An overview of diffusion models for intracellular dynamics analysis

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Abstract

We present an overview of diffusion models commonly used for quantifying the dynamics of intracellular particles (e.g., biomolecules) inside living cells. It is established that inference on the modes of mobility of molecules is central in cell biology since it reflects interactions between structures and determines functions of biomolecules in the cell. In that context, Brownian motion is a key component in short distance transportation (e.g., connectivity for signal transduction). Another dynamical process that have been heavily studied in the past decade is the motor-mediated transport (e.g., dynein, kinesin, myosin) of molecules. Primarily supported by actin filament and microtubule network, it ensures spatial organization and temporal synchronization in the intracellular mechanisms and structures. Nevertheless, the complexity of internal structures and molecular processes in the living cell influence the molecular dynamics and prevent the systematic application of pure Brownian or directed motion modeling. On the one hand, cytoskeleton density will hinder the free displacement of the particle, a phenomenon called subdiffusion. On the other hand, the cytoskeleton elasticity combined with thermal bending can contribute a phenomenon called superdiffusion. This paper discusses the basics of diffusion modes observed in cells, by introducing the essential properties of these processes. Applications of diffusion models include protein trafficking and transport, and membrane diffusion.

Keywords: diffusion, Brownian motion, stochastic models, intracellular dynamics, microscopy.

Contents

1 Introduction **2**

2 Stochastic Processes, Brownian motion, and Diffusions **5**

2.1 Stochastic Process 6

2.2 Brownian Motion 7

2.3 Diffusion Process 8

2.4 Stochastic Differential Equation (SDE) 9

2.5 Fractional Brownian Motion 10

2.6 Summary 12

3 Diffusion for Modeling Intracellular Trajectories **12**

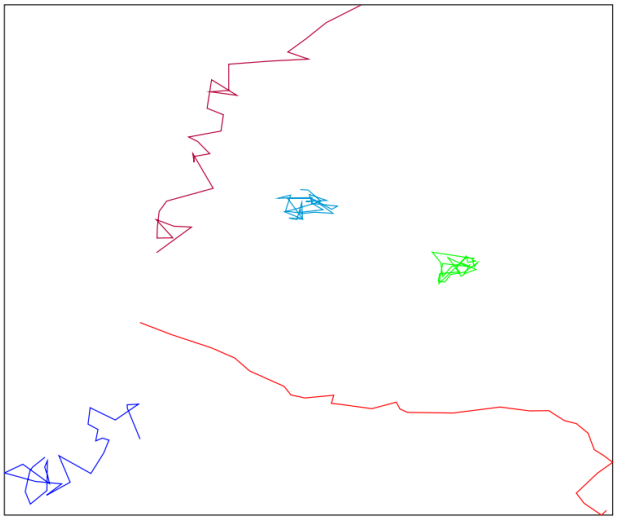

Figure 1: Representative trajectories from simulated data. The blue trajectory is Brownian; the purple trajectory is from a Brownian motion with drift (67) and illustrates superdiffusion; the red trajectory is from a fractional Brownian motion (22) (parameter $\mathfrak{h} > 1/2$) and illustrates superdiffusion; the cyan trajectory is from an Ornstein-Uhlenbeck process (62) and illustrates confined diffusion; the green trajectory is from a fractional Brownian motion (22) ($\mathfrak{h} < 1/2$) and illustrates anomalous diffusion.

3.1 Einstein's Approach 12
3.2 Langevin's Approach 16
3.3 Subdiffusion 19
3.4 Superdiffusion 24

4 Conclusion **24**

1 Introduction

As the interior of a living cell is a fluctuating environment, we model the trajectories of particles with stochastic processes with continuous paths. Diffusions belong to this class of processes and can model a large range of intracellular movements. They are widely used in the biophysical literature [Qian et al., 1991, Saxton and Jacobson, 1997]. Biophysicians distinguish four main types of diffusions, namely Brownian motion (also referred to as free diffusion), superdiffusion, confined diffusion and anomalous diffusion. Trajectories illustrating these four types of diffusion are represented in Figure 1. These different diffusions correspond to specific biological scenarios. A particle evolving freely inside the cytosol or along the plasma membrane is modeled by free diffusion. Its motion is due to the constant collisions with smaller particles animated by thermal fluctuations. Then, the particle does not travel along any particular direction and can take a very long time to go to a precise area in the cell. Active intracellular transport can overcome this difficulty so that motion is faster and direct specific. The particles (called in this context cargo) are carried by molecular motors along microtubular filament networks. Superdiffusions model the motion of molecular motors and their cargo.

Confined or restricted diffusion [Metzler and Klafter, 2000, Hoze and Holcman, 2017] is characteristic of trapped particles: the particle encounters a binding site, then it pauses for a while before

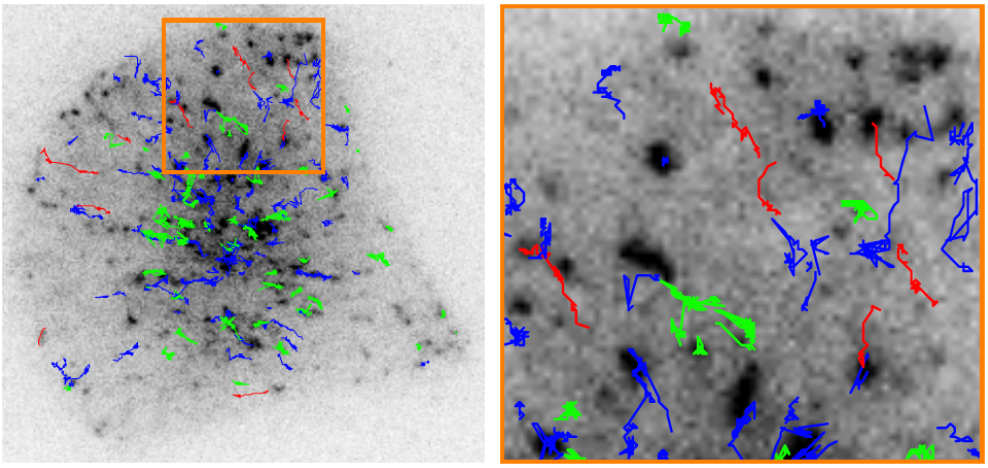

Figure 2: Classification of two-dimensional trajectories from the Rab11 protein sequence in a single cell observed in TIRF microscopy (Courtesy of UMR 144 CNRS Institut Curie PICT IBiSA). We use the three-decision test procedure developed in [Briane et al., 2018] at level $\alpha = 5\%$. The Brownian trajectories are in blue, the subdiffusive trajectories in green and the superdiffusive trajectories in red.

dissociating and moving away. Anomalous diffusion includes particles which encounters dynamic or fixed obstacles [Saxton, 1994, Berry and Chaté, 2014], or particles slowed by the contrary current due to the viscoelastic properties of the cytoplasm. A classification of protein trajectories into the three types of diffusion ((Brownian, superdiffusion, and subdiffusion) is shown in Figure 2. This classification is obtained with our three-decision test procedure described in [Briane et al., 2018].

Mean Square Displacement

In biophysics, the different types of diffusions are characterized by the mean square displacement (MSD) [Qian et al., 1991]. Given a particle trajectory $(X_t)_{t>0}$, the MSD is defined as the function,

$$\mathrm{MSD}(t) = \mathbb{E}\left(\|X_{t+t_0} - X_{t_0}\|^2\right), \tag{1}$$

where $\|\cdot\|$ is the euclidean norm and $\mathbb{E}$ is the expectation of the probability space. The MSD function of Brownian motion is linear $\mathrm{MSD}(t) \propto t$), while the MSD function of subdiffusion (respectively superdiffusion) grows slower (respectively faster) than the linear function.

This property makes the MSD a popular criterion to analyze intracellular motion as Brownian motion is the process of reference. The typical MSD curves of the different diffusion models are represented in Figure 3. In practical imaging, we observe the successive positions of a single particle $X_{t_0}, X_{t_1}, \ldots, X_{t_n}$ in the two or three dimensions at equidistant times, that is $t_{i+1} - t_i = \Delta$. The MSD is estimated at lag j by:

$$\widehat{\mathrm{MSD}}(j\Delta) = \frac{1}{n-j+1}\sum_{k=0}^{n-j}\|X_{t_{k+j}} - X_{t_k}\|^2. \tag{2}$$

Computing the estimator (2) at different lag j gives an estimation of the MSD function (1). Then the simplest rule to classify a trajectory is based on a fit of the MSD function (1) to $t \to t^\beta$. [Feder et al., 1996] states that the trajectory is subdiffusive if $\beta < 0.9$, superdiffusive if $\beta > 1.1$ and Brownian if $0.9 < \beta < 1.1$. If $\beta < 0.1$ it states that the particle does not move, see Figure 4.

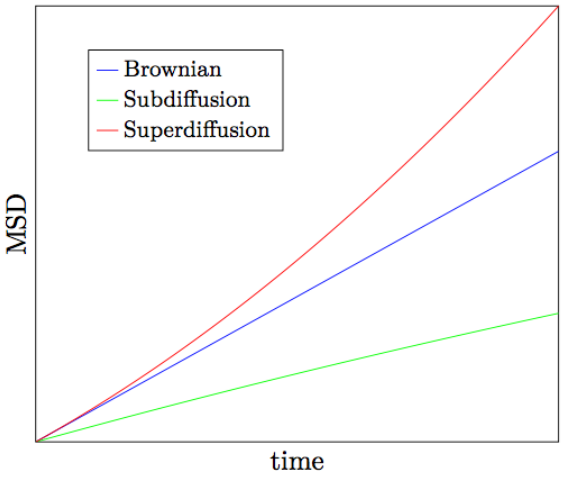

Figure 3: Typical MSD curves of the different diffusion types.

In this paper, we compute the theoretical MSD (1) for each presented motion model and classify it as Brownian, superdiffusion or subdiffusion accordingly. However, (and even if it is out of the scope of this paper), we must emphasize that MSD has some limitations.

Limitations

First, the MSD function is a summary measure based on a second order moment and is not sufficient to characterize the dynamics of the trajectory. Accordingly, several authors (e.g. [Tejedor et al., 2010, Gal et al., 2013]) proposed other statistics which can be associated to MSD for trajectory analysis. [Lund et al., 2014] propose a decision tree for selection motion model combining MSD, Bayesian information criterion and the radius of gyration. [Lysy et al., 2016] present a likelihood-based inference as an alternative to MSD for the comparison between two models of subdiffusions: fractional Brownian motion and a generalized Langevin equation.

Secondly, the estimation of the MSD function (1) is tricky as the variance of estimator (2) increases with the time lag. Figure 4 illustrates this problem in the case of Brownian trajectories. It suggests that the classification of [Feder et al., 1996] based on parameter β overdetects subdiffusion and superdiffusion while it is Brownian motion. Moreover the MSD variance is also severely affected at short time lags by dynamic localization error and motion blur. [Michalet, 2010] details an iterative method, known as the Optimal Least Square Fit (OLSF) for determining the optimal number of points to obtain the best fit to MSD in the presence of localization uncertainty.

In order to take account of the variance of the MSD estimate, several authors use a set of independent trajectories rather than single trajectories. These trajectories may have different lengths but are assumed to have the same kind of motion. For instance, [Pisarev et al., 2015] consider weighted-least-square estimate for β by estimating the variance of pathwise MSD. Their motion model selection is then based on the modified Akaike's information criterion. [Monnier et al., 2012] propose a Bayesian approach to compute relative probabilities of an arbitrary set of motion models (free, confined, anomalous or directed diffusion). In general, this averaging process can lead to oversimplication and misleading conclusions about the biological process [Gal et al., 2013].

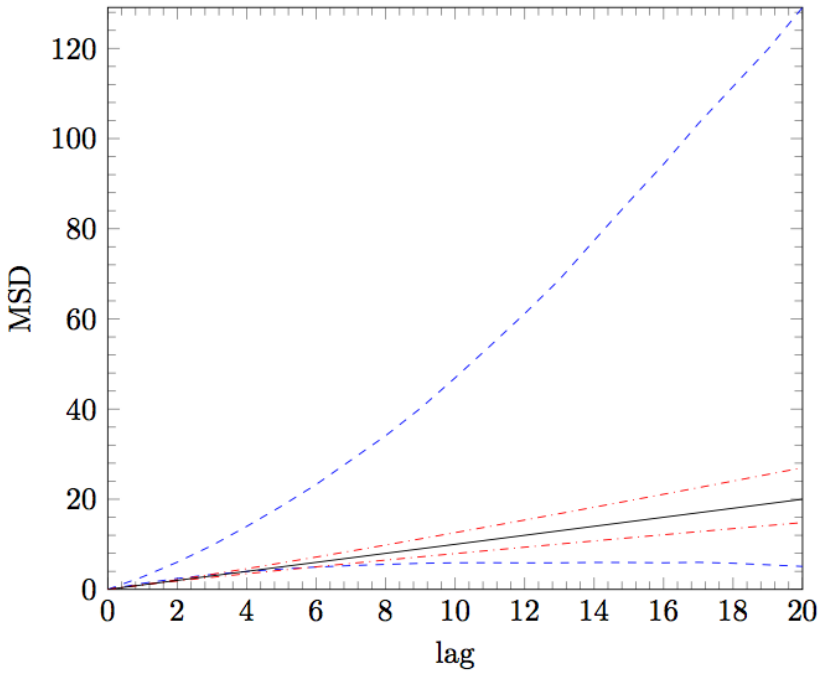

Figure 4: A classification rule for motion modes from MSD. The dashdotted lines are the bound defined by [Feder et al., 1996], $t \to t^\beta$, $\beta = 0.9$ and 1.1. The dashed lines are the pointwise high probability interval of 95% associated to the empirical MSD curve for a standard Brownian motion trajectory of length $n = 30$. The bounds of the interval are the 2.5% and 97.5% empirical quantile of (2) and are computed by Monte Carlo simulation from 10 001 Brownian trajectories of size $n = 30$.

Paper organization

The remainder of the paper is organized as follows. In the next section, we present the probabilistic tools in order to define diffusion processes. Such processes are of great importance for modeling intracellular dynamics. To this end, we focus on d-dimensional processes with $d = 2$ or $d = 3$. In Section 3, we present the three main types of diffusion studied in biophysics to model intracellular motion, namely Brownian motion, subdiffusion and superdiffusion. We also described the different biological scenarios associated to each mode of diffusion.

2 Stochastic Processes, Brownian motion, and Diffusions

It is worth noting that the biophysics literature uses the word diffusion in a very broad sense [Meroz and Sokolov, 2015]. Here we introduce the probabilistic concept of diffusion presented in [Karlin, 1981] and [Klebaner et al., 2012]. First, we define the notion of stochastic processes. Then, we put an emphasis on Brownian motion, the cornerstone process which allows to build all the diffusion processes. We describe diffusion processes driven by Brownian motion. Finally, we deal with an extension of Brownian motion, namely fractional Brownian motion [Mandelbrot and Van Ness, 1968]; we present quickly diffusion processes driven by fractional Brownian motion.

2.1 Stochastic Process

Let $(\Omega, \mathcal{F}, P)$ a probability space where Ω is the sample space, $\mathcal{F}$ a field and P a probability measure. A d-dimensional *stochastic process* is a function:

$$\begin{aligned} I \times \Omega &\to \mathbb{R}^d \\ (t, \omega) &\mapsto X(t, \omega) \end{aligned} \tag{3}$$

where I is a time interval. We note this application $(X_t)_{t \in I}$ or simply (X_t). We present briefly stochastic processes from two angles.

Let $t \in I$, the application,

$$\begin{aligned} \Omega &\to \mathbb{R}^d \\ \omega &\mapsto X(t, \omega) \end{aligned} \tag{4}$$

is the random state of the process at time t. It is a random variable defined on $(\Omega, \mathcal{F}, P)$. Then, a stochastic process can be seen as the collection of random variables $\{\omega \mapsto X(t, \omega),\, t \in I\}$.

Let $\omega \in \Omega$, the application

$$\begin{aligned} I &\to \mathbb{R}^d \\ t &\mapsto X(t, \omega) \end{aligned} \tag{5}$$

is called a *trajectory* or a *path* of the stochastic process $(X_t)_{t \in I}$.

A stochastic process may be seen as an application from Ω to the set of functions from $I = [0, T]$ to $\mathbb{R}^d$. As previously mentioned, we consider only the stochastic processes whose trajectories are continuous, that is for almost $\omega \in \Omega$ $t \to X_t(\omega)$ is continuous.

Finite-Dimensional Distribution

A stochastic process may be seen as a random variable from $(\Omega, \mathcal{F}, P)$ to the measurable space,

$$\left(\mathfrak{F}([0, T], \mathbb{R}^d), \otimes_{t \in [0,T]} \mathcal{B}_d\right),$$

where $\mathfrak{F}([0, T], \mathbb{R}^d)$ is the set of functions from $[0, T]$ to $\mathbb{R}^d$, $\mathcal{B}_d$ is the Borelian sigma-algebra and $\otimes_{t \in [0,T]} \mathcal{B}_d$ is the sigma-algebra generated by all the finite dimensional cylindrical sets of $\mathfrak{F}([0, T], \mathbb{R}^d)$. Then the stochastic process X induces a probability measure on $\left(\mathfrak{F}([0, T], \mathbb{R}^d), \otimes_{t \in [0,T]} \mathcal{B}_d\right)$ which is defined through the finite-dimensional distribution.

Now we define the concept of finite-dimensional distribution. Let $J = \{t_0, t_1, \ldots, t_n\}$ such that $t_i \in I$ and $t_0 < t_1 <, \ldots, < t_n$. We note,

$$X_J = (X_{t_0}, \ldots, X_{t_n}), \tag{6}$$

the random vector whose components $X_{t_i} \in \mathbb{R}^d$. The distribution μ_J of X_J is the joint distribution:

$$\mu_J(A) = P(X_{t_0} \in A_0, \ldots, X_{t_n} \in A_n), \tag{7}$$

where $A_i \in \mathbb{R}^d$ and $A = A_0 \times \cdots \times A_n$.

The *finite-dimensional distributions* of X is the family of distributions $\{\mu_J | J \text{a finite set of } I\}$. If the finite-dimensional distributions μ_J satisfy a technical criterion called consistency then the Kolmogorov extension theorem guarantees the existence of a stochastic process X with finite-dimensional distributions μ_J on $(\Omega, \mathcal{F}, P)$ [Gallardo, 2008][Chapter 1, Section 1.1].

Filtered Probability Space

We state previously that a stochastic process can be seen as a collection of random variables defined on $(\Omega, \mathcal{F}, P)$. More precisely the random variable (4) is defined on $(\Omega, \mathcal{F}_t, P)$ where $\mathcal{F}_t \subset \mathcal{F}$. This reflects that the outcome of the random variable (4) depends on what happened before t, that is on the historic of the process until time t.

Then we define the concept of filtration. A *filtration* $\mathbb{F}$ is a family $(\mathcal{F}_t)$ of increasing fields on $(\Omega, \mathcal{F})$ that is $\mathcal{F}_s \subset \mathcal{F}_t \subset \mathcal{F}$ for $s < t$. $\mathbb{F}$ specifies how the information is revealed over time. The property that a filtration is increasing corresponds to the fact the information is not forgotten. Finally, a stochastic process X is called adapted to a filtration $\mathbb{F}$ if, for all t, the random variable $\omega \mapsto X(t, \omega)$ is $\mathcal{F}_t$-measurable.

2.2 Brownian Motion

The observation of the erratic motion of a pollen particle suspended in a fluid by the botanist R. Brown in 1828 marks the first step in the development of the Brownian motion theory. In 1905, Einstein argued that the movement of the particle is due to its bombardment by the particles of the fluid; he obtained the equations of Brownian motion. The underlying probability theory was derived by N. Wiener in 1923 that is why Brownian motion is also known as the Wiener process. In this section, we define the one-dimensional Brownian motion and characterize it as a Gaussian process. Then, we define the $d-$dimensional Brownian motion.

Definition

The *one-dimensional Brownian motion* (B_t) is a stochastic process with the following properties:

- (B_t) is a process with *independents increments*. For all $t > s$, $B_t - B_s$ is independent of the field $\mathcal{F}_s$ generated by the historic of the process $(B_u)_{u \in [0,s]}$ until the time s.
- For all $t > s$, $B_t - B_s$ has normal distribution with mean 0 and variance $t - s$.
- The paths of (B_t) are almost surely continuous.

Gaussian Process

A *Gaussian process* is a process for which all the finite-dimensional distributions are multivariate normal. We have the following theorem:

Theorem 2.1. *A Brownian motion started at zeros is a Gaussian process with zero mean and covariance function* $\min(t, s)$. *Conversely, a Gaussian process with zero mean and covariance* $\min(t, s)$ *is a Brownian motion.*

Multivariate Brownian Motion

As we already stated, we are interested in modeling the trajectories of particle in dimension 2 and 3. We define the *d-dimensional Brownian motion* $(d \geq 1)$ as the random vector $B_t = (B_t^1, \ldots, B_t^d)$ where all coordinates B_t^i are independent one-dimensional Brownian motions.

2.3 Diffusion Process

We present briefly the family of stochastic processes of interest in this paper, namely the diffusion processes. First, we recall the Markov property which is a central notion for defining the diffusion processes. Then, we give the definition of diffusions and some characterizations of theses processes.

Markov Property

The Markov property states that if we know the present state of the process, the future behavior of the process is independent of its past. For instance, a simple model of weather forecast assumes that the probability to have rain at day j given the information of the weather on the previous days is the same as the probability to have rain at day j given the restricted information of the weather at day $j-1$. Let note (X_i) the process giving the weather at each day i and note k the modality corresponding to rain. In this discrete set up, the Markov property can be written as:

$$P(X_j = k|X_{j-1}, \ldots, X_0) = P(X_j = k|X_{j-1}). \tag{8}$$

As we work with stochastic processes defined continuously in time, the historic of the process given by $X_{j-1}, \ldots, X_0$ in the discrete case is replaced by the field $\mathcal{F}_t$ at time t. Then, a d-dimensional continuous stochastic process (X_t) is Markovian if:

$$P(X_{t+s} \in A|\mathcal{F}_t) = P(X_{t+s} \in A|X_t), \tag{9}$$

where $A \in \mathbb{R}^d$. Then we have the following theorem:

Theorem 2.2. *The Brownian motion (B_t) has the Markov property.*

Remark 2.1. *Another difference (apart from the conditioning) between Equations* (8) *and* (9) *is the different nature of the events $\{X_j = k\}$ and $\{X_{t+s} \in A\}$. It is due to the fact that in Equation* (8) *the state space of the stochastic process (modality of weather) is countable while the state space of the stochastic process is the whole space $\mathbb{R}^d$ (not countable) in* (9) .

Diffusions

A *diffusion process* (X_t) is a continuous time process which possesses the Markov property and for which the sample paths are continuous. Moreover, every diffusion process satisfies three key conditions see [Karlin, 1981][Chapter 15, Section 1]. The first condition states that large displacements of magintude exceeding $\epsilon > 0$ are very unlikely over sufficiently small intervals,

$$\lim_{\Delta \to 0} \frac{1}{\Delta} P(\|X_{t+\Delta} - X_t\| > \epsilon | X_t = x) = 0, \quad \forall \epsilon > 0, \quad \forall x \in \mathbb{R}^d, \tag{10}$$

where $\|\cdot\|$ denotes the Eucidean norm. In other words, condition (10) prevents the diffusion process from having discontinuous jumps. The two last conditions characterize the mean and the variance of the infinitesimal displacements and affirm the existence of the limits:

$$\lim_{\Delta \to 0} \mathbb{E}(X_{t+\Delta} - X_t | X_t = x) = \mu(x, t), \quad \forall x \in \mathbb{R}^d, \tag{11}$$

$$\lim_{\Delta \to 0} \mathbb{E}((X_{t+\Delta} - X_t)(X_{t+\Delta} - X_t)^\top | X_t = x) = \sigma^2(x, t), \quad \forall x \in \mathbb{R}^d, \tag{12}$$

where $\top$ denotes the transpose operator; $\mu(x,t) : \mathbb{R}^d \times \mathbb{R}^+ \to \mathbb{R}^d$ is the drift parameter; $\sigma^2(x,t) : \mathbb{R}^d \times \mathbb{R}^+ \to S_+^d$ is the diffusion coefficient where S_+^d is the set of positive semi-definite matrix of size d.

In particular, Brownian motion is a diffusion process: its drift is the null function, and its diffusion coefficient is constant.

2.4 Stochastic Differential Equation (SDE)

The most common approach for defining diffusion processes is to see them as the solution of stochastic differential equations.

Physical Model

Initially diffusion models were developed to describe the motion of a particle in a fluid submitted to a deterministic force due to the fluid and a random force due to random collisions with others particles. That is why we model efficiently the motion of intra-cellular particles with diffusion. Let $X_t \in \mathbb{R}^d$ be the position of the particle at time t and (B_t) a $d-$dimensional Brownian motion; assume that $X_t = x$. Then the displacement of the particle between t and $t + \Delta$ is approximately given by:

$$X_{t+\Delta} - x \approx \mu(x,t)\Delta + \sigma(x,t)(B_{t+\Delta} - B_t). \tag{13}$$

The component $\mu(x,t)\Delta$ is the displacement due to the fluid where the velocity of the fluid is given by the drift $\mu(x,t)$. The term $\sigma(x,t)(B_{t+\Delta} - B_t)$ expresses the random component of the motion due to random collisions. More specifically the collisions increased with the temperature of the fluid; the influence of temperature is modeled by the diffusion coefficient $\sigma(x,t)$. We note that the model (13) implies that, due to the normality of the Brownian increment, the displacement of the particle $X_{t+\Delta} - x$ is approximated by a Gaussian random variable of mean $\mu(x,t)\Delta$ depending on the drift and of variance $\sigma(x,t)\sqrt{\Delta}$ depending on the diffusion coefficient.

Heuristically, a *stochastic differential equation* is obtained from Equation (13) by replacing Δ by dt, $(B_{t+\Delta} - B_t)$ by dB_t and $X_t + \Delta - X_t$ by dX_t. Then we have the following definition:

Definition 2.1. *Let (B_t) be a $d-$dimensional Brownian motion. Let $\mu : \mathbb{R}^+ \times \mathbb{R}^d \to \mathbb{R}^d$ and $\sigma(x,t) : \mathbb{R}^+ \times \mathbb{R}^d \to \mathcal{M}^d$ be given functions ($\mathcal{M}^d$ denoting the set of square matrix of size d). A stochastic differential equation (SDE) is defined as:*

$$dX_t = \mu(X_t,t)dt + \sigma(X_t,t)dB_t, \tag{14}$$

where (X_t) is the unknown process. The function μ is referred to as the drift while the function σ is called the diffusion coefficient.

Solution of SDE

There are two types of solutions respectively called *strong* and *weak solutions*. A strong solution is a weak solution but the reverse is false.

Definition 2.2. *Let $\mathcal{F}_t$ the field induced by the initial condition X_0 and the Brownian motion (B_t) which drives the stochastic differential* (14)*. We say that Equation* (14) *has a strong solution (X_t) on the probability space $(\Omega, \mathcal{F}, P)$ with respect to (B_t) and initial condition X_0 if the stochastic process X_t satisfies* (14)*, has continuous paths and that X_t is $\mathcal{F}_t$-measurable for all t.*

The fact that X_t is $\mathcal{F}_t$-measurable is crucial. It means that X_t depends only on the historic of the Brownian motion which drives the stochastic differential equation and the initial condition. Then we can interpret X_t as an output of the system parametrized by $\mu(x,t)$ and $\sigma(x,t)$ whose input is the Brownian motion (B_t). It reflects the principle of causality of the system. If X_t could depend on the future, that is on B_s with $s > t$, causality would fail.

The concept of strong solution relies on the fact that the Brownian motion is given. A weak solution of a SDE consists in building at the same time a couple of processes (X_t, B_t) where (X_t) is a solution of the SDE driven by the Brownian (B_t). We will not give the exact definition of weak solution as it has technical points not of interest for the understanding of the concept.

Then the solution of the stochastic differential equation is written as:

$$X_t = X_0 + \int_0^t \mu(X_s, s)ds + \int_0^t \sigma(X_s, s)dB_s. \tag{15}$$

We note that the fact that the two integrals are defined is equivalent to the fact that X_t is (strong or weak) solution. In particular the integral with integrand dB_t is a random variable $\mathcal{F}_t$-measurable. Details of the construction of such integrals is given in [Klebaner et al., 2012][Chapter 4].

2.5 Fractional Brownian Motion

Fractional Brownian motion (fBm) was introduced to model scale-invariant phenomenons processes showing long-range dependence. [Kolmogorov, 1941] developed a turbulence theory based on two hypotheses of scale invariance. In his study of long-term storage capacity and design of reservoirs, [Hurst, 1951] observed hydrological events invariant to changes in scale. [Mandelbrot and Van Ness, 1968] defined the fractional Brownian motion of exponent has a *"moving average of $dB(t)$, in which past increments of $B(t)$ are weighted by the kernel $(t-s)^{2\mathfrak{h}-1}$."* This kernel is at the origin of the long range dependence property (for a certain choice of parameter $\mathfrak{h}$). The parameter $\mathfrak{h}$ is known as the Hurst index or Hurst parameter. In this section, we define fractional Brownian motion and give its main properties. Fractional Brownian motion is then defined in dimension d.

Self-Similarity and Fractional Brownian Motion

A real-valued stochastic process (X_t) is *self-similar* with index $\mathfrak{h} > 0$ ($\mathfrak{h} - ss$) if, for any $a > 0$ the processes (X_{at}) and $(a^{\mathfrak{h}}X_t)$ have the same finite dimensional distributions. Then, a Gaussian $\mathfrak{h} - ss$ process $(B_t^{\mathfrak{h}})$ with stationary increments and Hurst index $0 < \mathfrak{h} < 1$ is a *fractional Brownian motion.*

Now we give some properties of the fBm. First, the fBm has continuous paths. We have $\mathbb{E}(B_t^{\mathfrak{h}}) = 0$ for all t. It is said to be standard if the variance of $B_1^{\mathfrak{h}}$ is equal to one. For the standard fBm we have:

$$\mathrm{Cov}(B_t^{\mathfrak{h}}, B_s^{\mathfrak{h}}) = \frac{1}{2}(|t|^{2\mathfrak{h}} + |s|^{2\mathfrak{h}} - |t-s|^{2\mathfrak{h}}) \tag{16}$$

Then we can show that a fBm with $\mathfrak{h} = 1/2$ is simply a (one-dimensional) Brownian motion.

Long Range Dependence

A stationary time series $(X_n)_{n\in\mathbb{N}}$ exhibits *long-range dependence* if $\mathrm{Cov}(X_n, X_0) \to 0$ as $n \to \infty$ but,

$$\sum_{n=0}^{\infty} |\mathrm{Cov}(X_n, X_0)| = \infty. \tag{17}$$

In other words the covariance between X_0 and X_n tends to 0 but so slowly that their sum diverges. Then, we define the stationary process known as fractional Gaussian noise:

$$X_k = B^{\mathfrak{h}}_{k+1} - B^{\mathfrak{h}}_k, \quad k \in \mathbb{N}, \tag{18}$$

where $(B^{\mathfrak{h}}_t)$ is a standard fBm of Hurst index $\mathfrak{h}$. Due to the properties of fBm the fractional Gaussian noise (X_n) is a stationary centered Gaussian process with auto-covariance function:

$$\gamma(k) = \mathbb{E}(X_{i+k}X_i) = \frac{1}{2}(|k+1|^{2\mathfrak{h}} + |k-1|^{2\mathfrak{h}} - 2|k|^{2\mathfrak{h}}). \tag{19}$$

Then for $k \neq 0$ we can show that $\gamma(k) = 0$ if $\mathfrak{h} = 1/2$, $\gamma(k) < 0$ if $0 < \mathfrak{h} < 1/2$ and $\gamma(k) > 0$ if $1/2 < \mathfrak{h} < 1$. Now, for $\mathfrak{h} = 1/2$ we have:

$$\gamma(k) = \mathfrak{h}(2\mathfrak{h}-1)|k|^{2\mathfrak{h}-1} + o(1), \tag{20}$$

where $o(1) \to 0$ as $k \to \infty$. Consequently $\gamma(k) \to 0$ as $k \to \infty$ for $0 < \mathfrak{h} < 1$. From Equation (20) we deduce:

$$\sum_{k=0}^{\infty} \gamma(k) = \infty, \ 1/2 < \mathfrak{h} < 1,$$
$$\sum_{k=0}^{\infty} \gamma(k) < \infty, \ 0 < \mathfrak{h} < 1/2.$$

Consequently, if $1/2 < \mathfrak{h} < 1$, fractional Gaussian noise (hence fBm) (X_n) exhibits long range dependence.

Stochastic Integration and Fractional Brownian Motion

As stated in the introduction, [Mandelbrot and Van Ness, 1968] define the fBm as a moving average of dB_t. [Decreusefond et al., 1999] shows that fBm can be written as the following stochastic integral driven by Brownian motion:

$$B^{\mathfrak{h}}_t = \int_0^t K_{\mathfrak{h}}(t,s) dB_s, \tag{21}$$

where the properties and analytical form of function $K_{\mathfrak{h}}(t,s)$ (called kernel) are given in [Decreusefond et al., 1999].

Multivariate Fractional Brownian Motion

[Coutin and Qian, 2002] give the following definition of a $d-$dimensional fractional Brownian motion:

Definition 2.3. *A fractional Brownian motion in dimension $d > 1$ is the random vector $B_t^{\mathfrak{h}} = (B_t^{\mathfrak{h},1}, \ldots, B_t^{\mathfrak{h},d})$ where all coordinates $B_t^{\mathfrak{h},i}$ are independent one-dimensional fractional Brownian motions of Hurst parameter $0 < \mathfrak{h} < 1$.*

Again a $d-$dimensional fBm reduces to a $d-$dimensional Brownian motion in the case $\mathfrak{h} = 1/2$.

SDE Driven by Fractional Brownian Motion

We can extent the stochastic differential equation (14) to define a ($d-$ dimensional) stochastic differential driven by a ($d-$dimensional) fBm of Hurst index $0 < \mathfrak{h} < 1$:

$$dX_t = \mu(X_t, t)dt + \sigma(X_t, t)dB_t^{\mathfrak{h}}. \tag{22}$$

The same concepts of strong and weak solutions hold for the SDE (22). The SDE driven by Brownian motion (14) is of the form of the SDE (22) with $\mathfrak{h} = 1/2$.

In the remainder of this paper, we will call diffusion any processes solution of (22). We note that it does not match with the definition of [Karlin, 1981, Chapter 15, Section 1] given in Section 2.3, as the Markov property no longer holds due to the correlations between the fBm increments.

2.6 Summary

In this section, we presented Brownian motion from a probabilistic perspective. This process is of paramount importance in mathematics, physics and biophysics. We also presented diffusion as solutions of a stochastic differential equation (SDE) and introduced the fractional Brownian motion (fBm) which generalized Brownian motion adding correlations between its increments.

In the next section, we give the physical derivation of Brownian motion. We will also describe the motion models used in biophysics for describing intracellular dynamics, with a particular emphasis on the diffusion models defined in this section.

3 Diffusion for Modeling Intracellular Trajectories

First, we present the physical models underlying Brownian motion. More specifically, we introduce the theory of [Einstein, 1905] and the Langevin approach. Then, we present subdiffusion processes which is often split in two parts: anomalous and confined diffusion. Finally, we deal with superdiffusion. Also, we compute the MSD for each presented model as it is the criterion to classify the motion model as free diffusion, subdiffusion or superdiffusion. We note that we also exhibit motion models which are not diffusion in the sense of Section 2, in particular in the case of subdiffusions.

3.1 Einstein's Approach

In this section, we present the approach of [Einstein, 1905] introduced for modeling the motion of *"small suspended particles"* in a liquid. We develop the concept of Brownian motion in the exact same way as [Einstein, 1905]. First we depict the related physical experiment. Secondly, we show that the concentration of suspended particles is governed by a diffusion in the sense of Fick. Finally,

the motion of individual suspended particles is modeled by a process corresponding to Brownian motion.

Physical Context

Einstein considers a particular physical situation. In first place, he assumes that z moles of a chemical specie is dissolved in a liquid of volume V. He also supposes that the solute is confined in a volume $V^\star$ separated from the pure solvent by a wall that is permeable to the solvent but not to the solute. In this situation, the solute produces a pressure on the wall called the osmotic pressure. Provided $z/V^\star$ is small enough, that is the solute concentration is low, we have:

$$pV^\star = RTz, \tag{23}$$

where p is the osmotic pressure, R is the gas constant and T is the temperature. Secondly, instead of the solute, Einstein considers suspended particles. Now the wall is permeable to the solvent but not to the particles. In this case, the theory of thermodynamics do not expect that the suspended particles will produce an osmotic pressure on the wall. However, according to the molecular-kinetic of heat, the only difference between a dissolved molecule and a suspended body is their size. Then, Einstein points out that both the dissolved molecules and the suspended particles should produce the same osmotic pressure as long as their number is equal. Then he assumes that *"the suspended bodies perform an irregular, albeit very slow, motion in the liquid due to the liquids molecular motion"*. This motion –we will see later that it corresponds to Brownian motion– is at the origin of the osmotic pressure. In fact, when the moving particles bounce on the wall, they exert a pressure as in the case of the solute. Then, we can derive a similar equation as (23):

$$pV^\star = RT\frac{n}{N}, \tag{24}$$

where n is the number of suspended particles and N the Avogadro number. Then n/N is the number of moles of the suspended particles.

In the sequel, for sake of simplicity, [Einstein, 1905] derives his theory in one dimension. In other words, the motion of the particles is along the x-axis and consequently we are only interested in the x-component of the forces applied on the particles.

Fick's Diffusion

In this paragraph, we are interested in the evolution of the concentration in space and time $\nu(x,t) = n(x,t)/dx$ where $n(x,t)$ in the number of suspended particles at time t in the small volume dx. [Einstein, 1905] assumes that a force K, depending on the position but not on the time, acts on each particle.

First, at the equilibrium we have:

$$K\nu - \frac{\partial p}{\partial x} = 0, \tag{25}$$

that is the force K and the force induced by the pressure p compensate each other. Using the definition of ν and Equation (24), we can rewrite Equation (25) as:

$$K\nu - \frac{RT}{N}\frac{\partial \nu}{\partial x} = 0. \tag{26}$$

On the other hand, the concentration ν is governed by a diffusion in the sense of [Fick, 1855]. In this case, diffusion refers to the evolution of a macroscopic quantity as the heat in a metal or the

concentration of a chemical specie in a liquid. It is characterized by the two laws of [Fick, 1855]. Once combined, they give the diffusion equation which is written in our case as:

$$\frac{\partial \nu}{\partial t} = D\frac{\partial^2 \nu}{\partial^2 x}, \tag{27}$$

where D is the diffusion coefficient characterizing the diffusion.

Now, to fully determined the diffusion of ν we need to derive D as a function of the parameters of the problem. To this end, we use the first law of [Fick, 1855] stating that *"the diffusion flux between two points of different concentrations in the fluid is proportional to the concentration gradient between these points"*. In our case it can be written as:

$$J = -D\frac{\partial \nu}{\partial x}, \tag{28}$$

where J is the diffusion flux and D is the diffusion coefficient characterizing the diffusion. Now we must derive the diffusion flux J that is the number of particles going through an area of unit one per unit of time. [Einstein, 1905] assumes that the suspended particles are spheric of radius a. Additionally, if the liquid has coefficient of viscosity k, then the force K gives to each particle the velocity,

$$\frac{\nu K}{6\pi k a}. \tag{29}$$

Consequently the diffusion flux is:

$$J = \frac{\nu K}{6\pi k a}. \tag{30}$$

In fact, a dimension analysis reveals that the inverse of a volume ($\nu = n/V^\star$) multiplied by a velocity (Equation (29)) defines a flux.

Finally, the first law of [Fick, 1855] gives:

$$\frac{\nu K}{6\pi k a} = -D\frac{\partial \nu}{\partial x}. \tag{31}$$

From Equations (26) and (31), the Fick's diffusion governing ν has for diffusion coefficient:

$$D = \frac{RT}{N 6\pi k a}. \tag{32}$$

Brownian Motion

Finally, [Einstein, 1905] models the *"disordered motions"* due to thermal molecular agitation of the n suspended particles. More importantly, Einstein links these individual motions to the Fick's diffusion examined in the previous paragraph. He assumes that the motions of individual particles are independent from each other. Moreover, he assumes that the displacements of a same particle on consecutive time intervals are independent as long as these time intervals are not too small. Then, in the following, we denote Δ the length of the time interval which is small compared to the observable time intervals but still satisfy the independence property of displacements. We recall that the displacements occur along the x-axis only. We denote Δ_x the displacement occurring during the period Δ. [Einstein, 1905] assumes that Δ_x is a random variable whose distribution function ϕ is symmetric. Then, the probability that a particle experiences a displacement lying between u and $u + du$ is $\phi(u)du$. The average number of particles experiencing such a displacement during a period Δ is:

$$dn = n\phi(u)du. \tag{33}$$

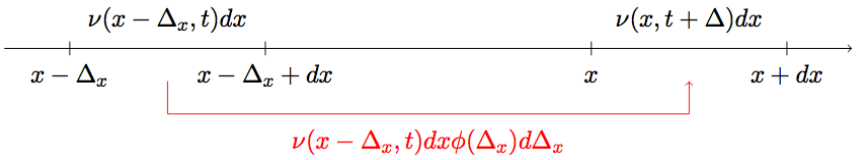

Figure 5: Scheme illustrating the transfer of particles from $x-\Delta_x$ to x between the times t and $t+\Delta$. There are $\nu(x-\Delta_x,t)dx$ particles in $[x-\Delta_x, x-\Delta_x+dx]$ at time t. Among them a proportion of $\phi(\Delta_x)d\Delta_x$ jump to $[x, x+dx]$ between t and $t+\Delta$. Integrating over all the displacements Δ_x, we obtain $\nu(x,t+\Delta)dx$ particles at time t in $[x, x+dx]$.

Now, we can deduce the number of particles $\nu(x,t+\Delta)dx$ from the the numbers of particles at time t and ϕ. In Figure 5, we show how the particles go from $x-\Delta_x$ at time t to x at time $t+\Delta$ using Equation (33). Integrating over all the possible displacements we get:

$$\nu(x,t+\Delta)dx = dx.\int_{\mathbb{R}} \nu(x-\Delta_x,t)\phi(\Delta_x)d\Delta_x. \tag{34}$$

As Δ is small we can expand $\nu(x,t+\Delta)$ as:

$$\nu(x,t+\Delta) = \nu(x,t) + \Delta\frac{\partial\nu(x,t)}{\partial t}.$$

We also expand the left side of Equation (34) in Taylor series:

$$\int_{\mathbb{R}} \nu(x-\Delta_x,t)\phi(\Delta_x)d\Delta_x = \nu(x,t)\times 1 + \frac{\partial\nu(x,t)}{\partial x}\times 0 + \frac{\partial^2\nu(x,t)}{\partial^2 x}\int_{\mathbb{R}}\frac{\Delta_x^2}{2}\phi(\Delta_x)d\Delta_x,$$

where we use that $\int\phi(u)du = 1$ as ϕ is a distribution function and $\int u\phi(u)du = 0$ as ϕ is symmetric. We can equalize the right side of the two previous equations according to the equality given in Equation (34). Then, we deduce that ν respects the diffusion equation (27) predicted by the theory of [Fick, 1855] with diffusion coefficient given by:

$$D = \frac{1}{\Delta}\int_{\mathbb{R}}\frac{\Delta_x^2}{2}\phi(\Delta_x)d\Delta_x. \tag{35}$$

Therefore with a specific definition of the individual motion of n independent particles, [Einstein, 1905] shows that the concentration of such particles follows the Fick's equation.

At this step [Einstein, 1905] only assumed that the displacement of each particle over consecutive time intervals –for intervals not too small– are independent random variables from a symmetric distribution ϕ. Consequently, the particle motion fulfils the independence property of the Brownian increment, see Subsection 2.2. For the moment, we can not see why the displacement of the particles should be Gaussian as for Brownian particle. This link can be made by solving the diffusion equation (27).

We need additional conditions to solve Equation (27). Until this point, we have used the same coordinate system for all the particles. As there are independent of each other, we can define one coordinate system for each particle. [Einstein, 1905] states that the center of gravity of each particle at time $t=0$ is the origin of their coordinate system. Then $\nu(x,t)dx$ now denotes the number of particles whose displacements between the times 0 and t is comprised between x and $x+dx$. In other words, x denotes the displacement and not the absolute position in a common coordinate

system any more. Function ν still verify Equation (27) under this new scheme. Now we have the straightforward conditions:

$$\begin{aligned} \nu(x,0) &= 0, \quad \forall x \neq 0 \\ \int_{\mathbb{R}} \nu(x,0)dx &= n, \end{aligned} \tag{36}$$

Finally the solution of the diffusion equation (27) with conditions (36) is:

$$\nu(x,t) = n\frac{e^{\frac{-x^2}{4Dt}}}{\sqrt{4\pi Dt}}, \tag{37}$$

with x interpreted as a displacement as we have just said. With this meaning of x, $e^{-x^2/(4Dt)}/\sqrt{4\pi Dt}dx$ is the probability that the displacement of a single particle lies in $[x, x+dx]$. Therefore, the particle displacement is Gaussian. We also know that the displacements over consecutive time intervals are independent. Then the motion of the suspended particles defined by [Einstein, 1905] correspond to the Brownian motion defined in Subsection 2.2. Therefore the physical derivation of Brownian motion by [Einstein, 1905] is equivalent to the so-called Wiener process in mathematics. Due to the physical constraints, the diffusion coefficient D has a particular value given by Equation (32).

We can extend this theory to the d-dimensional case ($d = 2, 3$). In this context, each component follows a one-dimensional Brownian motion and the components are independent from each other. Not surprisingly, it corresponds to the Definition 2.3 of multi-dimensional Brownian motion.

Remark 3.1. *We note that, in this paper, in case of the one-dimensional Brownian motion (B_t) the diffusion coefficient σ is defined as $\sigma = Var(B_1)$. Then we have the relationship $\sigma = 2D$.*
Remark 3.2. *From Equation* (33) *and* (37) *and the definition of ϕ we deduce that $\phi(x) = e^{-x^2/(4D\Delta)}/\sqrt{4\pi D\Delta}$. It is coherent with the equality* (35)*.*

3.2 Langevin's Approach

Physicists define the motion of suspended particles in another way using the approach of [Langevin, 1908] (see [Kou, 2008] and [Schuss, 2009][Chapter 1]). This motion is sometimes refer to as Brownian motion which can be confusing. In this subsection, we present this alternative approach. First, we introduce the underlying physical model and the corresponding hypotheses about the particle motion. Secondly, we show that, in this case, the particle movement is governed by a well known stochastic differential equation. Thirdly, we explain why the particle motion defined by [Einstein, 1905] and by [Langevin, 1908] are mixed up. Finally, we explain which concept of Brownian motion we will use in the paper. In this subsection, we derive the model directly in dimension d.

Langevin Equation

[Langevin, 1908] characterizes the particle motion through the $d-$dimensional (Langevin) equation:

$$m\frac{dv(t)}{dt} = -\zeta v(t) + L(t), \tag{38}$$

where $v : \mathbb{R}^+ \mapsto \mathbb{R}^d$ is the velocity of the particle, m its mass, $\zeta > 0$ the friction coefficient and $L : \mathbb{R}^+ \mapsto \mathbb{R}^d$ a random force resulting from the collisions with the surrounding particles. In case of spherical particles of radius a immersed in a liquid of viscosity coefficient k, the friction coefficient is $\zeta = 6\pi ka$ where k is the viscosity coefficient of the surrounding liquid.

[Uhlenbeck and Ornstein, 1930] constrained $L(t)$ with two additional assumptions. First, the mean of $L(t)$ over a large number of independent colliding particles is 0, that is $\mathbb{E}(L(t)) = \mathbf{0}_d$, where $\mathbf{0}_d$ is the null vector of $\mathbb{R}_d$. In their physical model, [Uhlenbeck and Ornstein, 1930] also assume that the colliding particles are similar to the particle of interest and have same initial speed v_0. Secondly, the autocorrelation function is given by:

$$\mathbb{E}(L(t)L(s)^T) = \sigma\delta(t-s)\mathbf{I}_d, \tag{39}$$

where $\sigma > 0$ is a constant, δ is the Kronecker function and $\mathbf{I}_d$ the identity matrix of size d. The idea is that each collision is practically instantaneous and that successive collisions are uncorrelated. Actually, [Uhlenbeck and Ornstein, 1930] originally model the autocorrelation function as a function of $t - s$ with a sharp peak of width equal to the duration of a single collision. The autocorrelation (39) is preferred nowadays [Van Kampen, 1992][chapter 9]. Such a force $L(t)$ is called a Langevin force.

Ornstein-Uhlenbeck Process

We did not fully define the stochastic process $L(t)$ as we provide only information on its first and second moment. Such a process is known as white noise in statistics. If we further assume that $L(t)$ is Gaussian, we entirely define this process as a Gaussian process is determined by its first two moments. Then, $L(t)$ is called a Gaussian white noise. As explained in [Karlin, 1981][Chapter 15, Subsection 14], the Gaussian white noise $L(t)$ can be informally defined as the derivative of the Wiener process –equivalently the mathematical Brownian motion defined in Subsection 2.2 – $L(t) = \sigma dB_t/dt$. We use the word informally as in fact the Wiener process is nowhere differentiable. Finally, we can rewrite the Langevin equation (38) as the $d-$dimensional stochastic differential equation:

$$mdv(t) = -\zeta v(t)dt + \sigma dB_t. \tag{40}$$

The solution of the stochastic equation (40) is known as the Ornstein-Uhlenbeck process. It is a Gaussian process with:

$$\mathbb{E}(v(t)) = \mathbf{0}_d, \tag{41}$$

$$\mathbb{E}(v(t)v(s)^T) = \frac{\sigma^2}{2\zeta m} e^{-(\zeta/m)|t-s|}\mathbf{I}_d. \tag{42}$$

[Waterston and Rayleigh, 1892] states that, at the equilibrium (that is as $t \to \infty$), the mean square velocity verifies:

$$\lim_{t\to\infty} \mathbb{E}(\|v(t)\|_2^2) = d\frac{k_B T}{m}, \tag{43}$$

where k_B is the Boltzmann constant and T is the temperature. Each component of the velocity vector has the same variance, so that:

$$\lim_{t\to\infty} \mathbb{E}(v_i(t)^2) = \frac{k_B T}{m}, \quad i = 1, \ldots, d. \tag{44}$$

Then, equalizing the variances of $v_i(t)$ obtained with Equation (42) with $t = s$ and obtained with Equation (44), we have the relationship:

$$\sigma = \sqrt{2\zeta k_B T}. \tag{45}$$

Finally, the Brownian motion of [Langevin, 1908] is defined as:

$$X_t = \int_0^t v(s)ds \tag{46}$$

where $v(t)$ is the Ornstein-Uhlenbeck process solution of the SDE (40). Due to the Gaussian nature of $v(t)$, (X_t) is also a Gaussian process.

Mean Square Displacement

One reason explaining the confusion between the particle motion respectively defined by [Einstein, 1905] and [Langevin, 1908] is that they both exhibit a linear mean square displacement asymptotically. In the case of the d-dimensional Brownian motion of [Einstein, 1905], we can easily show that the mean square displacement is:

$$\begin{aligned} \mathbb{E}(\|X_t - X_0\|^2) &= d2Dt \\ &= d\frac{2RT}{N6\pi ka}t \\ &= d\frac{2k_BT}{\zeta}t, \end{aligned} \tag{47}$$

where $k_B = R/N$ is the Boltzmann constant and $\zeta = 6\pi ka$ is the friction coefficient.

In the case of the motion defined by [Langevin, 1908] (assuming $X_0 = 0$ for simplicity) we have:

$$\begin{aligned} \mathbb{E}(\|\|X_t - X_0\|\|^2) &= \sum_{i=1}^{d} \mathbb{E}\left(\int_0^t \int_0^t v^i(s)v^i(u)dsdu\right) \\ &= d\int_0^t \int_0^t \mathbb{E}(v^1(s)v^1(u))dsdu \\ &= d\frac{2k_BT}{\zeta}\left(t - \frac{m}{\zeta}(1 - e^{-(\zeta/m)t})\right) \\ &= d\frac{2k_BT}{\zeta}t + o(t) \end{aligned} \tag{48}$$

where $o(t) \to 0$ as $t \to \infty$.

Choice of the Definition of Brownian Motion

Each approach relies on different physical models. We emphasize that the Brownian motion of [Einstein, 1905] (corresponding to the Wiener process) is nowhere differentiable and then has a rough (but still continuous) path. On the other hand, the particle motion defined by [Langevin, 1908] is differentiable due to its definition as the integration of the Ornstein-Uhlenbeck process (Equation

(46)). Then its path is smooth. [Bressloff, 2014] argues that both processes can be used to model intracellular dynamics in the case where the particle evolves freely inside the cytosol or along the plasma membrane.

In what follows, Brownian motion will refer to the motion defined by [Einstein, 1905]. It corresponds to the mathematical Brownian motion defined in Subsection 2.2 called also Wiener process in the mathematical literature.

3.3 Subdiffusion

Subdiffusion, which includes confined diffusion and anomalous diffusion, are the translations of several biological scenarios. In this subsection, we present models associated to these two types of diffusion. We note that certain models are called diffusion while there are not solutions of SDE.

Anomalous Diffusion

In biophysics, [Saxton and Jacobson, 1997, Meroz and Sokolov, 2015], an *anomalous diffusion* (X_t) is characterized by a MSD which is proportional to the monome t^β,

$$\mathbb{E}(\|X_t - X_0\|^2) \propto t^\beta, \tag{49}$$

with $\beta < 1$. The first two presented models are solutions of a SDE driven by fBm (22) (the first being simply fBm). Then we present other type of processes used in biophysics.

Fractional Brownian motion As a particle moves through the cytoplasm, the latter pushes it back, due to macromolecular crowding and the presence of elastic elements generating correlations in the particles trajectory [Jeon et al., 2011]. A fBm with Hurst index $0 < \mathfrak{h} < 1/2$ is a good candidate to model this situation. First, it is straightforward to show that its MSD is given by (49) with $\beta = 2\mathfrak{h} < 1$ (see Equation (16)). Secondly, we saw in Subsection 2.5 that fBm has its increments negatively correlated when $0 < \mathfrak{h} < 1/2$. As an example, [Weber et al., 2010] study the mechanisms underlying subdiffusive motion in live Escherichia coli cells thanks to fluorescently labeled chromosomal loci and RNA-protein particles. They conclude that the observed motion was well modeled by fBm.

Generalized Langevin equation (GLE) As we have just explained, particles can be slowed by the contrary current due to the viscoelastic properties of the cytoplasm. This time we are interested in long-time correlations (and not just correlations) in diffusive motion. Then, [Kou, 2008] models such phenomenon with a stochastic differential equations driven by the fBm with Hurst index $1/2 < \mathfrak{h} < 1$; in fact we saw in Subsection 2.5 that in this case fBm exhibits long range dependence. Then, [Zwanzig, 2001] and [Chandler, 1987] proposed the generalized Langevin equation (GLE):

$$m\frac{dv(t)}{dt} = -\zeta \int_{-\infty}^{t} v(u)K(t-u)du + G(t), \tag{50}$$

where, in comparison with the Langevin equation (38), $G(t)$ is a noise having memory replacing the memoryless white noise $L(t)$; the velocity is convolved with a kernel K. These two features make the solution of the Equation (50) a non-Markovian process. We note that both K and G must

appear in the equation in order to fulfill a physical constraint comparable to Equation (43) (also called fluctuation-dissipation principle in [Chandler, 1987]):

$$\mathbb{E}(G(t)G(s)^T) = 2\zeta k_B T K(t-s)\mathbf{I}_d. \tag{51}$$

Not surprisingly, we observe that if we choose $K = \delta$ –the Dirac function– we find that the GLE (50) is equivalent to the Langevin equation (38) and the condition on the second moment (51) is equivalent to the condition (39). [Kou, 2008] chooses to define $G(t)$ as fractional Gaussian noise (18) with Hurst index $1/2 < \mathfrak{h} < 1$ for exhibiting long range dependence. From condition (51), they deduce the kernel K (noted now $K_\mathfrak{h}$):

$$K_\mathfrak{h}(t) = 2\mathfrak{h}(2\mathfrak{h}-1)|t|^{2\mathfrak{h}-2}. \tag{52}$$

Then the related stochastic differential equation is:

$$mdv(t) = -\zeta\left(\int_{-\infty}^{t} v(u)K(t-u)du\right)dt + \sigma dB_t^\mathfrak{h}, \tag{53}$$

where $\sigma = 2\zeta k_B T$ and $(B_t^\mathfrak{h})$ is a fBm with $1/2 < \mathfrak{h} < 1$. Finally, [Kou, 2008] shows that the integrated process $X_t = \int v(u)du$ verifies as $t \to \infty$:

$$\mathbb{E}(\|X_t - X_0\|^2) \propto t^{2-2\mathfrak{h}}, \tag{54}$$

It fulfils the MSD condition (49) asymptotically with $\beta = 2 - 2\mathfrak{h} < 1$ for $1/2 < \mathfrak{h} < 1$.

Remark 3.3. *[Kou, 2008] studies only one-dimensional process. Here, we explain how we can extend the models of [Kou, 2008] in higher dimensions. It is quite natural to define physical Brownian motion in higher dimensions as a stack of one-dimensional physical Brownian motion. It is what we implied writing Equation* (42) *with* $\mathbf{I}_d$*. In fact, in this case, the Langevin force* $L(t)$ *is modeled as a white noise and the component of* $d-$*dimensional white noise are independent. However, when we use the GLE* (50)*, we can wonder if the components of the noise* G *are necessarily independent. For instance, we could create some correlations through the kernel* K*. Here, for simplicity, we considered that all the components were independent and shared the same (one-dimensional) kernel.*

Continuous time random walk (CTRW) Intracellular particles can also bind to molecular complexes. Then, the particle motion is a permanent switch between binding events and movement toward another spot where it can bind again. [Scher and Montroll, 1975] introduce the continuous time random walk (CTRW) to model anomalous transport properties of charge carriers in amorphous materials. In their framework, the electron dynamics are successively trapped in different energy wells; the total time spent in the trapped states is much larger than the time spent in free motion. In this model, a particle performs random jumps whose step length is generated by a probability density with finite second moments. The waiting times between jumps are assumed to be distributed according to a probability distribution $\psi(t)$. If $\psi(t)$ has a finite first moment that is $\int t\psi(t)dt < \infty$ then the mean square displacement of the CTRW is linear in time. For instance, we can use the exponential distribution:

$$\psi(t) = (1/\tau)e^{-t/\tau},\ t > 0, \tag{55}$$

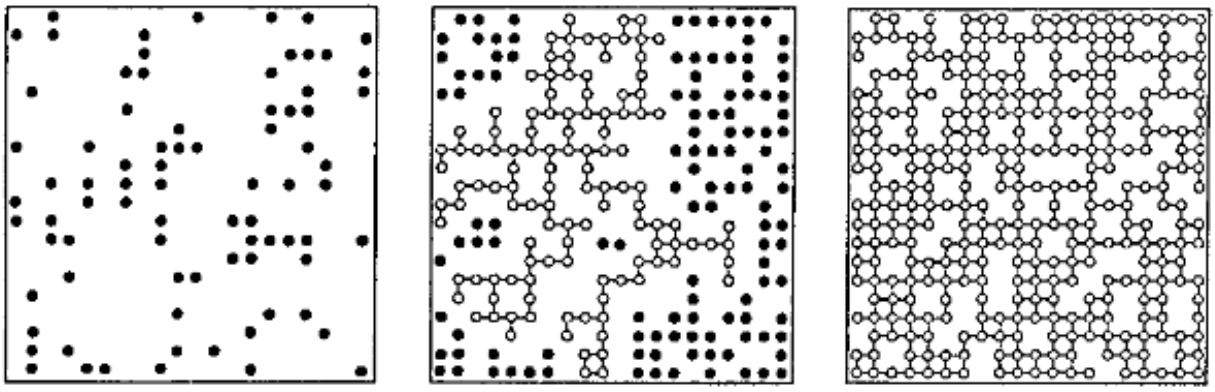

Figure 6: Percolation clusters on a square lattice for different values of p. We use a 20×20 lattice. From left to right percolation clusters obtained with $p = 0.20, 0.59, 0.80$ (the middle image correspond to the case $p = p_c$). Sites belonging to finite clusters are marked by full circles, and sites on the 'infinite' clusters are marked by open circles. (extracted from [Havlin and Ben-Avraham, 1987]).

where $\tau > 0$ is called the characteristic time. We note that, in this case, the random walk has the Markov property (due to the memoryless property of the exponential distribution). On the contrary, if $\int t\psi(t)dt = \infty$ the mean square displacement of the CTRW is given by (49). A typical choice is a power law distribution:

$$\psi(t) = 1/(1 + t/\tau)^{1+\beta},\ t > 0, \tag{56}$$

with $\tau > 0$ the characteristic time and $0 < \beta < 1$.

In neurobiology, [Zhizhina et al., 2015] propose to investigate CTRW to model the axon growth. The growth of an axon to its target is guided by chemical signals from the cellular environment. The authors describe this interaction by a random waiting time thereby defining a CTRW. They observe that "normal" axons and "mutant" axons are driven by CTRW with different waiting time distribution.

Random walk on fractal The inner environment of a cell is crowded with small solutes and macromolecules which occupy 10-50% of the volume [Dix and Verkman, 2008]. If the concentration of obstacles is sufficiently high, the mean square displacement of the particle is given by Equation (49) [Havlin and Ben-Avraham, 1987, Saxton, 1994]. In this case, the domain where they evolve develops a fractal-like structure. Then, a popular model is the random walk on percolation clusters [Havlin and Ben-Avraham, 1987].

For simplicity, we present the model on a $2-$dimension square lattice. Each vertex of the lattice has probability $1 - p$ to be an obstacle that is the particle can not go on this kind of vertex. The other vertices can be occupied by particles. They form connected clusters on which particles are assumed to undergo a random walk. In this very case, there exists a critical probability $p_c = 0.592745$ below which there exists only finite clusters and above which there exists one infinite cluster (see Figure 6) [Havlin and Ben-Avraham, 1987]. When $p = p_c$, the random walk on the infinite cluster have its MSD given by Equation (49) [Havlin and Ben-Avraham, 1987]. In the literature of diffusion on fractals, they parametrize the MSD (49) by $\beta = d/d_w$ where d is the dimension and d_w a parameter called the fractional dimension of the random walk. In the two-dimensional case ($d = 2$), the fractional dimension of the random walk on a square lattice with

$p = p_c$ is $d_w = 2.8784$ [Grassberger, 1999] leading to $\beta = 0.6948$. [Havlin and Ben-Avraham, 1987] also consider other choices of p and random walks on both the finite and infinite percolation clusters. However, in these cases, the MSD is not a power function. As another two-dimensional example, the fractional dimension of a random walk on the Sierpinski gasket fractal gives $d_w = 2.32$ (then $\beta = 0.8621$)[Havlin and Ben-Avraham, 1987]. [Berry and Chaté, 2014] argues that the exponents β observed from real experiments span a wide range of values and that random walks on fractal can not model all these possibilities. Then some authors [Berry and Chaté, 2014, Saxton, 1994] prefer relying on Monte-Carlo simulations with different designs of obstacles (mobiles or not) to propose a model explaining the observed power function form of the MSD.

Confined Diffusion

In biophysics [Saxton and Jacobson, 1997, Monnier et al., 2012], a *confined diffusion* (X_t) is characterized by a MSD of the form:

$$\mathbb{E}(\|X_t - X_0\|^2) = \frac{r_c^2}{a}(1 - be^{-c\sigma^2/(2r_c^2)}), \tag{57}$$

where parameters r_c is the characteristic size of the region of confinement, a is a scale parameter and b and c depends on the shape of the region. Parameter $\sigma > 0$ is the constant diffusion coefficient. We present two models of confined diffusion and give their mean square displacements. For the first model, the MSD (57) is a simplification of the true MSD. We find the MSD (57) for a particular case of the second model. We note that parameter a does not appear in [Saxton and Jacobson, 1997, Monnier et al., 2012]. We use this extra scale parameter a to have the common expression (57) for the MSD of the two presented models.

Diffusion within confined geometries The plasma membrane is parceled up into compartments where proteins undergo short-term confined diffusion. More specifically these compartments are separated by the actin-based membrane skeleton [Kusumi et al., 2005]. Then, the motion can be modeled by the SDE (14) adding boundary conditions. Equation (57) is based on the first term of the exact series solution of the MSD of a Brownian particle trapped in a square or circular corral (in dimension 2) or in a sphere (in dimension 3) [Kusumi et al., 1993, Saxton, 1993]. As an example, [Bickel, 2007] shows that, for a certain type of boundary condition, the MSD of a Brownian motion confined in a circular domain of radius r_c is given by:

$$\mathbb{E}(\|X_t - X_0\|^2) = r_c^2 \left(1 - 8\sum_{i=1}^{\infty} \exp\left[-\iota_{1i}^2 \frac{t}{\tau}\right] \frac{1}{\iota_{1i}^2(\iota_{1i}^2 - 1)}\right), \tag{58}$$

where $0 < \iota_{1,1} < \iota_{1,2} < \dots$ are the positive zeros of J_1', the first derivative of the Bessel function of order one J_1 and $\tau = 2r_c^2/\sigma^2$ is the characteristic time. We note that, as expected, the MSD saturates to r_c^2 in the long-time limit $t \gg \tau$. Then, Equation (57) is the first term of the sum (58) with $a = 1$, $b = 8/(\iota_{11}^2(1 - \iota_{11}^2))$ and $c = \iota_{11}^2$. Parameters σ and r_c are unchanged in the two equations (58) and (57).

Diffusion in a potential well We can state that a particle is attracted by an external force modeled by a potential well U. Originally, [Kramers, 1940] introduced such a model for describing chemical reactions. His model can be seen as the ($d-$dimensional) Langevin equation (40) (written here as a SDE) with an extra term depending on U:

$$mdv(t) = -\zeta v(t)dt - \nabla U(X_t) + \sqrt{2\zeta k_B T} dB_t, \tag{59}$$

where ∇ denotes the gradient operator. Now we make other assumptions on Equation (59) to obtain a process with the MSD (57). First, we suppose that the viscosity is very large, that is the friction coefficient ζ tends to infinity. Then, the acceleration term $mdv(t)$ is negligible. This corresponds to the so-called overdamped condition in physics [Van Kampen, 1992]. The model reduces to:

$$\zeta dX_t = -\nabla U(X_t) + \sqrt{2\zeta k_B T} dB_t, \tag{60}$$

where $dX_t = v(t)dt$. Now, we assume that the potential U is uni-modal; in other words the particle is trapped in a single domain. In this case, U can be approximated by a polynomial of order 2. For simplicity, suppose that the potential is given by the following polynomial:

$$U(x_1, \ldots, x_d) = (1/2) \sum_{i=1}^{d} k_i (x_i - \theta_i)^2, \tag{61}$$

where $k_i > 0$, $\theta_i \in \mathbb{R}$ and d is the dimension of the process. Then the SDE (60) turns into:

$$dX_t^i = -\lambda_i (X_t^i - \theta_i) dt + \sigma dB_t^i, \qquad i = 1, \ldots, d, \tag{62}$$

where $\sigma = \sqrt{2k_B T \zeta}$ and $\lambda_i = k_i/\zeta > 0$. As in the case of Equation (40), the solution of the SDE (62) is the Ornstein-Uhlenbeck process (different parametrization compared to the SDE (40) with the extra parameters θ_i though). The parameter k_i measures the strength of attraction of the potential (related to the potential depth) while $\theta = (\theta_1, \ldots, \theta_d)$ is the equilibrium position of the particle. As we already mentioned, the Ornstein-Uhlenbeck is a Gaussian process with normal stationary distribution. In the case of the Ornstein-Uhlenbeck, the mean and covariance of the stationary distribution are:

$$\mathbb{E}(X_t) = \theta, \tag{63}$$

$$\mathrm{Cov}(X_t, X_s) = \frac{\sigma^2}{2} \begin{pmatrix} (1 - e^{-\lambda_1 |t-s|})/\lambda_1 & & 0 \\ & \ddots & \\ 0 & & (1 - e^{-\lambda_d |t-s|})/\lambda_d \end{pmatrix}. \tag{64}$$

The MSD of the Ornstein-Uhlenbeck process (**??**) is given by:

$$\mathbb{E}(\|X_t - X_0\|^2) = \sigma^2 (1 - e^{-\lambda t}) \sum_{i=1}^{d} (1/\lambda_i), \tag{65}$$

when X_0 is drawn with the stationary distribution. When $\lambda_i = \lambda$ for $i = 1, \ldots, d$ Equation (65) reduces to:

$$\mathbb{E}(\|X_t - X_0\|^2) = \frac{d\sigma^2 (1 - e^{-\lambda t})}{\lambda}. \tag{66}$$

Then, we obtain the MSD (57) with $r_c^2 = \sigma^2/(2\lambda)$, $a = 2/d$ and $b = c = 1$.

As an example, [Hozé, 2013] studies the postsynaptic AMPA-type glutamate receptor (AMPAR), a protein involved in the fast excitatory synaptic transmission. AMPAR plays a crucial part in many aspects of brain functions including learning, memory and cognition. Aberrant AMPAR trafficking is implicated in neurodegenerative process [Henley et al., 2011]. [Hoze and Holcman, 2017] uses the overdamped Equation (60) with a polynomial of order 2 for the potential U to model potential wells attracting AMPAR in the synapses.

3.4 Superdiffusion

We note that less attention has been paid to superdiffusion in biophysics. We present here the most popular models.

Brownian with Drift

At the macroscopic level, the main type of active intracellular transport involves molecular motors which carry particles (cargo) along microtubular filament tracks. The molecular motors and their cargo undergo superdiffusion on a network of microtubules in order to reach a specific area quickly. The molecular motor moves step by step along the microtubules thanks to a mechano-chemical energy transduction process. A single step of the molecular motor is modeled by the so-called Brownian ratchet [Reimann, 2002]. When we observe the motion of the molecular motor along a filament on longer time-scales (several steps), its dynamic can be approximated by a Brownian motion with constant drift (also called directed Brownian) [Peskin and Oster, 1995, Elston, 2000].

The Brownian motion with drift is solution of the SDE:

$$dX_t^i = v_i dt + \sigma dB_t^{1/2,i}, \qquad i = 1, \dots, d, \tag{67}$$

where $v = (v_1, \dots, v_d) \in \mathbb{R}^d$ is the constant drift parameter modeling the velocity of the molecular motor. Then the MSD of the directed Brownian motion is given by:

$$\mathbb{E}(\|X_t - X_0\|^2) = \|v\|_2^2 t^2 + d\sigma^2 t, \tag{68}$$

the linear component coming from the Brownian part while the quadratic part is due to the constant drift. In absence of the Brownian component the MSD is quadratic, the motion is described as ballistic that is the particle goes straight.

Anomalous Superdiffusion

Anomalous superdiffusions are the analogue to anomalous subdiffusion. Then the MSD of an *anomalous superdiffusion* (X_t) is characterized by a MSD which is proportional to the monome t^β,

$$\mathbb{E}(\|X_t - X_0\|^2) \propto t^\beta, \tag{69}$$

with $1 < \beta < 2$.

Fractional Brownian motion Superdiffusion can also be modeled by the fractional Brownian motion with Hurst parameter $1/2 < \mathfrak{h} < 1$. In fact, we know that the MSD of the fBm is given by Equation (69). However, we note that in biophysics the use of the fractional Brownian motion is mainly related to subdiffusion.

4 Conclusion

In this paper, we presented three main classes of diffusions, namely Brownian motion, subdiffusion and superdiffusion, which are tractable microscopic and macroscopic models of intracellular transport. The diffusion phenomenon, described by Robert Brown in the early 19th, is mainly due to the thermal agitation in the medium resulting from the shocks between molecules and causing stochastic trajectories. For each diffusion type, we gave examples of models used in biophysics. Typically, we

focused on the Ornstein-Uhlenbeck process and the fBm (with $0 < \mathfrak{h} < 1/2$) for modeling subdiffusion. We used the Brownian with drift and the fBm (with $1/2 < \mathfrak{h} < 1$) for modeling superdiffusion. However, there exists a wide variety of models for subdiffusion and superdiffusion. We emphasized that, in biophysics, some processes are considered as subdiffusive or superdiffusive even if there are not diffusions according to the probabilistic definition. As an example, continuous time random walks (CTRW) are not diffusions since their paths are not continuous. We gave mathematically detailed formulas, and define the classification through the MSD criterion.

Meanwhile, an important challenge is to estimate model parameters [Hoze and Holcman, 2017], and to classify tracks computed with dedicated algorithms [Chenouard et al., 2014]. In [Briane et al., 2018], we defined several test procedures to classify the observed trajectories into the three diffusion types. Another issue is to simulate more sophisticated models as presented in [Bressloff and Newby, 2013, Bressloff, 2014, Etoc et al., 2018], including multi-scale models to take into account complex interactions, signaling pathways, environment of the cytoplasm, properties of the cytoskeleton, geometry of the cell, and interaction with neighboring cells.

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