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Anomalous fluctuation relations

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Abstract. We study Fluctuation Relations (FRs) for dynamics that are anomalous, in the sense that the diffusive properties strongly deviate from the ones of standard Brownian motion. We first briefly review the concept of transient work FRs for stochastic dynamics modeled by the ordinary Langevin equation. We then introduce three generic types of dynamics generating anomalous diffusion: Lévy flights, long-time correlated Gaussian stochastic processes and time-fractional kinetics. By combining Langevin and kinetic approaches we calculate the work probability distributions in the simple nonequilibrium situation of a particle subject to a constant force. This allows us to check the transient FR for anomalous dynamics. We find a new form of FRs, which is intimately related to the validity of fluctuation-dissipation relations. Analogous results are obtained for a particle in a harmonic potential dragged by a constant force. We argue that these findings are important for understanding fluctuations in experimentally accessible systems. As an example, we discuss the anomalous dynamics of biological cell migration both in equilibrium and in nonequilibrium under chemical gradients.

1.1

Introduction

With *Fluctuation Relations* (FRs) we denote a set of symmetry relations describing large-deviation properties (see the Chapter by Touchette and Harris in this book) of the probability distribution functions (PDFs) of statistical physical observables far from equilibrium. First forms of one subset of them, often referred to as *Fluctuation Theorems*, emerged from generalizing fluctuation-dissipation relations to nonlinear stochastic processes [1, 2]. They were then discovered as generalizations of the Second Law of Thermodynamics for thermostated dynamical systems, i.e., systems interacting with thermal reservoirs, in nonequilibrium steady states [3, 4, 5, 6]; see the Chapters by Reid et al. and by Rondoni and Jepps for this deterministic approach. Another subset, so-called *Work Relations*, generalize a relation between work and free energy, known from equilibrium thermodynamics, to nonequilibrium situations [7, 8]; see the Chapters by Alemany et al. and by Spinney and Ford for this line of research. These two fundamental classes were later on amended and generalized by a variety of other FRs from which they can partially be derived as special cases [9, 10, 11, 12], as has already been discussed starting from the Chapters by Spinney and Ford up to the one by Gaspard in this book. Research performed over the past

ten years has shown that FRs hold for a great variety of systems thus featuring one of the rare statistical physical principles that is valid even very far from equilibrium: see summaries in [13, 14, 15, 16, 17, 18] for stochastic processes, [19, 20, 21, 22, 23, 24] for deterministic dynamics and [25, 26] for quantum systems. Many of these relations have meanwhile been verified in experiments on small systems, i.e., systems on molecular scales featuring only a limited number of relevant degrees of freedom [27, 28, 29, 30, 31, 32], cf. the Chapters by Ciliberto et al., Alemany et al., and Sagawa and Ueda.

The term *anomalous* in the title of this chapter refers to *anomalous dynamics*, which are loosely speaking processes that do not obey the laws of conventional statistical physics and thermodynamics [33, 34, 35]; see, e.g., the Chapter by Zhang et al. for anomalous deviations from Fourier's Law of heat conduction in small systems. Paradigmatic examples are diffusion processes where the long-time mean square displacement does not grow linearly in time: That is, $\langle x^2 \rangle \sim t^\alpha$, where the angular brackets denote an ensemble average, does not increase with $\alpha = 1$ as expected for Brownian motion but either *subdiffusively* with $\alpha < 1$ or *superdiffusively* with $\alpha > 1$ [36, 37, 38]. After pioneering work on amorphous semiconductors [39], anomalous transport phenomena have more recently been observed in a wide variety of complex systems, such as plasmas [40], nanopores [41], epidemic spreading [42], biological cell migration [43] and glassy materials [44], to mention a few [45, 46]. This raises the question to which extent conventional FRs are valid for anomalous dynamics. Theoretical results for generalized Langevin equations [47, 48, 49, 50], Lévy flights [51, 52] and Continuous-Time Random Walk models [53] as well as computer simulations for glassy dynamics [54] showed both validity and violations of the various types of conventional FRs referred to above, depending on the specific type of anomalous dynamics considered and the nonequilibrium conditions that have been applied [55].

The purpose of this chapter is to outline how the two different fields of FRs and anomalous dynamics can be cross-linked in order to explore to which extent conventional forms of FRs are valid for anomalous dynamics. With the term *Anomalous Fluctuation Relations* we refer to deviations from conventional forms of FRs as they have been discussed in the previous chapters, which are due to anomalous dynamics. Here we focus on generic types of stochastic anomalous dynamics by only checking *Transient Fluctuation Relations* (TFRs), which describe the approach from a given initial distribution towards a (non)equilibrium steady state. Section 1.2 motivates the latter type of FRs by introducing simple scaling relations, as they are partially used later on in this chapter. As a warm-up, we then first derive the conventional TFR for the trivial case of Brownian motion of a particle moving under a constant external force modeled by standard Langevin dynamics. Section 1.3 introduces three generic types of stochastic anomalous dynamics: long-time correlated Gaussian stochastic processes, Lévy flights and time-fractional kinetics. We check these three stochastic models for the existence of conventional TFRs under the simple nonequilibrium condition of a constant external force. Section 1.4 introduces a system exhibiting anomalous dynamics that is experimentally accessible, which is biological cell migration. We then outline how an anomalous transient fluctuation relation might be

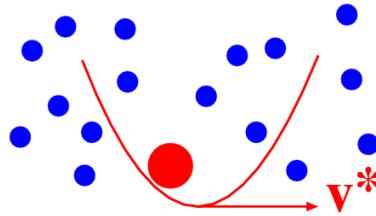


Figure 1.1 Sketch of a colloidal particle confined within a harmonic trap that is dragged through water with a constant velocity v^* , cf. the experiment by Wang et al. [27].

verified for cells migrating under chemical gradients. We summarize our results in Section 1.5 by highlighting an intimate connection between the validity of conventional TFRs and the validity of fluctuation-dissipation relations.

1.2 Transient fluctuation relations

1.2.1 Motivation

Consider a particle system evolving from some initial state at time $t = 0$ into a nonequilibrium steady state for $t \rightarrow \infty$. A famous example that has been investigated experimentally [27], cf. also the Chapter by Alemany et al. is a colloidal particle immersed into water and confined by an optical harmonic trap, see Fig. 1.1. The trap is first at rest but then dragged through water with a constant velocity v^* . Another paradigmatic example, whose nonequilibrium fluctuations have been much studied by molecular dynamics computer simulations [3], is an interacting many-particle fluid under a shear force, which starts in thermal equilibrium by evolving into a nonequilibrium steady state [4].

The key for obtaining FRs in such systems is to obtain the PDF $\rho(\xi_t)$ of suitably defined dimensionless entropy production ξ_t over trajectory segments of time length t . The goal is to quantify the asymmetry between positive and negative entropy production in $\rho(\xi_t)$ for different times t since, as we will demonstrate in a moment, this relation is intimately related to the Second Law of Thermodynamics. For a very large class of systems, and under rather general conditions, it was shown that the following equation holds [13, 14, 20, 22, 23]:

$$\ln \frac{\rho(\xi_t)}{\rho(-\xi_t)} = \xi_t \quad . \quad (1.1)$$

Given that here we consider the transient evolution of a system from an initial into a steady state, this formula became known as the *transient fluctuation relation* (TFR). The left hand side we may call the fluctuation ratio. Relations exhibiting this functional form have first been proposed in the seminal work by Evans, Cohen and

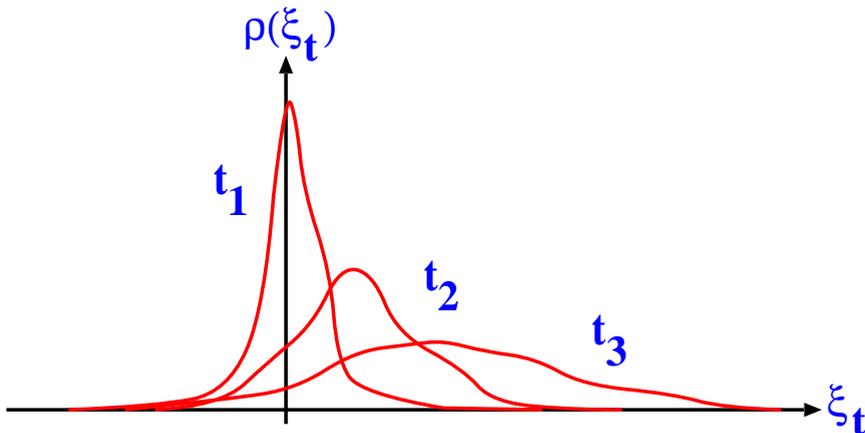


Figure 1.2 Illustration of the dynamics of the probability density function for entropy production $\rho(\xi_t)$ for different times $t_1 < t_2 < t_3$.

Morris [3], although in the different situation of considering nonequilibrium steady states. Such a steady state relation was proved a few years later on by Gallavotti and Cohen for deterministic dynamical systems, based on the so-called chaotic hypothesis [5, 6]. The idea to consider such relations for transient dynamics was first put forward by Evans and Searles [4].

Fig. 1.2 displays the temporal evolution of the PDF for entropy production in such a situation and may be compared to Fig. 12 in the chapter of (Ciliberto) for analogous results extracted from experimental measurements. The asymmetry of the evolving distribution, formalized by the fluctuation relation Eq. (1.1), is in line with the Second Law of Thermodynamics. This easily follows from Eq. (1.1) by noting that

$$\rho(\xi_t) = \rho(-\xi_t) \exp(\xi_t) \geq \rho(-\xi_t), \quad (1.2)$$

where ξ_t is taken to be positive or zero. Integration from zero to infinity over both sides of this inequality after multiplication with ξ_t and defining the ensemble average over the given PDF as $\langle \dots \rangle = \int_{-\infty}^{\infty} d\xi_t \rho(\xi_t) \dots$ yields

$$\langle \xi_t \rangle \geq 0. \quad (1.3)$$

1.2.2 Scaling

By using FRs one is typically interested in assessing large deviation properties of the PDF of entropy production. That is, one wishes to sample the tails of the distributions for large times, and not so much the short-time dynamics, or the centre of the distribution. For this purpose it is useful to introduce suitably scaled variables that

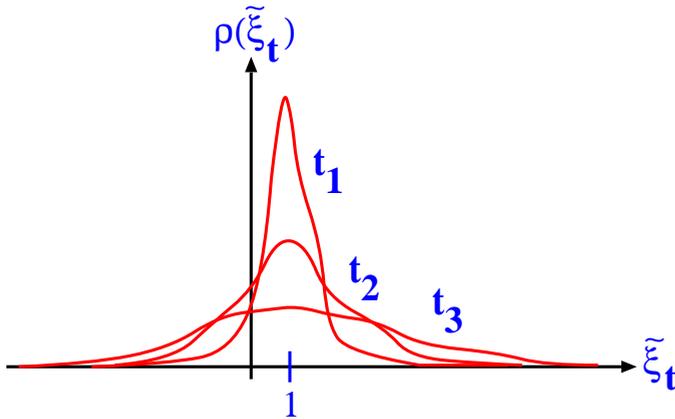


Figure 1.3 Illustration of the dynamics of the probability density function for entropy production $\rho(\xi_t)$ for different times $t_1 < t_2 < t_3$ by using the scaled variable Eq. (1.4).

enable us to eliminate the drift associated with the positive average entropy production Eq. (1.3). A first option is to look at the PDF $\rho(\tilde{\xi}_t)$ of the scaled variable [52]

$$\tilde{\xi}_t = \frac{\xi_t}{\langle \xi_t \rangle}, \quad (1.4)$$

as illustrated in Fig. 1.3. By definition, the PDF is now centred at $\langle \tilde{\xi}_t \rangle = 1$, hence we have eliminated any contributions to the left hand side of Eq. (1.1) that comes from the drift, by purely focusing on the asymmetric shape of the distribution.

Another way of scaling was used by Gallavotti and Cohen [5, 6] by employing the scaled time average

$$\hat{\xi}_t = \frac{\xi_t}{t \langle \xi_t \rangle}, \quad (1.5)$$

yielding the PDF for entropy production displayed in Fig. 1.4. With this scaling, and for ergodic systems, clearly

$$\rho(\hat{\xi}_t) \rightarrow \delta(1 - \hat{\xi}_t) \quad (t \rightarrow \infty) \quad (1.6)$$

with

$$\frac{\xi_t}{t} \rightarrow \langle \xi_t \rangle \geq 0 \quad (t \rightarrow \infty) \quad (1.7)$$

thus illustrating the relation between FRs and the Second Law again.

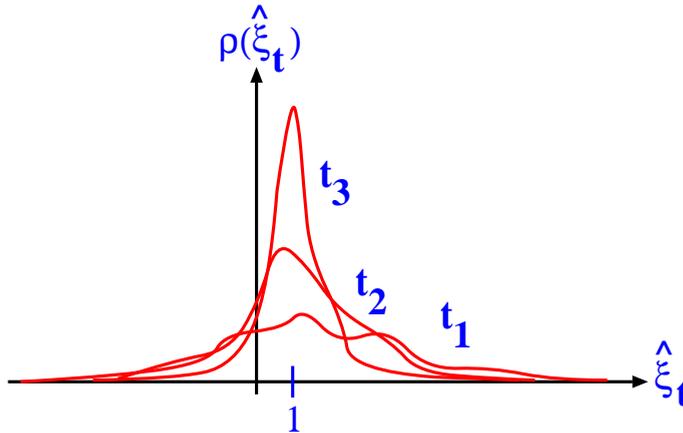


Figure 1.4 Illustration of the dynamics of the probability density function for entropy production $\rho(\hat{\xi}_t)$ for different times $t_1 < t_2 < t_3$ by using the scaled time average Eq. (1.5).

1.2.3

Transient fluctuation relation for ordinary Langevin dynamics

As a preparation for what follows, we may first check the TFR for the ordinary overdamped *Langevin equation* [56]

$$\dot{x} = F + \zeta(t) \quad , \quad (1.8)$$

with a constant external force given by F and Gaussian white noise $\zeta(t)$. Note that for sake of simplicity, here we set all the other constants that are not relevant within this specific context equal to one. For Langevin dynamics with a constant force the entropy production ξ_t defined by the heat, or equivalently the dissipative work, is simply equal to the mechanical work [57]

$$W_t = Fx(t) \quad . \quad (1.9)$$

It follows that the PDF for entropy production, which here is identical to the one for the mechanical work, is trivially related to the PDF of the position x of the Langevin particle via

$$\rho(W_t) = F^{-1} \varrho(x, t) \quad . \quad (1.10)$$

This is very convenient, since it implies that all that remains to be done in order to check the TFR Eq. (1.1) is to solve the Fokker-Planck equation for the position PDF $\varrho(x, t)$ for a given initial condition. Here and in the following, we choose $x(0) = 0$, i.e., in terms of position PDFs we start with a delta-distribution at $x = 0$. Note that for ordinary Langevin dynamics in a given potential, typically the equilibrium density is taken as the initial density [57, 58]. However, since in the following we

will consider dynamics that may not exhibit a simple equilibrium state, without loss of generality here we make a different choice.

For the ordinary Langevin dynamics Eq. (1.8) modeling a linear Gaussian stochastic process, the position PDF is Gaussian exhibiting normal diffusion [56, 59], cf. also the Chapter by Ford and Spinney,

$$\varrho(x, t) = \frac{1}{\sqrt{2\pi\sigma_{x,0}^2}} \exp\left(-\frac{(x - \langle x \rangle)^2}{2\sigma_{x,0}^2}\right) . \quad (1.11)$$

With the subscript zero we denote ensemble averages in case of zero external field. By using the PDF-scaling Eq. (1.10) and plugging this result into the TFR Eq. (1.1), we easily derive that the TFR for the work W_t holds if

$$\langle W_t \rangle = \frac{\sigma_{W_t,0}^2}{2} , \quad (1.12)$$

which is nothing else than an example of the *Fluctuation-Dissipation Relation of the first kind* (FDR1) [56, 60], cf. also the Chapter by Gradenigo et al. We thus arrive at the seemingly trivial but nevertheless important result that for this simple Gaussian stochastic process, the validity of FDR1 Eq. (1.12) implies the validity of the work TFR Eq. (1.1). For a full analysis of FRs of ordinary Langevin dynamics we refer to van Zon and Cohen Refs. [57, 58].

Probably inspired by the experiment of Ref. [27], typically Langevin dynamics in a harmonic potential moving with a constant velocity has been studied in the literature [48, 49, 50, 61], cf. Fig. 1.1. Note that in this slightly more complicated case the (total) work is not equal to the heat [57]. While for the work one recovers the TFR in its conventional form Eq. (1.1) in analogy to the calculation above, surprisingly the TFR for heat looks different for large enough fluctuations. This is due to the system being affected by the singularity of the harmonic potential, as has nicely been elucidated by van Zon and Cohen [58]. A similar effect has been reported by Harris et al. for a different type of stochastic dynamics, the asymmetric zero-range process [62]. For deterministic dynamics involving Nosé-Hoover thermostats analogous consequences for the validity of the Gallavotti-Cohen FR have been discussed in Ref. [63]. See Ref. [13] for a brief review about the general mechanism underlying this type of violation of conventional forms of TFRs.

In the following we check for yet another source of deviations from the conventional TFR Eq. (1.1) than the one induced by singular potentials. We explore the validity of work TFRs if one makes the underlying microscopic dynamics more complicated by modeling dynamical correlations or using non-Gaussian PDFs. In order to illustrate the main ideas along these lines it suffices to consider a nonequilibrium situation simply generated by a constant external force.

1.3

Transient work fluctuation relations for anomalous dynamics

Our goal is to check the TFR Eq. (1.1) for three generic types of stochastic processes modeling anomalous diffusion [46]: (1) *Gaussian stochastic processes*, (2) *Lévy flights*, and (3) *time-fractional kinetics*. All these dynamics we model by generalized Langevin equations. This section reports results from Ref. [55], which may be consulted for further details.

1.3.1

Gaussian stochastic processes

The first type we consider are Gaussian stochastic processes defined by the overdamped generalized Langevin equation

$$\int_0^t dt' \dot{x}(t') \gamma(t-t') = F + \zeta(t) \quad (1.13)$$

with Gaussian noise $\zeta(t)$ and friction that is modeled with a memory kernel $\gamma(t)$. By using this equation a stochastic process can be defined that exhibits normal statistics but with anomalous memory properties in form of non-Markovian long-time correlated Gaussian noise. Equations of this type can be traced back at least to work by Mori and Kubo around 1965 (see [60] and further references therein). They form a class of standard models generating anomalous diffusion that has been widely investigated, see, e.g., Refs. [56, 64, 65]. FRs for this type of dynamics have more recently been analyzed in Refs. [47, 48, 49, 50]. Examples of applications for this type of stochastic modeling are given by generalized elastic models [66], polymer dynamics [67] and biological cell migration [43].

We now split this class into two specific cases.

1.3.1.1 Correlated internal Gaussian noise

The first case corresponds to *internal* Gaussian noise, in the sense that we require the system to exhibit the *Fluctuation-Dissipation Relation of the second kind* (FDR2) [56, 60]

$$\langle \zeta(t) \zeta(t') \rangle \sim \gamma(t-t'), \quad (1.14)$$

again by neglecting all constants that are not relevant for the main point we wish to make here. We now consider the specific case that both the noise and the friction are correlated by a simple power law,

$$\gamma(t) \sim t^{-\beta}, \quad 0 < \beta < 1. \quad (1.15)$$

Because of the linearity of the generalized Langevin equation (1.13) the position PDF must be the Gaussian Eq.(1.11), and by the scaling of Eq. (1.10) we have $\rho(W_t) \sim \varrho(x, t)$. It thus remains to solve Eq. (1.13) for mean and variance, which can be done

in Laplace space [55] yielding *subdiffusion*,

$$\sigma_{x,F}^2 \sim t^\beta, \quad (1.16)$$

by preserving the FDR1 Eq. (1.12). Here and in the following we denote ensemble averages in case of a non-zero external field with the subscript F . For Gaussian stochastic processes we have seen in Section 1.2.3 that the conventional work TFR follows from FDR1. Hence, for the above power-law correlated internal Gaussian noise we recover the conventional work TFR Eq. (1.1).

1.3.1.2 Correlated external Gaussian noise

As a second case, we consider the overdamped generalized Langevin equation

$$\dot{x} = F + \zeta(t), \quad (1.17)$$

which represents a special case of Eq. (1.13) with a memory kernel modeled by a delta-function. Again we use correlated Gaussian noise defined by the power law

$$\langle \zeta(t)\zeta(t') \rangle \sim |t - t'|^{-\beta}, \quad 0 < \beta < 1, \quad (1.18)$$

which one may call *external*, because in this case we do not postulate the existence of FDR2. The position PDF is again Gaussian, and as before $\rho(W_t) \sim \varrho(x, t)$. However, by solving the Langevin equation along the same lines as in the previous case, here one obtains *superdiffusion* by breaking FDR1,

$$\langle W_t \rangle \sim t, \quad \sigma_{W_t,F}^2 \sim t^{2-\beta}. \quad (1.19)$$

Calculating the fluctuation ratio, i.e., the left hand side of Eq. (1.1), from these results yields the *anomalous work TFR*

$$\ln \frac{\rho(W_t)}{\rho(-W_t)} = C_\beta t^{\beta-1} W_t \quad 0 < \beta < 1, \quad (1.20)$$

where C_β is a constant that depends on physical parameters [55]. Comparing this equation with the conventional form of the TFR Eq. (1.1) one observes that the fluctuation ratio is still linear in W_t thus exhibiting the exponential large deviation form [52], cf. the Chapter by Touchette and Harris. However, there are two important deviations: (1) the slope of the fluctuation ratio as a function of W_t is not equal to one anymore, and in particular (2) it decreases with time. We may thus classify Eq. (1.20) as a *weak violation of the conventional TFR*.

We remark that for driven glassy systems FRs have already been obtained displaying slopes that are not equal to one. Within this context it has been suggested to capture these deviations from one by introducing the concept of an ‘effective temperature’ [61, 68, 69]. As far as the time dependence of the coefficient is concerned, such behavior has recently been observed in computer simulations of a paradigmatic two dimensional lattice gas model generating glassy dynamics [54]. Fig. 1.5 shows the fluctuation ratio as a function of the entropy production at different times τ as

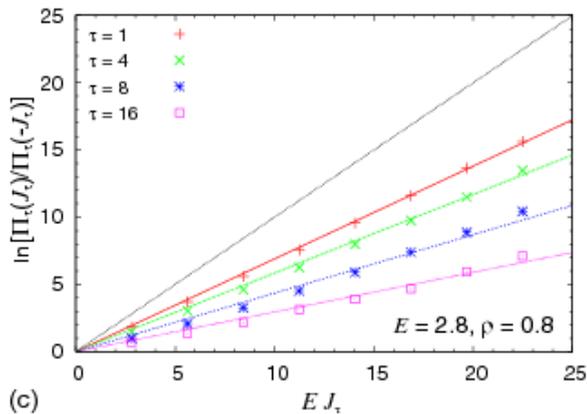


Figure 1.5 The fluctuation ratio $\ln(\Pi_\tau(J_\tau)/\Pi_\tau(-J_\tau))$ for the entropy production $W_\tau = EJ_\tau$ with particle current J_τ and field strength E for particle density ρ at different times τ . The full line, with slope one, displays the result of the conventional FR Eq. (1.1) in a nonequilibrium steady state. The figure is from Ref. [54].

extracted from computer simulations of this model, where the PDF has first been relaxed into a nonequilibrium steady state. It is clearly seen that the slope decreases with time, which is in line with the prediction of the anomalous TFR Eq. (1.20). However, to which extent the nonequilibrium dynamics of this lattice gas model can be mapped onto the generalized Langevin equation Eq. (1.17) is an open question.

1.3.2

Lévy flights

A second fundamental type of anomalous dynamics can as well be defined by the overdamped Langevin equation (1.17). However, this time we choose white Lévy noise, that is, the random variable ζ is distributed according to the PDF

$$\chi(\zeta) \sim \zeta^{-1-\alpha} \quad (\zeta \rightarrow \infty), \quad 0 \leq \alpha < 2. \tag{1.21}$$

In general, the full Lévy stable PDF is defined by its characteristic function. In this case we are thus dealing with Markovian stochastic processes that are not Gaussian distributed generating so-called Lévy flights, which are due to the heavy tails of the underlying PDF. An introduction to the theory of Lévy flights can be found in Chapter 5 of Ref. [46]; the rigorous mathematical theory is presented in, e.g., Ref. [70]. Lévy flights define one of the most paradigmatic models of anomalous dynamics with wide applications, for example, in fluid dynamics [71], in the foraging of biological organisms [72] and in glassy optical material [44], to highlight only a few cases.

It can be shown that the position PDF $\varrho(x, t)$ characterizing the process defined by

Eqs. (1.17),(1.21) obeys the *space-fractional* Fokker-Planck equation

$$\frac{\partial \varrho}{\partial t} = -F \frac{\partial \varrho}{\partial x} + \frac{\partial^\alpha \varrho}{\partial |x|^\alpha}, \quad (1.22)$$

where the last term is given by the *Riesz fractional derivative*, which in real space is a complicated integro-differential operator. It is thus more convenient to represent this derivative by its Fourier transform, which takes the simple expression

$$\mathcal{F} \{ \partial^\alpha \varrho / \partial |x|^\alpha \} = -|k|^\alpha \mathcal{F} \{ \varrho \}. \quad (1.23)$$

Fractional derivatives provide generalizations of ordinary derivatives by reproducing them in case of integer values of the derivative parameter. Being defined by power law memory kernels, they have proven to be extremely useful in order to mathematically model anomalous dynamics. The well-developed discipline of *fractional calculus* rigorously explores the properties of these mathematical objects; for introductions to fractional derivatives see, e.g., Refs. [34, 35, 46, 73]. A systematic and comprehensive mathematical exposition of fractional calculus is given in Ref. [74]. After solving Eq. (1.22) in Fourier space, the resulting position PDF needs to be converted into the work PDF by using Eq. (1.10). In this case it is sensible to apply the scaling Eq. (1.4) [52], which here yields the scaled variable $\tilde{W}_t = W_t / F^2 t$. Expressing the work PDF in this variable and using the asymptotics of the Lévy stable PDF Eq. (1.21), we arrive at the asymptotic TFR for Lévy flights

$$\lim_{\tilde{W}_t \rightarrow \pm\infty} \frac{\rho(\tilde{W}_t)}{\rho(-\tilde{W}_t)} = 1. \quad (1.24)$$

This result has first been reported by Touchette and Cohen in Ref. [51] by using a different technique for the different situation of a harmonic potential dragged with a constant velocity. Note that for $\alpha = 2$ in the above model we recover the conventional TFR Eq. (1.1). For $0 < \alpha < 2$, however, we obtain the surprising result that asymptotically large positive and negative fluctuations of the scaled work are equally probable for Lévy flights. The underlying work PDF is nevertheless still generically asymmetric. Note that the fluctuation ratio Eq. (1.24) does not display the exponential large deviation form, hence one may denote this as a *strong violation of the conventional TFR*.

1.3.3

Time-fractional kinetics

The third and final fundamental type of stochastic anomalous dynamics that we consider here can be modeled by the so-called *subordinated* Langevin equation [75, 76]

$$\frac{dx(u)}{du} = F + \zeta(u) \quad , \quad \frac{dt(u)}{du} = \tau(u) \quad (1.25)$$

with Gaussian white noise $\zeta(u)$ and white Lévy noise $\tau(u) > 0$ with $0 < \alpha < 1$. It can be shown that subordinated Langevin dynamics is intimately related to *Continuous Time Random Walk Theory*, which provides a generalization of ordinary random

walk theory by generating non-trivial jump dynamics. The latter approach has in turn been used, e.g., to understand measurements of anomalous photo currents in copy machines [39], microsphere diffusion in the cell membrane [45], translocations of biomolecules through membrane pores [77] and even dynamics of prices in financial markets [78]. It was demonstrated that this Langevin description leads to the time-fractional Fokker-Planck equation [75, 76]

$$\frac{\partial \varrho}{\partial t} = \frac{\partial^{1-\alpha}}{\partial t^{1-\alpha}} \left[-\frac{\partial F \varrho}{\partial x} + \frac{\partial^2 \varrho}{\partial x^2} \right] \quad (1.26)$$

for $0 < \alpha < 1$ with *Riemann-Liouville fractional derivative* on the right semi-axis

$$\frac{\partial^\delta \varrho}{\partial t^\delta} = \frac{\partial}{\partial t} \left[\frac{1}{\Gamma(1-\delta)} \int_0^t dt' \frac{\varrho(t')}{(t-t')^\delta} \right] \quad (1.27)$$

for $0 < \delta < 1$. This equation obeys a (generalized) Einstein relation for friction and diffusion coefficients (which here are both set to unity, for sake of simplicity). From Eq. (1.26), equations for the first and second moments can be derived and then solved in Laplace space. The second moment in the absence of an external force yields *subdiffusion*,

$$\sigma_{x,0}^2 \sim t^\alpha. \quad (1.28)$$

A calculation of the current $\langle x \rangle$ shows that the FDR1 Eq. (1.12) is preserved by this dynamics. Solving Eq. (1.26) in Laplace space and putting everything together, one recovers the conventional form of the TFR Eq. (1.1) for this type of dynamics. This confirms again that a distinctive role is played by FDR1 for the validity of conventional TFRs, even if the work PDFs are not Gaussian, as in this case.

We remark that analogous results are obtained by studying these three types of anomalous dynamics for the case of a particle moving in a harmonic potential that is dragged with a constant velocity [55].

1.4

Anomalous dynamics of biological cell migration

In order to illustrate the application of anomalous dynamics, and possibly of anomalous FRs, to realistic situations, in this section we discuss experiments and theory about the migration of single biological cells crawling on surfaces or in 3d matrices as examples. We first introduce to the problem of cell migration by considering cells in an equilibrium situation, i.e., not moving under the influence of any external gradients or fields. This case is investigated by extracting results for the mean square displacement (MSD) and for the position PDFs from experimental data. We then show how the experimental results can be understood by a mathematical model in form of a fractional Klein-Kramers equation. As far as MSD and velocity autocorrelation function are concerned, this equation bears some similarity to a generalized Langevin equation that is of the same type as the one that has been discussed in

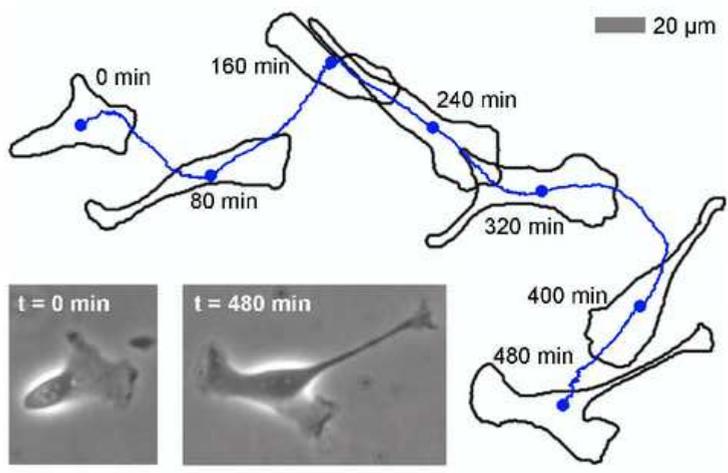


Figure 1.6 Overlay of a biological cell migrating *in vitro* on a substrate. The cell frequently changes its shape and direction during migration, as is shown by several cell contours extracted during the migration process. The inset displays phase contrast images of the cell at the beginning and to the end of its migration process [43].

Section 1.3.1.2. We finally give an outlook to the nonequilibrium problem of cell migration under chemical gradients and describe first results obtained from experiments and data analysis. This research paves the way to eventually checking the existence of anomalous work TFR in biological cell migration. The results on cell migration in equilibrium outlined in this section are based on Ref. [43].

1.4.1
Cell migration in equilibrium

Nearly all cells in the human body are mobile at a given time during their life cycle. Embryogenesis, wound-healing, immune defense and the formation of tumor metastases are well known phenomena that rely on cell migration [79, 80, 81]. Fig. 1.6 depicts the path of a single biological cell crawling on a substrate measured in an *in vitro* experiment [43]. At first sight, the path looks like the trajectory of a Brownian particle generated, e.g., by the ordinary Langevin dynamics of Eq. (1.8). On the other hand, according to Einstein’s theory of Brownian motion a Brownian particle is *passively* driven by collisions from the surrounding fluid molecules, whereas biological cells move *actively* by themselves converting chemical into kinetic energy. This raises the question whether the random-looking paths of crawling biological cells can really be understood in terms of simple Brownian motion [82, 83] or whether more advanced concepts of dynamical modeling have to be applied [84, 85, 86, 87, 88].

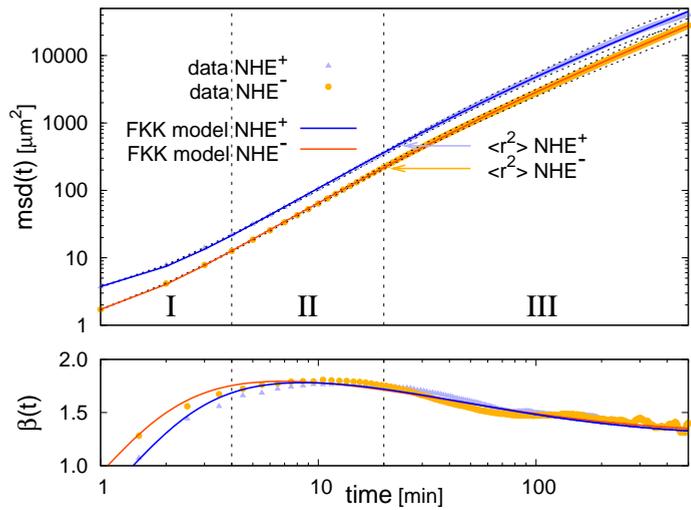


Figure 1.7 Upper part: Double-logarithmic plot of the mean square displacement (MSD) as a function of time. Experimental data points for both cell types are shown by symbols. Different time scales are marked as phases I, II and III as discussed in the text. The solid lines represent fits to the MSD from the solution of our model, see Eq. (1.34). All parameter values of the model are given in [43]. The dashed lines indicate the uncertainties of the MSD values according to Bayes data analysis. Lower part: Logarithmic derivative $\beta(t)$ of the MSD for both cell types as defined by Eq. (1.29).

1.4.1.1 Experimental results

The cell migration experiments that we now discuss have been performed on two types of tumor-like migrating *transformed renal epithelial Madin Darby canine kidney (MDCK-F)* cell strains: wild-type (NHE^+) and NHE -deficient (NHE^-) cells. Here NHE^+ stands for a molecular sodium hydrogen exchanger that either is present or deficient. It can thus be checked whether this microscopic exchanger has an influence on cell migration, which is a typical question asked particularly by cell physiologists. The cell diameter is about $20\text{-}50\mu\text{m}$ and the mean velocity of the cells about $1\mu\text{m}/\text{min}$. Cells are driven by active protrusions of growing actin filaments (*lamellipodial dynamics*) and coordinated interactions with myosin motors and dynamically re-organizing cell-substrate contacts. The leading edge dynamics of a polarized cell proceeds at the order of seconds. Thirteen cells were observed for up to 1000 minutes. Sequences of microscopic phase contrast images were taken and segmented to obtain the cell boundaries shown in Fig. 1.6; see Ref. [43] for full details of the experiments.

According to the Langevin description of Brownian motion outlined in Section 1.2.3, Brownian motion is characterized by a MSD $\sigma_{x,0}^2(t) \sim t$ ($t \rightarrow \infty$) designating normal diffusion. Fig. 1.7 shows that both types of cells behave differently: First of all, MDCK-F NHE^- cells move less efficiently than NHE^+

cells resulting in a reduced MSD for all times. As is displayed in the upper part of this figure, the MSD of both cell types exhibits a crossover between three different dynamical regimes. These three phases can be best identified by extracting the time-dependent exponent β of the MSD $\sigma_{x,0}^2(t) \sim t^\beta$ from the data, which can be done by using the logarithmic derivative

$$\beta(t) = \frac{d \ln \text{msd}(t)}{d \ln t} . \quad (1.29)$$

The results are shown in the lower part of Fig. 1.7. Phase I is characterized by an exponent $\beta(t)$ roughly below 1.8. In the subsequent intermediate phase II, the MSD reaches its strongest increase with a maximum exponent β . When the cell has approximately moved beyond a square distance larger than its own mean square radius (indicated by arrows in the figure), $\beta(t)$ gradually decreases to about 1.4. Both cell types therefore do not exhibit normal diffusion, which would be characterized by $\beta(t) \rightarrow 1$ in the long time limit, but move anomalously, where the exponent $\beta > 1$ indicates superdiffusion.

We next study the PDF of cell positions. Since no correlations between x and y positions could be found, it suffices to restrict ourselves to one dimension. Fig. 1.8 (a), (b) reveals the existence of non-Gaussian distributions at different times. The transition from a peaked distribution at short times to rather broad distributions at long times suggests again the existence of distinct dynamical processes acting on different time scales. The shape of these distributions can be quantified by calculating the *kurtosis*

$$\kappa(t) := \frac{\langle x^4(t) \rangle}{\langle x^2(t) \rangle^2} , \quad (1.30)$$

which is displayed as a function of time in Fig. 1.8 (c). For both cell types $\kappa(t)$ rapidly decays to a constant that is clearly below three in the long time limit. A value of three would be the result for the spreading Gaussian distributions characterizing Brownian motion. These findings are another strong manifestation of the anomalous nature of cell migration.

1.4.1.2 Theoretical modeling

We now present the stochastic model that we have used to reproduce the experimental data yielding the fit functions shown in the previous two figures. The model is defined by the *fractional Klein-Kramers equation* [89]

$$\frac{\partial \varrho}{\partial t} = -\frac{\partial}{\partial x} [v \varrho] + \frac{\partial^{1-\alpha}}{\partial t^{1-\alpha}} \gamma_\alpha \left[\frac{\partial}{\partial v} v + v_{th}^2 \frac{\partial^2}{\partial v^2} \right] \varrho , \quad 0 < \alpha < 1 . \quad (1.31)$$

Here $\varrho = \varrho(x, v, t)$ is the PDF depending on time t , position x and velocity v in one dimension, γ_α is a friction term and $v_{th}^2 = k_B T / M$ stands for the thermal velocity squared of a particle of mass $M = 1$ at temperature T , where k_B is Boltzmann's constant. The last term in this equation models diffusion in velocity space. In contrast to Fokker-Planck equations such as Eq. (1.22), this equation features time

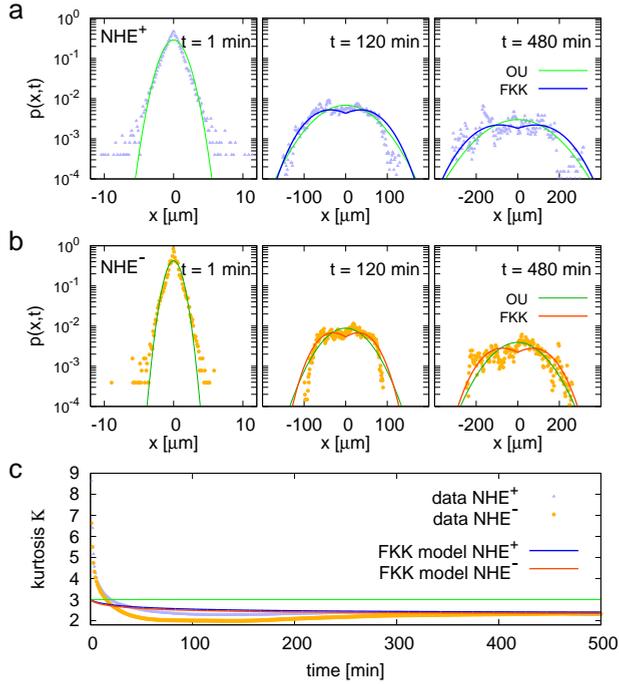


Figure 1.8 Spatio-temporal probability distributions $P(x, t)$. (a),(b): Experimental data for both cell types at different times in semilogarithmic representation. The dark lines, labeled FKK, show the long-time asymptotic solutions of our model Eq. (1.31) with the same parameter set used for the MSD fit. The light lines, labeled OU, depict fits by the Gaussian distributions Eq. (1.11) representing Brownian motion. For $t = 1$ min both $P(x, t)$ show a peaked structure clearly deviating from a Gaussian form. (c) The kurtosis $\kappa(t)$ of $P(x, t)$, cf. Eq. (1.30), plotted as a function of time saturates at a value different from the one of Brownian motion (line at $\kappa = 3$). The other two lines represent $\kappa(t)$ obtained from the model Eq. (1.31) [43].

evolution both in position and velocity space. What distinguishes this equation from an ordinary Klein-Kramers equation, the most general model of Brownian motion [59], is the presence of the Riemann-Liouville fractional derivative of order $1 - \alpha$, Eq. (1.27), in front of the terms in square brackets. Note that for $\alpha = 1$ the ordinary Klein-Kramers equation is recovered. The analytical solution of this equation for the MSD has been calculated in Ref. [89] to

$$\sigma_{x,0}^2(t) = 2v_{th}^2 t^2 E_{\alpha,3}(-\gamma_\alpha t^\alpha) \rightarrow 2 \frac{D_\alpha t^{2-\alpha}}{\Gamma(3-\alpha)} \quad (t \rightarrow \infty) \quad (1.32)$$

with $D_\alpha = v_{th}^2/\gamma_\alpha$ and the *two-parametric* or *generalized Mittag-Leffler function* (see, e.g., Chapter 4 of Ref. [46] and Refs. [73, 90])

$$E_{\alpha,\beta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k + \beta)}, \quad \alpha, \beta > 0, \quad z \in \mathbb{C} \quad (1.33)$$

Note that $E_{1,1}(z) = \exp(z)$, hence $E_{\alpha,\beta}(z)$ is a generalized exponential function. We see that for long times Eq. (1.32) yields a power law, which reduces to the long-time Brownian motion result in case of $\alpha = 1$.

In view of the experimental data shown in Fig. 1.7, Eq. (1.32) was amended by including the impact of random perturbations acting on very short time scales for which we take Gaussian white noise of variance η^2 . This leads to [91]

$$\sigma_{x,0;noise}^2(t) = \sigma_{x,0}^2(t) + 2\eta^2 \quad . \quad (1.34)$$

The second term mimicks both measurement errors and fluctuations of the cell cytoskeleton. In case of the experiments with MDCK-F cells [43], the value of η can be extracted from the experimental data and is larger than the estimated measurement error. Hence, this noise must largely be of a biological nature and may be understood as being generated by microscopic fluctuations of the lamellipodia in the experiment.

The analytical solution of Eq. (1.31) for $\varrho(x, v, t)$ is not known, however, for large friction γ_α this equation boils down to a fractional diffusion equation for which $\varrho(x, t)$ can be calculated in terms of a Fox function [92]. The experimental data in Figs. 1.7 and 1.8 was then fitted consistently by using the above solutions with the four parameters v_{th}^2, α, γ and η^2 in Bayesian data analysis [43].

In summary, by statistical analysis of experimental data we have shown that the equilibrium migration of the biological cells under consideration is anomalous. Related anomalies have also been observed for other types of migrating cells [84, 85, 86, 87, 88]. These experimental results are coherently reproduced by a mathematical model in form of a stochastic fractional equation. We now elaborate on possible physical and biological interpretations of our findings.

First of all, we remark that the solutions of Eq. (1.31) for both the MSD and the velocity autocorrelation function match precisely to the solutions of the generalized Langevin equation [65]

$$\dot{v} = - \int_0^t dt' \gamma(t-t')v(t') + \xi(t) \quad . \quad (1.35)$$

Here $\xi(t)$ holds for Gaussian white noise and $\gamma(t) \sim t^{-\alpha}$ for a time-dependent friction coefficient with a power law memory kernel, which alternatively could be written by using a fractional derivative [65]. For $\gamma(t) \sim \delta(t)$ the ordinary Langevin equation is recovered. Note that the position PDF generated by this equation is Gaussian in the long time limit and thus does not match to the one of the fractional Klein-Kramers equation Eq. (1.31). However, alternatively one could sample from a non-Gaussian $\xi(t)$ to generate a non-Gaussian position PDF. Strictly speaking, despite equivalent MSD and velocity correlations Eqs. (1.31) and (1.35) define different classes of anomalous stochastic processes. The precise cross-links between the Langevin description and the fractional Klein-Kramers equation are subtle [93] and to some extent still unknown. The advantage of Eq. (1.35) is that it allows more straightforwardly a possible biophysical interpretation of the origin of the observed anomalous MSD and velocity correlations, at least partially, in terms of the existence of a memory-dependent friction coefficient. The latter, in turn, might be explained

by anomalous rheological properties of the cell cytoskeleton, which consists of a complex biopolymer gel [94].

Secondly, what could be the possible biological significance of the observed anomalous cell migration? There is an ongoing debate about whether biological organisms such as, e.g., albatrosses, marine predators and fruit flies have managed to minimize the search time for food in a way that matches to optimizing search strategies in terms of stochastic processes; see Refs. [72, 95] and further references therein. In particular, it has been argued that Lévy flights are superior to Brownian motion in order to find sparsely, randomly distributed, replenishing food sources [95]. However, it was also shown that in other situations *intermittent dynamics* is more efficient than pure Lévy motion [95]. For our cell experiment, both the experimental data and the theoretical modeling suggest that there exists a slow diffusion on short time scales, whereas the long-time motion is much faster, which resembles intermittency as discussed in Ref. [95]. Hence, the results on anomalous cell migration presented above might be biologically relevant in view of suitably optimized foraging strategies.

1.4.2

Cell migration under chemical gradients

We conclude this section with a brief outlook to cell migration under chemical gradients [96]. In new experiments conducted by Lindemann and Schwab [97], *murine neutrophil* cells have been exposed to concentration gradients of chemo-attractants. A plot of trajectories of an ensemble of cells crawling under chemotaxis is shown in Fig. 1.9.

Statistical analysis of the experimental data [98] yielded a linear drift in the direction of the gradient,

$$\langle x(t) \rangle \sim t \quad . \quad (1.36)$$

The MSD in the co-moving frame, on the other hand, was found to be

$$\sigma_{x,F}^2(t) - \langle x(t) \rangle^2 \sim t^\beta \quad (1.37)$$

with the same exponent $\beta > 1$ as obtained for the equilibrium dynamics discussed before. Consequently FDR1, cf. Eq. (1.12), is broken. These results suggest that, for obtaining a stochastic model, the force-free fractional Klein-Kramers equation Eq. (1.31) needs to be generalized by including an external force as discussed by Metzler and Sokolov [99],

$$\frac{\partial \varrho}{\partial t} = -\frac{\partial}{\partial x} [v\varrho] + \frac{\partial^{1-\alpha}}{\partial t^{1-\alpha}} \gamma_\alpha \left[\frac{\partial}{\partial v} v - \frac{F}{\gamma_\alpha m} \frac{\partial}{\partial v} + v_{th}^2 \frac{\partial^2}{\partial v^2} \right] \varrho. \quad (1.38)$$

Note that there exist two different ways in the literature of how to include the force F in Eq. (1.31) [89, 99]. These choices lead to different results for drift and MSD. The above results obtained from experimental data analysis clearly select the version of Ref. [99] as the adequate type of stochastic model in this case by rejecting that of

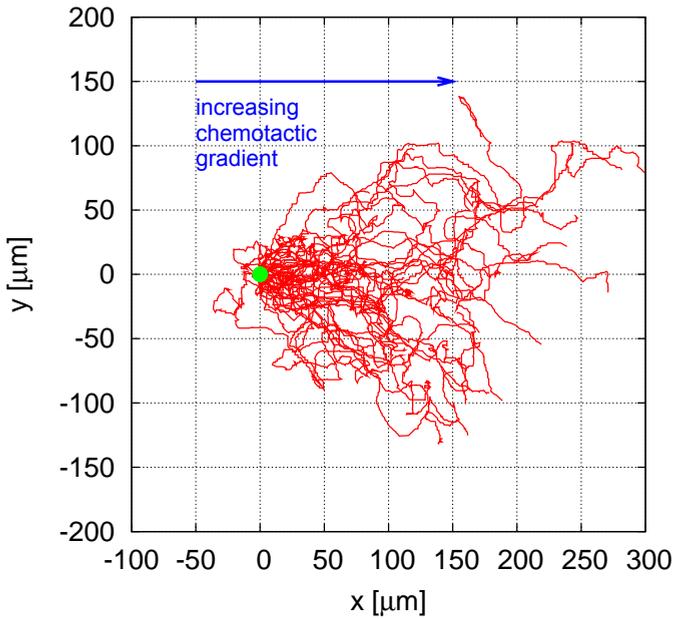


Figure 1.9 Trajectories of an ensemble of 40 murine neutrophil cells exposed to a chemical gradient of the chemoattractant fMLP which increases along the positive x -axis. Cells were observed over 30 min with a time interval of 5 sec. Starting points have been transformed to the origin of the coordinate system (filled circle). It can be seen that there is an average drift of the ensemble towards the positive x -axis [97].

Ref. [89] which, however, might well work in other situations. The (approximate) analytical solutions of Eq. (1.38) reproduce correctly drift, MSD, velocity correlations and (for large enough friction coefficient γ_α and long enough times) the position PDFs of the measured nonequilibrium cell dynamics [98].

Along these lines, one might also check for the form of the work TFR in case of cell migration. This has already been done in an experiment on the cellular slime mold *Dictyostelium discoideum*, in this case under electrotaxis [100]. By plotting the fluctuation ratio as a function of the cell positions at two different times it was concluded that the conventional TFR Eq. (1.1) was confirmed by this experiment. In Fig. 1.10, however, we show experimental results for the fluctuation ratio of the neutrophils of Fig. 1.9 as a function of the cell positions at three different times. In complete formal analogy to Fig. 1.5, the slopes clearly decrease with increasing time, which indicates a violation of the conventional TFR Eq. (1.1). To further explore the validity of work TFRs in cell migration experiments thus appears to be a very interesting, important open problem.

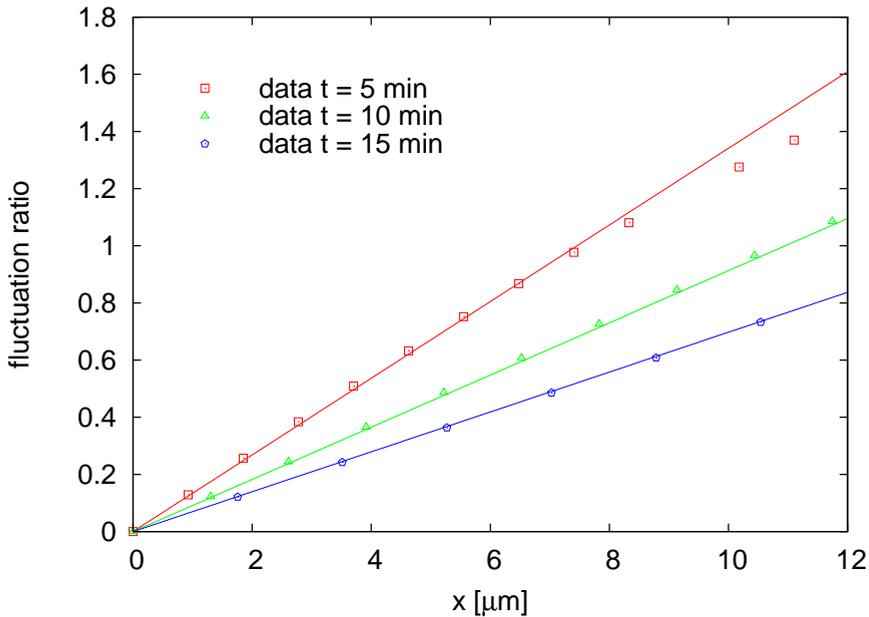


Figure 1.10 The fluctuation ratio $\ln(P(A)/P(-A))$ as a function of $A = x(\tau) - x(0)$ for $\tau = 5$ min (open squares), $\tau = 10$ min (open triangles) and $\tau = 15$ min (open pentagons) obtained from 90 independent trajectories of murine neutrophils moving in a chemotactic gradient of the substance fMLP as depicted in Fig. 1.9. Data show a linear increase in A , however, the reduction of the slope as a function of τ indicates deviations from the conventional TFR Eq. (1.1).

1.5 Conclusions

In this chapter we have applied the concept of FRs as discussed in the previous book chapters to anomalous stochastic processes. This cross-linking enables us to address the question whether conventional forms of FRs are valid for more complicated types of dynamics involving non-Markovian memory and non-Gaussian distributions. We have answered this question for three fundamental types of anomalous stochastic dynamics:

For *Gaussian stochastic processes with correlated noise* the existence of FDR2 implies the existence of FDR1, and we have found that FDR1 in turn implies the existence of work TFR in conventional form. That is, analytical calculations showed that the conventional work TFR holds for internal noise. However, a weak violation of the conventional form was detected in case of external noise yielding a pre-factor that is not equal to one and in particular depends on time. A strong violation of the conventional work TFR was derived for *space-fractional Lévy dynamics* confirming previous results from the literature. We have also found that the conventional work

TFR holds for a typical example of *time-fractional dynamics*. These generic models suggest an intimate connection between FDRs and FRs in case of anomalous dynamics.

As a realistic example of anomalous dynamics, we have then discussed biological cell migration. By extracting the MSD and the position PDF from experimental data for cells crawling in an equilibrium *in vitro* situation, we found that the cells under investigation exhibited different dynamics on different time scales deviating from simple Brownian motion. For longer times, these cells moved superdiffusively. These experimental findings were reproduced by a stochastic model in form of a fractional Klein-Kramers equation. For cells moving in nonequilibrium under chemotaxis, new data showed a breaking of FDR1 leading to a stochastic modeling in form of a suitably extended fractional Klein-Kramers equation. Further analysis of this data indicated the existence of anomalous work TFRs.

To better understand work TFRs in biological cell migration both theoretically and experimentally remains an important open problem. However, it might also be interesting to experimentally check for anomalous work TFR in case of a particle dragged through a highly viscous gel instead of through water [27], for the fluctuations of a driven pendulum in gel [101], for granular gases exhibiting subdiffusion [102], or for glassy systems [54, 61, 69]. On the theoretical side, the basic results reported in this chapter suggest to systematically check the remaining variety of conventional fluctuation relations [9, 10, 11] for anomalous generalizations.

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