $\Omega = \mathbb{R} - \mathcal{B}_R^1(0)$. Let's interpret this result: the walker is moving on a one-dimensional continuous line with a boundary in one direction. The probability of eventually hitting this boundary during its walk is equal to one, no matter how far away the walker starts. Also, as a direct consequence, the walker hits the boundary infinitely often. Random walks with this property are called *recurrent*.

$d = 2$: We find the solution in the theory of electrostatics again, which yields $q(\mathbf{x}) = q(x) = A + B \ln(x/R)$. With analogous reasoning as in the one-dimensional case we obtain $B = 0$ and $A = 1$. Therefore, the 2-dimensional random walk is recurrent as well.

$d \geqslant 3$: The solution is $q(\mathbf{x}) = q(x) = A + Bx^{d-2}$. Here, the limit of $x \to \infty$ does not lead to divergence. By using the boundary conditions we obtain

$$q(x) = \frac{(R/x)^{d-2} - (R/R_\infty)^{d-2}}{1 - (R/R_\infty)^{d-2}} \tag{4.2}$$

and by taking the limit

$$\lim_{R_\infty \to \infty} q(x) = \left(\frac{R}{x}\right)^{d-2} \qquad (4.3)$$

we obtain a formula which is equivalent to the Coulomb formula. We explicitly assumed a very specific shape for the hypersurface $\partial\Omega_2$, however one can heuristically explain that this result is independent of the shape of $\partial\Omega_2$ as long as the infimum of the distance of $\partial\Omega_2$ to the location of the walker (and thus to the inner sphere) is large, i.e. the surface $\partial\Omega_2$ is far away from everything. By setting $R_\infty \equiv \inf_{\mathbf{r} \in \partial\Omega_2} \|\mathbf{x} - \mathbf{r}\|_2 \gg x$, one can always find a hypersphere "within" $\partial\Omega_2$ for which one can derive Equation 4.2. Since $R \leqslant x \ll R_\infty$ the terms $(R/R_\infty)^{d-2}$ become negligibly small for far away outer surfaces. Although we do not give an exact mathematical proof at this point, the essence is that for $d \geqslant 3$ the hitting probability is given by the Coulomb formula 4.3 and therefore, hitting the inner sphere is not given with certainty as it was the case in lower dimensions. Such walks with nonzero probability to not hit every $\mathbf{x} \in \Omega$ are called *transient*.

The electrostatic approach helped us to derive the interesting property that random walks are recurrent for $d \leqslant 2$ and transient for higher dimensions. Since we are only interested in the MFPT, however, we hold the hitting probability in abeyance from here on and only concentrate on the MFPTs.

4.2.2.2 *First-passage time*

Again we consider a domain $\Omega \subseteq \mathbb{R}^d$ and we are interested in the average time $\langle\tau\rangle \in \mathbb{R}_0^+$ it takes the walker to reach a certain subset $U \subset \overline{\Omega}$ for the first time. Here, we want to constrain ourselves to $U = \partial\Omega$, i.e. we are interested in the time it takes the walker to hit the boundary of the domain Ω.

As a first step, again we simplify and consider the one-dimensional symmetric random walk in continuous space and time with diffusion coefficient D. We set $\Omega = \mathbb{R}^+$, $\partial\Omega = \{0\}$ and the starting position of the walker $x(t = 0) = x_0 \in \Omega$. From Section 4.2.2.1 we know that this walk is recurrent and will eventually visit the origin. To find $\langle\tau\rangle$ we need to take the average

$$\langle\tau\rangle \equiv \langle\tau(x_0)\rangle = \int_0^\infty \tau \mathcal{F}(0,\tau \,|\, x_0) \, d\tau, \qquad (4.4)$$

thus, we need to know the first-passage probability $\mathcal{F}(0,\tau \,|\, x_0)$ which is the probability density of hitting the origin at time τ under the

condition that the walk starts from x_0. In order to find $\mathcal{F}(0, \tau | x_0)$, we use another method from electrostatics. We first need to solve the diffusion equation 3.1 for the probability density $\mathcal{P}(x, t | x_0)$, which is the probability that the walker started from x_0, is at x at time t and has not yet reached the origin. Therefore, we use the image method and place another walker at $x = -x_0$ so that we have the initial and boundary value problem

$$
\begin{cases}
\dfrac{\partial \mathcal{P}(x, t | x_0)}{\partial t} = D \dfrac{\partial^2 \mathcal{P}(x, t | x_0)}{\partial x^2} & \text{if } x \in \Omega \\
\mathcal{P}(x, t | x_0) = 0 & \text{if } x = 0 \\
\mathcal{P}(x, t | x_0) = \delta(x - x_0) + \delta(x + x_0) & \text{if } t = 0.
\end{cases}
$$

The linearity of the diffusion equation allows us to quickly derive the solution with the aid of Equation 3.2

$$
\mathcal{P}(x, t | x_0) = \frac{1}{\sqrt{4\pi D t}} \left[e^{-(x - x_0)^2 / 4 D t} - e^{-(x + x_0)^2 / 4 D t} \right].
$$

Then the first-passage probability $\mathcal{F}(0, \tau | x_0)$ is the flux through the origin in the time interval $(\tau, \tau + d\tau)$, thus

$$
\mathcal{F}(0, \tau | x_0) = D \left. \frac{\partial \mathcal{P}}{\partial x} \right|_{x=0} = \frac{x_0}{\sqrt{4\pi D \tau^3}} e^{-x_0^2 / 4 D \tau}
$$

and we see that Equation 4.4 does not converge, i.e. $\langle \tau \rangle$ is infinite $\forall x_0 \in \Omega$. This means that the one-dimensional random walk in fact is recurrent and visits every $x \in \Omega$ infinitely often, however, the average time it takes to (re-)visit some x is infinite.

Again we can derive a more general solution approach from these findings. We consider a continuous d-dimensional random walk in a finite domain $\Omega \subset \mathbb{R}^d$. Then we have the initial and boundary problem

$$
\begin{cases}
\dfrac{\partial \mathcal{P}(\mathbf{x}, t | \mathbf{x_o})}{\partial t} = D \triangle \mathcal{P}(\mathbf{x}, t | \mathbf{x_o}) & \text{if } \mathbf{x} \in \Omega \\
\mathcal{P}(\mathbf{x}, t | \mathbf{x_o}) = 0 & \text{if } \mathbf{x} \in \partial\Omega \\
\mathcal{P}(\mathbf{x}, t | \mathbf{x_o}) = \delta(\mathbf{x} - \mathbf{x_o}) & \text{if } t = 0.
\end{cases}
$$

We then need to follow the same steps as in the one-dimensional case. First we need to solve the integral

$$
\mathcal{F}(\mathbf{x} \in \partial\Omega, \tau | \mathbf{x_o}) = -D \int_{\partial\Omega} \nabla \mathcal{P}(\mathbf{x}, \tau | \mathbf{x_o}) \, d\mathbf{S}
$$

and then we need to take the average

$$
\langle \tau \rangle = \int_0^\infty \tau \mathcal{F}(\mathbf{x} \in \partial\Omega, \tau | \mathbf{x_o}) \, d\tau.
$$

However, this procedure requires a decent amount of work and if we are only interested in the MFPT $\langle \tau \rangle$ we can take a more elegant approach which is analogous to the one in the intuitive approach in Section 4.2.1.

To follow this approach we consider the one-dimensional random walk in discrete space and continuous time, i.e. $\Omega = \mathbb{Z}$ and $\mathcal{T} = \mathbb{R}_0^+$. We can then phrase the change of $\tau(n)$ in an infinitesimal time interval dt as

$$\tau(n) = dt + \begin{cases} \tau(n) & \text{with probability } 1 - 2\,dt \\ \tau(n+1) & \text{with probability } dt \\ \tau(n+1) & \text{with probability } dt. \end{cases}$$

To find $\langle \tau \rangle$ we average to obtain

$$\langle \tau(n+1) \rangle - 2 \langle \tau(n) \rangle + \langle \tau(n-1) \rangle = -1.$$

Again we identify the discrete form of the second derivative, which we replace in the process of taking the continuum limit. Furthermore, for convenience, we introduce the diffusion coefficient $D = 1$ here to end with the equation

$$D \frac{d^2}{dx^2} \langle \tau(x) \rangle = -1.$$

We can generalize this result to higher dimensions

$$\triangle \langle \tau(\mathbf{x}) \rangle = -\frac{1}{D} \tag{4.5}$$

to find the *Poisson* equation, which again is well-known from electrostatics.

As another example we consider the d-dimensional continuous random walk within a hypersphere of radius R, i.e. $\Omega = \mathcal{B}_R^d(0)$ is a bounded domain. Because of symmetry, $\langle \tau(\mathbf{x}) \rangle = \langle \tau(x) \rangle$ only depends on the radial part $\|\mathbf{x}\|_2 = x$ and Equation 4.5 simplifies to

$$\frac{d^2}{dx^2} \langle \tau(x) \rangle + \frac{d-1}{x} \frac{d}{dx} \langle \tau(x) \rangle = -\frac{1}{D},$$

which essentially is an *Euler-Cauchy* equation and its solution can be obtained with the boundary condition $\langle \tau(x) \rangle = 0$, $\forall \mathbf{x} \in \partial\Omega$, as

$$\langle \tau(x) \rangle = \frac{R^2 - x^2}{2dD}.$$

If, however, we are also interested in the explicit form of the first-passage probability $\mathcal{F}$, but we do not want to know $\mathcal{P}$, then we can

avoid dealing with $\mathcal{P}$ and use the Laplace transformation in order to obtain an equation for the Laplace transform of $\mathcal{F}$, namely

$$\mathcal{F}(\mathbf{x} \in \partial\Omega, s \,|\, \mathbf{x_0}) = \int\limits_0^\infty e^{-s\tau} \mathcal{F}(\mathbf{x} \in \partial\Omega, \tau \,|\, \mathbf{x_0}) \, d\tau = \left\langle e^{-s\tau} \right\rangle.$$

We omit the derivation of the final equation, as we are usually only interested in the MFPT itself and, therefore, we only give the general result [27]:

$$s\mathcal{F}(\mathbf{x} \in \partial\Omega, s \,|\, \mathbf{x_0}) = D \triangle \mathcal{F}(\mathbf{x} \in \partial\Omega, s \,|\, \mathbf{x_0}). \tag{4.6}$$

4.2.3 *Further approaches*

We do not plan to go into the details of further possible approaches because in Section 4.2.2 we introduced the electrostatic approach in details as an example to show how the first-passage quantities of interest can be evaluated. For completeness, however, we want to name a few more approaches, namely the *absorbing boundary approach*, the *adjoint equation approach*, and the *renewal approach*. For further reading we also refer to the book "*Stochastic Processes in Physics and Chemistry*" [46].

4.3 SEARCH STRATEGIES BEYOND ORDINARY DIFFUSION PROCESSES

So far we have only looked at first-passage properties in the context of the SRW and thus ordinary diffusion dynamics. However, as we have emphasized many times before, motion in biological systems is rather active than purely random in most cases. Also, since we have talked about search strategies in Section 4.1 and diffusion is a highly inefficient strategy, in the following, we briefly introduce other types of dynamics which are more strategic. Furthermore, we want to outline other parameters of real systems which contribute to the complexity of search problems and need to be taken into consideration depending on the specific problem.

4.3.1 *Lévy walks*

The *Lévy* walk first arose in a purely mathematical context in the work of French mathematician Lévy (1937). Around half a century later, the Lévy-Walk was then associated with animal motion patterns for the first time. Since then there has been huge interest in Lévy walks and a lot of controversy. It was only recently, in September 2017, that leading researchers from life sciences, mathematicians and physicists met at a Company of Biologists' Workshop in order to discuss and resolve remaining questions around the origins and biological significance of Lévy walks with respect to motion patterns (for a detailed

summary we recommend [40]). One of the interesting conclusions were that "Lévy walks can emerge from optimal searching strategies rather than being an optimal searching strategy per se" and "Lévy walks are not some exotic form of movement pattern divorced from reality, but one that is entirely natural" [40].

So what characterizes a Lévy walk? First of all, the Lévy walk is an isotropic random walk, however, its step length distribution is heavy tailed, meaning that

$$P(l) \propto \frac{1}{l^{1+\mu}},$$

where $P(l)$ is the probability distribution of steps of length l and $\mu \in (0, 2) \subset \mathbb{R}$. This specific distribution leads to clusters of short steps, which are interrupted by longer steps in between (see Figure 4.3).
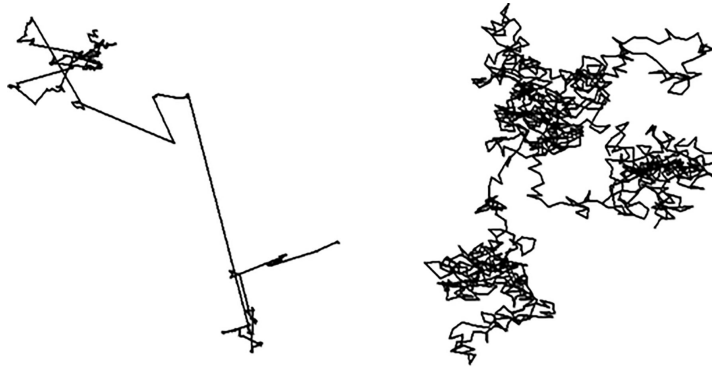
Figure 4.3: An example of a Lévy walk (left) and a Brownian walk (right). The Lévy walk is dominated by the longest steps, whereas the Brownian walk is dominated by the most common step [40].

The walk is scale invariant and forms fractal patterns. In this, one can also find the main idea and the original reasoning of why the Lévy walk has been associated with animal foraging behavior: after one territory has been explored for food, the animal then moves for a longer time in a random direction to find a new territory that has not been explored yet.

4.3.2 Intermittent search

The *intermittent search* is closely related to the saltatory motion of animals that we have mentioned in Section 2.1. The model includes two phases – characterized by the mean time spent in them – between which the searcher switches stochastically.

The first phase is the *scanning* phase, in which the searcher is able to detect the target in its immediate vicinity. During the scanning phase the searcher is considered to move slowly and thus it is modeled as a diffusive motion with diffusion coefficient D.

The second phase is the *motion* phase, in which the searcher moves rapidly and is unable to detect the target. This phase is usually modeled as ballistic motion with constant velocity V.
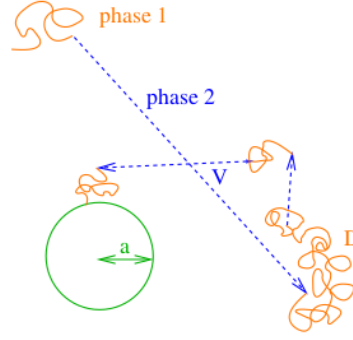

Figure 4.4: Abstract of the intermittent search model. The searcher stochastically switches between a scanning phase (orange) and a motion phase (blue). The target vicinity is depicted by the green circle [4].

The intermittent search serves as an alternative to the previously mentioned Lévy walk and can be advantageous under certain conditions [4].

4.3.3   *Sources of complexity in real systems*

The many different models for motion patterns or search strategies already give numerous parameters to consider, such as e.g. the step length or velocity distribution, the persistency, and the mean time spent in different phases. Besides that, in real systems there are many more parameters that influence the efficiency of a search strategy: the size of the search realm, the size of the target or equivalently the detection range of the searcher, information contained in the environment, obstacles in the environment, crowded environments, the number of targets and searchers, interactions between targets and/or searchers, and many more factors need to be considered when one aims to create an adequate model. With all these things in mind, we overview a minimal model in the next section, which leads to interesting results, although all additional complexity is omitted.

4.4   FIRST-PASSAGE TIMES OF PERSISTENT RANDOM WALKERS

Note: The unit length of the problem is defined by the step size, lattice grid size, or target size, which are all set to 1.

Let us consider a model based on the two-dimensional PRW on a lattice in discrete time introduced in Section 3.4.1 (see Figure 4.5). Specifically, we want to look at bounded cubic domains of dimension $\Omega = [0, X)^2 \subset \mathbb{N}^2$, where only one target site is located at $\mathbf{n}_{\text{tar}}$. Furthermore, we assume periodic boundary conditions and $X \gg 1$, i.e. the length of the lattice is much larger than the step size.
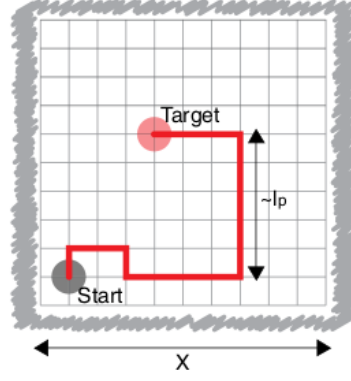
Figure 4.5: A persistent random walker on a cubic lattice, where one target site is located. The red line represents an example search trajectory [44].

This situation is suitable for both biologically meaningful situations of a single target centered in a finite domain, and of homogeneously distributed targets in an infinite domain with density $1/V$, where $V = X^2$ is the volume of the domain.

For simplicity, we set the turning probabilities $p_b = p_l = p_r \equiv q$, such that

$$q = \frac{1-p}{3},$$

i.e. all possibilities that change the direction of motion are equally probable. We can furthermore write the probability of having l consecutive steps in the same direction as

$$P(l) = (1-p)p^{l-1},$$

and we define the persistence length of the walk as

$$l_p = \langle l \rangle = \sum_{l=1}^{\infty} l P(l) = \frac{1}{1-p},$$

which we will use as a defining parameter.

Following [44], we want to analyze the dependence of the MFPT $\langle \overline{\tau} \rangle$ to the target site $\mathbf{n}_{tar}$ – averaged over all possible starting positions and velocities – on the persistence length l_p and the lattice size X.

Consider a random searcher starting from $\mathbf{n}$ with initial velocity $\mathbf{e}_i$, where $\{\mathbf{e}_1, \mathbf{e}_2\}$ defines a basis of the lattice. Similar to Section 4.2.1, we can write an exact backward equation for the MFPT $\langle \tau(\mathbf{n}, \mathbf{e}_i) \rangle$ to the target $\mathbf{n}_{tar}$:

$$\langle \tau(\mathbf{n}, \mathbf{e}_i) \rangle = p \langle \tau(\mathbf{n} + \mathbf{e}_i, \mathbf{e}_i) \rangle + q\{ \langle \tau(\mathbf{n} - \mathbf{e}_i, -\mathbf{e}_i) \rangle + \langle \tau(\mathbf{n} + \mathbf{e}_j, \mathbf{e}_j) \rangle \\ + \langle \tau(\mathbf{n} - \mathbf{e}_j, -\mathbf{e}_j) \rangle \} + 1, \tag{4.7}$$

where $j \neq i \in \{1, 2\}$. With the help of the Fourier transform,

$$\widetilde{f}(\mathbf{q}) = \sum_{\mathbf{n} \in \Omega} f(\mathbf{n}) \exp(-i\mathbf{q} \cdot \mathbf{n}),$$

of a function $f(\mathbf{n})$, where $q_i = 2\pi k_i/X$ with $k_i \in [0, X)$, Equation 4.7 can be solved explicitly. One can then average over all possible starting positions and velocities to obtain the final result [44]:

$$\langle \overline{\tau} \rangle = \frac{-\epsilon(X^2 - 1)}{1 - \epsilon} + \frac{1 + \epsilon^2}{1 - \epsilon^2} \sum_{\mathbf{q} \neq \mathbf{0}} \frac{1}{1 - h(\mathbf{q}, \epsilon)}, \qquad (4.8)$$

where we introduced $\epsilon = p - q$ and

$$h(\mathbf{q}, \epsilon) = \frac{(\epsilon - 1)^2}{2} \sum_{i=1}^{2} \frac{\cos(\mathbf{q} \cdot \mathbf{e}_i)}{1 + \epsilon^2 - 2\epsilon \cos(\mathbf{q} \cdot \mathbf{e}_i)}.$$

Equation 4.8 is an exact expression for the search time of a persistent random searcher in dependence on the parameter ϵ. We identify

$$l_p = \frac{1}{1 - p} = \frac{4}{3} \frac{1}{1 - \epsilon},$$

to emphasize that ϵ and the persistence length l_p can be considered equivalently. The result can be seen in Figure 4.6.
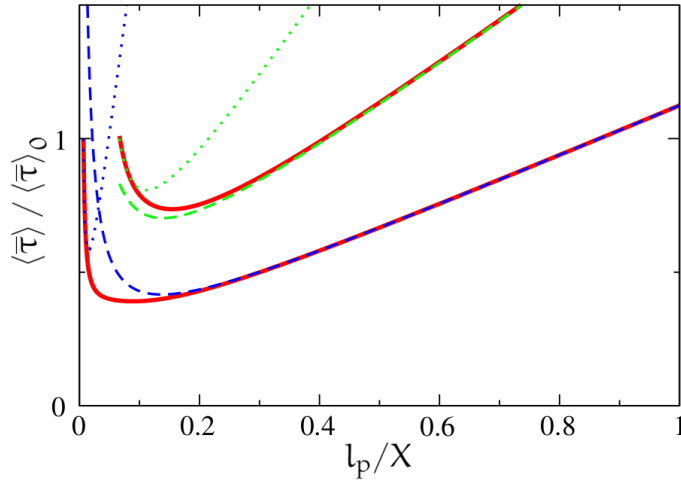

Figure 4.6: MFPT $\langle \overline{\tau} \rangle$ for a two-dimensional persistent random walker normalized by the MFPT $\langle \overline{\tau} \rangle_0$ for a diffusive random walker in dependence on the persistence length l_p normalized by the system size X, for $X = 10$ (upper set of curves) and $X = 100$ (lower set of curves) with exact results (red lines), approximation $\epsilon \ll 1$ (dotted lines) and $\epsilon \to 1$ (dashed lines) [44].

Let's take a look at two approximations made in [44]. In the first case $\epsilon \ll 1$ is small and therefore $l_p \approx 4/3$, i.e. the persistence length is comparable to the target size. For $\epsilon = 0$ we obtain a SRW as all directions become equally probable and we denote the search time of such a diffusive searcher by $\langle \overline{\tau} \rangle_0$. The MFPT in the regime $\epsilon \ll 1$ then reads [44]

$$\langle \overline{\tau} \rangle = A(\epsilon, V)(V - 1) + \frac{1}{D(\epsilon)} \langle \overline{\tau} \rangle_0, \qquad (4.9)$$

where $D(\epsilon) = \frac{1-\epsilon}{1+\epsilon}$ is the normalized diffusion coefficient of the persistent random walk and $A(\epsilon, V) = [B(V) - 1]\epsilon + \mathcal{O}[\epsilon^2]$ is a nontrivial additive correction to the search time of a diffusive walker with

$$B(V) = \frac{2}{V} \sum_{\mathbf{q} \neq 0} \frac{\frac{1}{2} \sum_{i=1}^{2} [1 - \cos(2\pi\mathbf{q} \cdot \mathbf{e}_i)]^2}{\left[\frac{1}{2} \sum_{i=1}^{2} 1 - \cos(2\pi\mathbf{q} \cdot \mathbf{e}_i) \right]^2}.$$

The approximation 4.9 is accurate for small persistence lengths l_p as can be seen in Figure 4.6.

In the opposite case of $\epsilon \to 1$ the persistence length $l_p \to \infty$ becomes large and diverges. In this regime the MFPT reads [44]

$$\langle \tau \rangle = \frac{2(X-1)}{1-\epsilon} + \frac{(X-1)^2}{2} + (1-\epsilon)\frac{(X-1)(X-2)(X+3)}{12} + \mathcal{O}[(1-\epsilon)^2],$$

which is accurate as long as $l_p \gg 1$ (see Figure 4.6). Obviously, the mean search time becomes infinitely large for $\epsilon = 1$. This can be understood as follows: the persistency is $p = (3\epsilon + 1)/4$ and therefore, for $\epsilon = 1$ the walker never changes its direction and gets stuck in infinitely long straight trajectories. As ϵ approaches 1 also the probability of getting trapped in such long unsuccessful ballistic excursions becomes larger and therefore the search time increases.
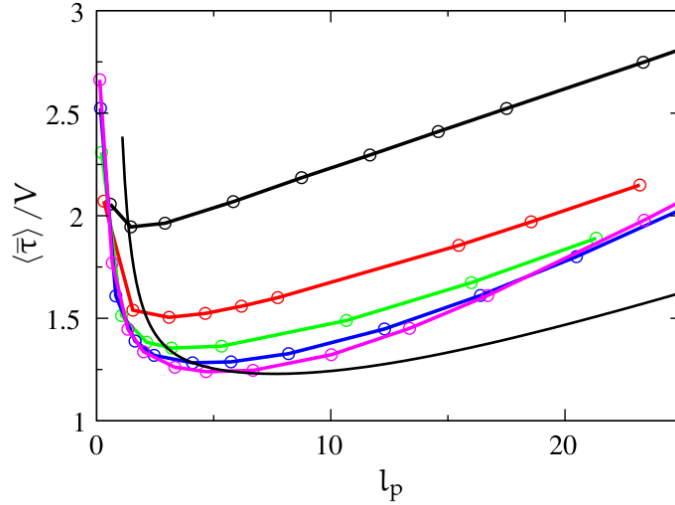

Figure 4.7: Numerical simulation of the MFPT for Lévy walks (lines with circles) and a persistent random walk (black line) on a two-dimensional lattice of size $X = 50$. The plots with circles belong to Lévy walks with the parameters (from top to bottom): $\mu = 1.2, 1.4, 1.6, 1.8,$ and 2 [44].

Nevertheless, the minimum of the MFPT $\langle \tau \rangle$ in dependence on the persistence length l_p can be found by analyzing the exact result from Equation 4.8 (see Figure 4.6). It appears that the persistence length needs to be of the same order of magnitude as the system size in order

to minimize the average search time [44]. For $l_p \ll X$, the search has diffusive properties and therefore is inefficient, whereas for $l_p \gg X$ the walker is likely to get trapped in long unsuccessful straight runs. Thus, one would expect the optimal persistence length to be in the regime $l_p \propto X$.

As a last point, we want to briefly compare the performance of the persistent random walk to the Lévy walk strategy as it has been presented in Section 4.3.1. From Figure 4.7 we see that the persistent random walk strategy leads to a minimum in the search time that is smaller than any minimum in the search times for the Lévy strategies. Only for the parameter $\mu = 2$ – for which the distribution of the lengths of ballistic excursions has a finite second moment and thus is no longer of the Lévy type – the Lévy walk can compete with the persistent random walk in the given scenario. Therefore, Tejedor, Voituriez, and Bénichou [44] conclude that the persistent random walk, as introduced above, performs better than any Lévy walk in the biologically relevant cases of either a single target or patterns of targets characterized by a peaked distribution of target to target distance.

SEARCH AND NAVIGATION IN THE PRESENCE OF LOCAL CUES

In all previous considerations of search problems we assumed the walker to be completely blind, i. e. the search is purely random. However, as we have mentioned before in Section 4.1, sometimes there are hints in the environment that contain valuable information of the whereabouts of the target. If the searcher is capable of perceiving and analyzing these hints, it can use the additional information in order to adapt its strategy and navigate more efficiently. Some examples include e. g. humans reading tracks or dogs sensing odors. However, the perceiving of hints during search is not restricted to more advanced life forms like humans and animals, but can also be observed in simpler organisms like bacteria and cells. In this chapter we will introduce hint-related navigation and search strategies of microorganisms, and we will present related current research.

5.1 DIRECTIONAL NAVIGATION (TAXIS)

Different organisms are able to detect or sense different types of hints or stimuli in their environment. In the case of *taxis*, the organism is able to gain information about the direction of the stimuli source from the hints in its environment. It then responds to a stimulus with directional movement, i. e. it moves towards or away from the source. If the stimulus induces movement towards the source, one speaks of positive taxis, whereas movement away from the source is denoted by negative taxis.

Taxis describes guided navigation as a response to a stimulus.

Taxes are generally categorized based on the type of stimulus which induces the response of the organism. A few examples are given in Table 5.1. In many cases, like e. g. chemotaxis and thermotaxis, the response movement occurs up (positive taxis) or down (negative taxis) a gradient.

5.1.1 *Chemotaxis*

Chemotaxis describes the taxis that is driven by chemical gradients. Many organisms are attracted or repelled by specific chemicals, as they are beneficial or harmful to them. In case of positive or negative chemotaxis, the inducing chemical is defined as *chemoattractant* or *chemorepellent*, respectively. A food source like e. g. glucose is an example for an attractant, whereas a poison like e. g. phenol is a repellent. Chemoattractants usually cause accumulation of organisms

Chemotaxis denotes the induced movement along the gradient of the concentration of a chemical.

TERM	STIMULUS	EXAMPLES OF RESPONSIVE SPECIES
Chemotaxis	Chemical	Bacteria, archaea, amoebae, white blood cells, sperm cells
Electrotaxis	Electrical field	Amoebae
Galvanotaxis	Electrical current	Bacteria, spermatozoa
Geotaxis or gravitaxis	Gravity	Bacteria, ciliates (*Paramecium*), flagellates
Magnetotaxis	Magnetic field	Bacteria
Phototaxis	Light	Bacteria, archaea, amoebae, flagellates
Thermotaxis	Temperature	Bacteria, ciliates, amoebae, nematodes, spermatozoa, trophoblastic cells, leukocytes

Table 5.1: Types of taxis with inducing stimuli and examples of responsive species (exert from [13]).

in locations with high concentrations, whereas chemorepellents lead to depletion in such regions. Note, however, that accumulation and depletion can also be caused by other mechanisms and therefore, they alone cannot be used as an indicator for chemotaxis.

Of course, chemotaxis helps the organism to reduce search times or to more efficiently avoid hazardous chemicals and therefore, in general, it is superior to a purely random movement pattern. Thus, organisms evolve chemotactic responses specific to the environmental conditions which they experience. In steady environments this is feasible, however, in many real environments the conditions fluctuate temporally and spatially. If such fluctuations occur too frequently, the organism is not able to adapt its chemotactic response in time. Therefore, it might be advantageous to omit any chemotaxis and change over to stochastic behavior. An alternative problem is that some environments have different states and a chemotactic response specific to one state might perform poorly in another. When the number of states is low, a specific response can be evolved and molecularly encoded in the organism for each individual state, while for many different states this is not possible. But which response does an organism then evolve in such situations?

This questions was addressed by Celani and Vergassola (2010) [8] for the chemotaxis of *Escherichia coli*. *E. coli* is known to perform a run-and-tumble like motion comparable to the intermittent search introduced in Section 4.3.2. In the presence of chemoattractants the duration of the run phases is modulated. Celani and Vergassola define the chemotactic response $K(t)$ at time t as the bias in the fraction

of time spent in the running vs. the tumbling phase after a pulse of chemoattractant. The switching rate then reads

$$\omega_{\text{run}\to\text{tumble}} = \frac{1}{\tau_{\text{run}}} \left[1 - \int_{-\infty}^{t} K(t-s)c(\mathbf{X}(s),s)\,ds \right],$$ (5.1)

where τ_{run} is the mean time spent in the running phase in the absence of any chemoattractant, $c(\mathbf{x},t)$ denotes the chemoattractant concentration field, and $\mathbf{X}(t)$ is the trajectory followed by the bacterium. Thus, $c(\mathbf{X}(s),s)$ is equivalent to the time history of chemoattractant encounters.

The interesting quantity, in order to compare different chemotactic responses $K(t)$, is the uptake of chemoattractant defined as

$$S = \int c(\mathbf{x},t)n(\mathbf{x},t)\,d\mathbf{x}\,dt,$$ (5.2)

where $n(\mathbf{x},t)$ is the probability density of the bacterium space-time coordinates, which depends on $K(t)$ in non-trivial ways (see [8] for further details). Note, that the term uptake does not necessarily mean that the chemical is metabolized, it is rather a quantity that measures the amount of chemical that is encountered by the bacterium along its trajectory. As we consider chemoattractants here, maximizing S by evolving a good response $K(t)$ is beneficial to the bacterium. Now instead of finding the best choice of $K(t)$ in dependence on the chemoattractant profile $c(\mathbf{x},t)$, i.e. a specific profile, which would be the analog to the evolution of a specific response in steady environments, Celani and Vergassola consider all possible chemoattractant profiles for a given $K(t)$. The goal of this strategy is to find the chemoattractant profile for which the given $K(t)$ performs the worst, i.e. has the minimum uptake, and iterate this step for all $K(t)$s of interest. Then, among all the responses $K(t)$, select the one with the largest minimum uptake. Celani and Vergassola call this response the *maximin* strategy, as it maximizes the uptake among all the worst-case responses.

The chemotactic responses $K(t)$ that are considered are of the form

$$K(t) = \lambda e^{-\lambda t}\left[\beta_1\lambda t + \beta_2(\lambda t)^2\right],$$ (5.3)

where λ controls the rescaling of the time variable, and β_1, β_2 specify the amplitude and the shape of $K(t)$. Furthermore, the parameter γ is introduced as

$$\gamma \propto \int_0^\infty K(t)\,dt,$$ (5.4)

in order to represent the bacterial response with a single variable.

The chemoattractant profiles $c(\mathbf{x}, t)$ that are considered are of parabolic form with a rapid exponential decay in time, i. e.

$$c(\mathbf{x}, t) \propto e^{-t/\tau_c}, \tag{5.5}$$

where τ_c is the degradation time. In the supporting material of [8] one can find explanations to why such profiles are sufficient. Because of the rapid decay in time, it is furthermore sufficient to only consider the local properties of the chemoattractant profile around the bacterial position. These local properties are also expressed by a single variable.

From the different bacterial responses and chemoattractant profiles Celani and Vergassola then derive a phase space for the uptake, which is shown in Figure 5.1.
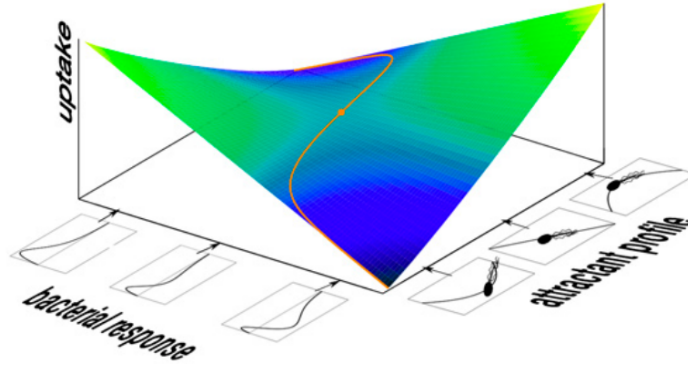
Figure 5.1: A schematic view for the phase space of the chemoattractant bacterial uptake S. The bacterial responses are represented by the parameter γ. Three exemplary response functions $K(t)$ with positive, zero, and negative γ are shown. Chemoattractant profiles $c(\mathbf{x}, t)$ are also represented by a single variable that condenses information about the local profile around the bacterial position. Responses with negative γ are advantageous in keeping the bacterium localized around a maximum of chemoattractant concentration and disadvantageous in escaping from a minimum. The opposite holds true for positive values of γ. Thus, extreme values of γ perform well under particular conditions and bad under others. The minimum uptake of chemoattractant for each bacterial response is indicated by the orange line; the orange circle marks the maximum among these minima (maximin strategy) [8].

What they find is that a chemotactic response $K(t)$ having a zero integral $\gamma = 0$ guarantees the highest minimal uptake of chemoattractants (maximin strategy), irrespectively of the chemoattractant profile. Furthermore, experimental data on the chemotactic response $K(t)$ of *E. coli* to aspartate is in good agreement with the theoretical prediction for $K(t)$ as shown in Figure 5.2.

But how can these results be explained? First of all, the zero integral filters out low-frequency (namely, constant) parts of $c(\mathbf{x}, t)$ and
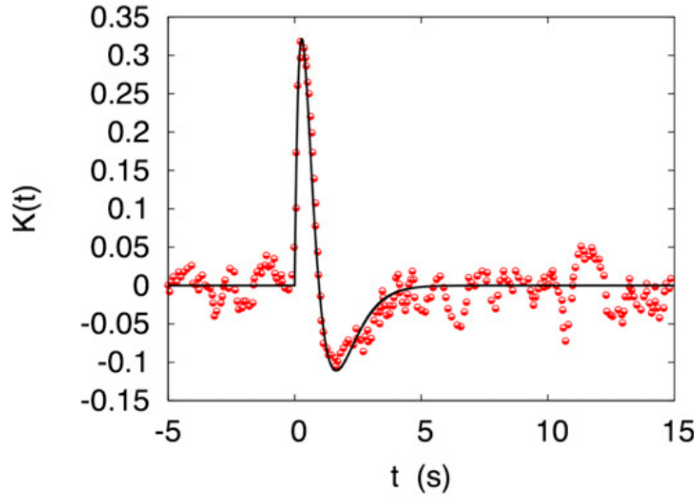
Figure 5.2: The experimental chemotactic response $K(t)$ of *E. coli* to aspartate (red circles). Bacteria are subject to a pulse of chemoattractant at $t = 0$. The positive and negative lobes of the response have approximately equal area, which corresponds to $\gamma = 0$. The solid black line is the theoretical prediction of the maximin strategy [8].

thus enables an efficient sensing of its gradient, independent of the background level. Additionally, we can understand the impact of the parameter γ if we consider its influence on the bacterial movement. Navigation with $\gamma < 0$ reduces the effective diffusivity, which is bad for escaping minima in the concentration profile, whereas positive $\gamma > 0$ increases diffusivity, which again is bad for staying around maxima. However, $\gamma \neq 0$ is not a bad chemotactic response per se as they outperform $\gamma = 0$ responses for specific chemoattractant profiles, i. e. we have a classical specialist vs. generalist trade-off situation, in which the generalist wins when performance is compared considering *all* chemoattractant profiles. Indeed, Celani and Vergassola find that the maximin response is the only one that outperforms motile nonchemotactic bacteria, i. e. $K(t) \equiv 0$, in all chemoattractant profiles.

This example shows that the choice of a chemotactic strategy heavily depends on the environmental conditions and justifies the use of chemotaxis as compared to random diffusion even in the case of rapidly changing environments. Nevertheless, changing environments among other factors can still be a reason to use a different strategy which will be introduced below.

5.2 NON-DIRECTIONAL NAVIGATION (KINESIS)

Similar to the case of taxis, in *kinesis* organisms are able to react to certain stimuli in the environment. However, the organism does not gain information about the direction of the stimuli source and thus is

not able to respond with directed movement. Instead, the organism responds with a change in activity, such as a change in e. g. velocity or persistency, which is dependent upon the stimulus intensity. As stimuli do not induce directed movement, there is no positive or negative kinesis as in the case of taxis.

Similarly to taxes, kinesis responses are also categorized based on the type of stimulus which induces the change of activity (see Table 5.1). In some organisms, such as sperm cells, taxis and kinesis may even occur in parallel.

5.2.1 *Chemokinesis*

Chemokinesis, similarly to chemotaxis, describes the kinesis which is driven by chemical concentrations. Rather than measuring gradients, here the organisms are only able to measure an absolute concentration. As most sources secrete chemicals in spherical symmetry, the concentration is directly connected to the distance to the source and thus, the organism is able to estimate how far away the source is located.

Chemokinesis is not as well researched and understood as its taxis counterpart and one might wonder why chemokinesis even exists, considering that chemotaxis is a superior strategy in finding the target. There are several confounding factors which limit the effectiveness of chemotaxis. As we have seen above, gradients can fluctuate strongly in natural environments and even though in such cases a chemotactic strategy still outperforms random diffusion, possibly a chemokinesis strategy performs even better. Furthermore, instead of fluctuating gradients one could have totally chaotic fields or very weak gradients, which appear constant to the sensing tools of the organism. Sometimes information is only sparse and therefore no gradient is available at all. In all of these scenarios the determination of the direction would fail, rendering chemotaxis useless. The chemotactic navigation is further influenced by external, internal and ligand-receptor binding noise [36]. Delayed responses, as schematically shown in Figure 5.3, can also lead to wrong navigation.

And last but not least, the sensing of gradients as compared to concentrations requires more advanced molecular abilities or memory, and therefore, it is not available to very simple organisms.

5.2.2 *Durokinesis*

Another example of kinesis is *durokinesis*, which describes rigidity driven kinesis. This means that the organism changes its activity according to the stiffness of the substrate it is moving on.

Most cells, for example, feature migration up a rigidity gradient [34]. This feature had been referred to as durotaxis, as the migra-
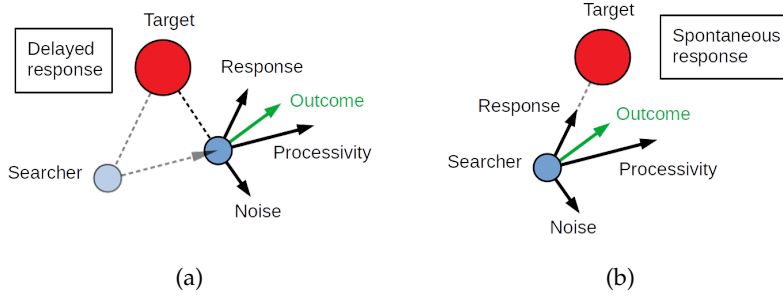
Figure 5.3: Schematic comparison of a delayed response (a) and a spontaneous response (b) in chemotactic navigation in the presence of other sources of error. Here, the delayed response leads to an inefficient navigation, i.e. the distance to the target may be even increased.

tion happens along a gradient and therefore seems to be comparable to chemotaxis. As we have outlined earlier, chemotaxis obviously is beneficial to organisms, however the advantage of durotaxis is questionable or at least less obvious. Therefore, Novikova et al. (2017) [34] took a closer look at this phenomenon in order to figure out whether it is a matter of taxis or not. Additionally, it was observed that the persistency of cellular motion itself changes with the rigidity of the substrate. Especially this observation gave rise to the question whether the overall motion along the gradient can be the consequence of a locally changing persistency alone. In this case, cells would not gain any directional information from the gradient, such as in taxis navigation, but they would only change their activity, i.e. their persistency, according to local information. Nonetheless, this would mean that the outcome of durokinesis and taxis strategies is similar, namely migration in response to a gradient.

In their simulation setup, Novikova et al. consider two-dimensional substrates with different constant and linear rigidity profiles along one dimension (x-axis). The rigidity is directly connected to the persistency, which is controlled by the persistence time τ_p, a quantity occurring in the MSD of a PRW

$$\left\langle |\mathbf{x}^2| \right\rangle (t) = 2v_c^2 \tau_p^2 \left(\frac{t}{\tau_p} + e^{-t/\tau_p} - 1 \right),$$

where v_c denotes the cell migration speed [34]. Figure 5.4 shows the influence of soft and stiff substrates and hence different persistence on cell migration. As one can see, the covered area is much larger in the case of higher persistency.

However, the effect of rigidity gradients is more interesting. Therefore, they introduce a gradient region that occupies a part of the substrate and is flanked by uniformly rigid regions. Within the gradient region, the persistence time increases linearly from $0.2\,h$ to $12\,h$ over
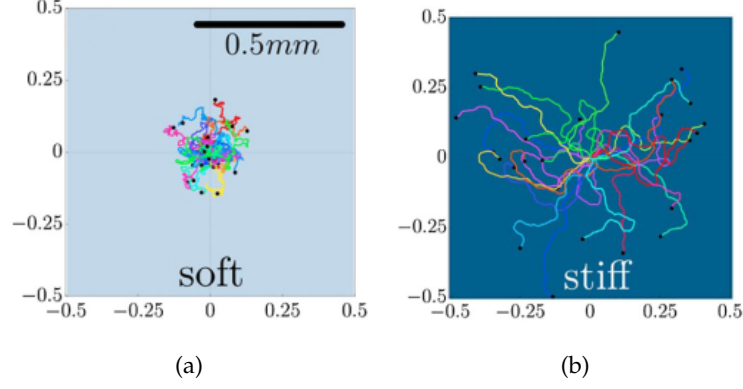
(a)   (b)

Figure 5.4: Simulated cell migration at different values of persistency, for constant low persistence time $\tau_p = 0.2\,h$ (a) and constant high persistence time $\tau_p = 2\,h$ (b). In both cases 25 cell trajectories have been recorded over a total time of 12 h. Trajectories start at the origin and end at the black dots [34].

the whole range and remains constant outside. By changing the width of the gradient region they realize different gradient steepnesses. The result for one of these realizations is shown in Figure 5.5a. One can see that migration happens preferentially in the direction of increasing stiffness, just as it would be the case in durotaxis, however, by the simulation setup, the cells do not sense the gradient at all, they only change their persistency according to local information, i. e. the local stiffness. Furthermore, with increasing steepness of the gradient, the average displacement in gradient direction increases as well (Figure 5.5b). Therefore, the rigidity-dependent persistency can indeed explain the migration along the gradient.

Nevertheless, both a purely durokinetic and a durotactic navigation feature migration along a rigidity gradient. So how can one distinguish between both? Novikova et al. propose to consider the durotactic (vector) index, which is defined as

$$\mathbf{DI}(t) = \begin{pmatrix} \mathrm{DI}_x(t) \\ \mathrm{DI}_y(t) \end{pmatrix} \equiv \frac{\langle \mathbf{x} \rangle (t)}{v_c t},$$

where $\langle \mathbf{x} \rangle (t)$ is the average cell displacement. Here, $\mathrm{DI}_y(t) = 0$ as there is no bias or gradient in the y-direction and it is sufficient to consider $\mathrm{DI}_x(t)$, exclusively. They find, that the durotactic index $\mathrm{DI}_x(t)$ of the durokinetic random walk introduced here shows significantly different behavior compared to the durotactic index of a chemotaxis walk with run-and-tumble behavior. While the durotactic index only gradually increases to its plateau value v_d/v_c (v_d being the average velocity in gradient direction) for the durokinetic walk, it rapidly increases for the run-and-tumble walk. Thus, the analysis of the short-time behavior of the durotactic index provides an adequate way to
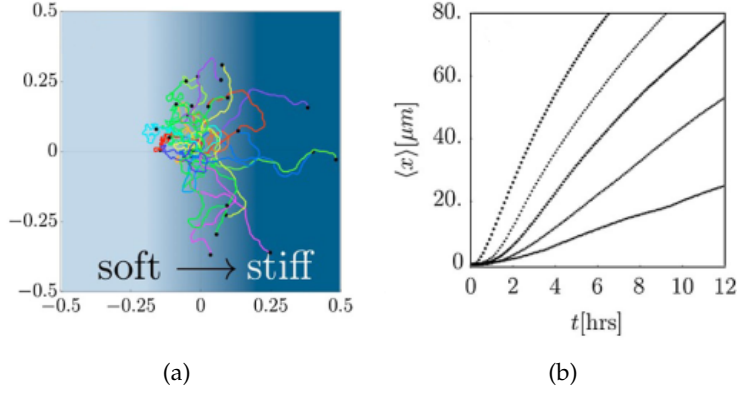
Figure 5.5: (a) Simulated cell migration for persistence time τ_p linearly increasing from $0.2\,\mathrm{h}$ to $12\,\mathrm{h}$ over the x-range $[-0.1, 0.1]\mathrm{mm}$ and (b) averaged x displacement for different gradient steepnesses (top to bottom: $\Delta\tau_p/\Delta x = 90\,\mathrm{h\,mm}^{-1}, 18\,\mathrm{h\,mm}^{-1}, 9\,\mathrm{h\,mm}^{-1}, 4.5\,\mathrm{h\,mm}^{-1}, 1.8\,\mathrm{h\,mm}^{-1}$) [34].

discriminate between the navigation discussed above and a "regular" taxis.

5.3 OUTLOOK AND FURTHER DIRECTIONS

In this last example, the work of Novikova et al. (2017) [34], the properties of a navigation purely based on a kinesis strategy resemble the migrational properties of navigation based on taxis strategies. Therefore, it seems promising to take a look at first-passage time properties of kinesis strategies as well.

In our work, we plan to study active motions with position-dependent activity, where the magnitude of the activity varies as a function of the distance to the target. The ultimate goal is to find the best functionality which optimizes the search time of such a random walker. Among other key parameters, the influence of particle velocity, boundary conditions, and target and system sizes on the search efficiency will be also adressed.

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