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REVIEW

Models of anomalous diffusion in crowded environments

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A particle's motion in crowded environments often exhibits anomalous diffusion, whose nature depends on the situation at hand and is formalized within different physical models. Thus, such environments may contain traps, labyrinthine paths or macromolecular structures, which the particles may be attached to. Physical assumptions are translated into mathematical models which often come with nice mathematical instruments for their description, *e.g.* fractional diffusion equations. The beauty of the instrument sometimes seduces an investigator to use it without any connection to the physical model. The author hopes that the present discussion will reduce the danger of such inappropriate use.

1 Motivation

The progress in understanding the molecular nature of intracellular processes in the last years is astonishing, and is due to tight collaborations of physicists, biologists and mathematicians, all working in the same direction and using specific methods of their sciences. Experiments on particle motion in living cells and in biological and artificial membranes aimed on understanding of the effects of molecular crowding¹ have shown that the diffusion in such environments is often anomalous, *i.e.* it does not correspond to the particle's mean squared displacement growing linearly in time, $x^2(t) \propto t$, as predicted by Fick's theory of diffusion, but follows another power-law pattern $x^2(t) \propto t^\alpha$, with

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$\alpha \neq 1$.² Typically, the values of α are significantly smaller than unity, *i.e.* the observation unveils subdiffusion,^{3–12} see ref. 13 for a review of earlier work. Both experimental and theoretical effort were put into understanding the nature of this subdiffusion. On the experimental part, this effort was put in getting microscopic hints towards the nature of the process, while the work by theoretical physicists was aimed at providing simple models able to describe this anomaly and using them for explaining and predicting other properties of the systems: the kinetics of biochemical reactions, the efficiency of searching for the corresponding genes and their transcription, *etc.* One has also to stress important contributions of mathematical groups aimed at elaboration of statistical tests able to reliably distinguish between the predictions of different models when fitted to experimental data. This review concentrates on the basic properties of different theoretical models of anomalous subdiffusion, and discusses the main physical and mathematical assumptions behind them. Deep understanding of these assumptions is extremely valuable both for theorists and for experimentalists when building theories and analyzing the results. The main line of the discussion is therefore: what are the possible physical assumptions done to explain a particular situation (*i.e.* what is the physical model of the situation), how do these assumptions translate into a mathematical model, what are the mathematical instruments used for its implementation, and what are the results which allow us to corroborate or falsify our initial physical assumptions.

2 Normal diffusion

The phenomenological description of diffusion was pioneered by A. Fick in 1855 and was motivated by biological applications (transport through membranes).¹⁴ Starting from what we would call now a linear response theory (Fick's first law) and from the conservation law for the total particle number, he derived the diffusion equation (Fick's second law) for the concentration of diffusing species

$$\frac{\partial}{\partial t} n(x, t) = D \frac{\partial^2}{\partial x^2} n(x, t), \quad (1)$$

(we put it here in one dimension) with D being the diffusion coefficient. Fick also solved eqn (1) for several geometries of the system. The same equation holds for the probability density function (PDF) $p(x, t)$ to find a particle at position x at time t , with trivial replacement of n by p . The PDF of the positions of particles starting from a concentrated droplet in an unbounded medium is Gaussian with variance $2Dt$. Translated into the language of single particles, this means that the particle's mean squared displacement (MSD) in the x -direction grows proportional to time, $\langle x^2 \rangle = 2Dt$, and the coefficient of this proportionality is given by twice the diffusion coefficient D . The same is true for other coordinates, so that the total mean squared displacement grows as $\langle r^2 \rangle = 2dDt$ where d is the dimension of space. In the present review we will hardly discuss any other properties of motion than this MSD.

It was not until A. Einstein's work in 1905 (ref. 15) that the microscopic, molecular nature of diffusion was understood. Einstein's approach was essentially a random walk one. It started from sampling particle positions at discrete instants of time separated by intervals of duration τ_0 . The experimental realization of the quantitative stroboscopic measurements of displacements of Brownian particles performed by J. Perrin in 1908–1909 (ref. 16) and by Seddig in 1908 (ref. 17), see ref. 18 for a critical historical overview, corresponded exactly to this situation. Assuming displacements s_i during different τ_0 -intervals ("steps") to be independent random variables, Einstein gave the microscopic derivation of the diffusion equation and further connected the diffusion coefficient with other properties of the system. A year later, M. Smoluchowski gave a consistent mathematical picture of a random walk based on combinatorial arguments.¹⁹

Let us discuss how the known MSD behavior in diffusion emerges from such a model. The particle's displacement (in the x -direction) is given by the sum of the corresponding steps:

$$x(t) = \sum_{i=1}^{N(t)} s_i, \quad (2)$$

where $N(t)$ is the total number of steps performed up to the time t . From this picture we get

$$\langle x^2(t) \rangle = \left\langle \left(\sum_{i=1}^{N(t)} s_i \right)^2 \right\rangle = \sum_{i,j=1}^{N(t)} \langle s_i s_j \rangle = \sum_{i=1}^{N(t)} \langle s_i^2 \rangle + \sum_{\substack{i,j=1 \\ i \neq j}}^{N(t)} \langle s_i s_j \rangle \quad (3)$$

expressing the MSD in terms of the step–step correlation function $C_{ij} = \langle s_i s_j \rangle$. This is a discrete analogue of the Taylor²⁰ (or Green–Kubo^{21,22}) formula discussed below. Since the steps are assumed to be independent (and thus uncorrelated) and symmetrically distributed around zero, the last term in eqn (3) vanishes. The mean squared displacement in one step is $\langle s_i^2 \rangle = a^2$ and thus $\langle x^2(t) \rangle = \sum_{i=1}^{N(t)} \langle s_i^2 \rangle = N(t)a^2$. Since in our case each step takes time τ_0 for its completion we get

$$\langle x^2(t) \rangle = \frac{a^2}{\tau_0} t, \quad (4)$$

so that the diffusion coefficient is $D = a^2/2\tau_0$, where we further can identify $1/\tau_0 = k$ as a rate of steps, *i.e.* the mean number of steps per unit time.

Another approach was taken by P. Langevin in 1908.²³ This picture is seemingly very different from the previous one (but essentially is closely related to the former) and assumes that the particle moving in a fluid medium follows Newtonian mechanics under the influence of external forces and friction, where the impacts of thermal motion of the molecules of the surrounding medium are modeled *via* an additional random force term ("noise"). The equation for an instantaneous particle's velocity in the x -direction reads

$$m\dot{v} = -\gamma v + f + \xi(t) \quad (5)$$

where m is the particle's mass, γ is the friction coefficient and $\xi(t)$ is the random force discussed above. The deterministic external force f is added to describe possible other interactions and will be put to zero in what follows. From this equation Langevin was able to get the mean squared displacement of the particle presumably not using any additional information except for the equipartition theorem giving the mean squared velocity of the particle *via* $m\langle v^2 \rangle/2 = (1/2)k_B T$ (with k_B being the Boltzmann constant and T the temperature of the system). Using an overdamped variant of this equation (*i.e.* neglecting the inertial term) may lead to simpler theories applicable in strong friction regimes.²⁴ This regime corresponds to low Reynolds numbers characterizing the particles' motion in the fluid, and is typical for small objects at the cellular and subcellular scale, see *e.g.* the discussion in ref. 25.

To come from velocities to positions, we do not follow the initial approach by Langevin, which can hardly be generalized to anomalous situation, but an alternative one by Taylor,²⁰ leading to the Taylor (or Green–Kubo) formula for the diffusion coefficient. Since the particle's displacement during time t is given by the integral $x(t) = \int_0^t v(t') dt'$ (a continuous analogue of eqn (2)), its squared displacement follows from a double integral $x^2(t) = \left(\int_0^t v(t') dt' \right)^2 = \int_0^t \int_0^t v(t') v(t'') dt' dt''$. Averaging this over realizations of the process (*i.e.* over the ensemble of different diffusing particles) we get $\langle x^2(t) \rangle = \left\langle \left(\int_0^t v(t') dt' \right)^2 \right\rangle = \int_0^t \int_0^t \langle v(t') v(t'') \rangle dt' dt''$. This is the analogue of eqn (3). The averaged value of the product of velocities at two times $C_{vv}(t', t'') = \langle v(t') v(t'') \rangle$ is the velocity–velocity correlation function. Evidently, it is a symmetric function of its arguments $C_{vv}(t', t'') = C_{vv}(t'', t')$, and moreover $C_{vv}(t, t) = \langle v^2(t) \rangle$ is equal to the (ensemble) mean squared velocity of the particle at time t . Due to symmetry we can restrict integration to the domain $t'' > t'$ and double the result: $\langle x^2(t) \rangle = 2 \int_0^t \int_{t'}^t C_{vv}(t', t'') dt'' dt'$. We now change integration variable t'' to time lag $\tau = t'' - t'$:

$$\langle x^2(t) \rangle = 2 \int_0^t dt' \int_0^{t-t'} C_{vv}(t'; \tau) d\tau. \quad (6)$$

In the case when the velocity is given by the Langevin equation, $C_{vv}(t', t'')$ can be evaluated (see *e.g.* ref. 26) and reads $C_{vv}(t', t'') = \langle v^2 \rangle \exp\left[-\frac{\gamma}{m}(t - t'')\right]$ so that

$C_{vv}(t';\tau) = \langle v^2 \rangle \exp[-(\gamma/m)\tau]$ is a function only of τ and not of t' , which is characteristic for *processes with stationary increments*. For $t \gg \tau_{\text{corr}} = m/\gamma$ the internal integral converges to $\int_0^t C_{vv}(t';\tau) d\tau = \langle v^2 \rangle \tau_{\text{corr}}$, so that $\langle x^2(t) \rangle = 2\langle v^2 \rangle \tau_{\text{corr}} t$, which allows us to identify D .

3 Models of anomalous diffusion

The classical models by Einstein, Smoluchowski and Langevin correspond to the motion of a particle in a homogeneous, quiescent fluid, *i.e.* in a rather simple environment. The interior of the cell is however crowded, *i.e.* full of obstacles, binding sites, moving parts, active pumps and other intracellular machinery. Physicists, however, replace this complicated order by a simpler one or (if this doesn't work) by a disorder (*i.e.* by some kind of randomness) formulating a roughest possible ("minimal") model still reasonably describing the behavior found in experiment. We start from listing the most popular of these models always borrowed from other domains of physics where their applicability is well-established, see ref. 27.

3.1 Trap models and CTRW

One of the most popular mathematical models corresponds to continuous time random walks (CTRW), which are discussed in detail in a recent book.²⁸ In the previous picture by Einstein (and in experiments by Perrin closely following the scheme) the step duration τ_0 was not an intrinsic property of the process but either was introduced to simplify theoretical description or was a property of the data acquisition procedure. In many cases, however, the steps are real. For example if the motion is governed by a sequence of binding–unbinding events,²⁹ and the time spent in bound states is much larger than the one spent in the free motion, the step times are practically given by the sojourn times in the bound states ("traps"). Each step is now characterized by the corresponding waiting time and by the displacement in space preceding the next binding event. Assuming the steps in space still to be independent and taking different times τ_i for their completion gives rise to CTRW models, which are highly relevant for modeling many kinds of biological diffusion. In such schemes times τ_i follows some probability density $\psi(\tau)$. One often assumes different τ_i to be independent, and describes the whole process as a renewal one.²⁸ Even in the case when the renewal structure of the whole process is violated (as it is the case in one-dimensional random trap models, see the discussion in ref. 27 and 30 as a newer work), the non-correlated nature of increments in the corresponding process still plays a role, and the main properties of such processes are close to ones of CTRW, although the details may differ. If the waiting time density possesses the first moment $\tau_0 = \int_0^\infty \tau \psi(\tau) d\tau$, we still have on the average $\langle N(t) \rangle = t/\tau_0$ and our equation for the mean squared displacement, eqn (4), still holds. If this moment diverges, as it is the case for power-law distributions $\psi(\tau) \propto \tau^{-1-\alpha}$ with $0 < \alpha < 1$, we have $\langle N(t) \rangle \approx (t/t_c)^\alpha$, where t_c is some characteristic time, and the whole process is slower than diffusion, $\langle x^2(t) \rangle = a^2 \langle N(t) \rangle \propto a^2 t^\alpha / t_c^\alpha$, *i.e.* is subdiffusive.^{28,31,32} The rate of steps, which was constant in normal diffusion, decays now as $k(t) \approx t^{\alpha-1}/t_c^\alpha$.

To obtain the mean number of steps, one can note that $\langle N(t) \rangle = \sum_{n=0}^\infty n \chi_n(t)$ where $\chi_n(t)$ is the probability to make exactly n steps up to the time t . The probability to make no steps

is given by $\chi_0 = 1 - \int_0^t \psi(\tau) d\tau$, and all other $\chi_n(t)$ are obtained iteratively by $\chi_n(t) = \int_0^t \psi(\tau) \chi_{n-1}(t-\tau) d\tau$. The easiest way to perform the calculations is to pass to the Laplace domain.²⁸

We note that the number of steps $N(t)$ may be considered as an internal, operational time of a walker, and this is a random but non-decaying function of the clock time t . In this situation the mathematicians speak about subordination of random processes.²⁸ The traps leading to binding events can have an energetic (binding sites) or geometrical nature: a nice exactly solvable conceptual model is given by a comb,³³ see Fig. 1. If the motion along the comb's spine (*i.e.* along the x -direction) is considered, the walk in a dangling end (tooth of the comb) corresponds to trapping: the trapping event finishes when the particle returns to the spine's site. This geometrical trapping is exactly of a kind which is relevant *e.g.* for the description of particle transport in Purkinje cells:^{34–36} here the realistic models are only slightly more complex. Since in many cases traps can be identified in independent experiments, trapping models (and CTRW as their mathematical counterpart) are reasonable candidates for explanation of diffusion anomalies. We also note that processes more complex than a CTRW (a simple random walk interrupted by rests), *e.g.* Lévy flights interrupted by rests, Lévy walks *etc.*, were considered in detail and applied to different situations, especially the ones showing superdiffusion, see ref. 28 and references therein.

An additional appealing property of CTRWs is the existence of an elegant mathematical tool for its description within the fractional diffusion equations^{32,37} (FDEs), *e.g.* of the type

$$\frac{\partial^\alpha}{\partial t^\alpha} P = D_\alpha \frac{\partial^2}{\partial x^2} P, \quad (7)$$

i.e. the equations where the first-order temporal derivative in eqn (1) is changed for an appropriately defined non-integral

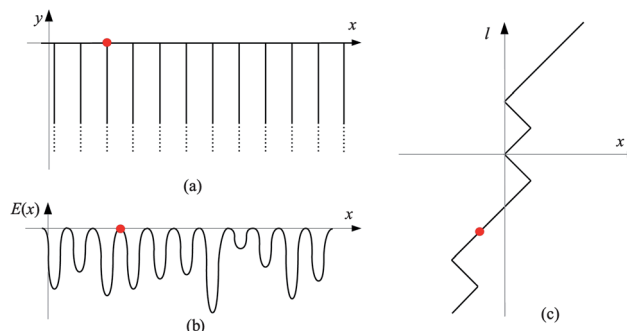


Fig. 1 Panels (a) and (b) illustrate two variants of trapping models in one dimension: a Havlin–Weiss comb model with infinitely long teeth, and the model with traps corresponding to potential wells. Note that the standard situation in (a) corresponds to the case when a particle starts on a spine of the comb. In the course of time particles find their way deeper and deeper into the teeth, and the system ages. In (b) aging corresponds to finding a deeper and deeper trap in the course of time. Panel (c) represents the Kutner–Kehr model, corresponding to the random walk on a random walk (RWRW). The model gives rise to exactly the same distribution of the particle's displacements as the comb one (*i.e.* is its "twin"), but differs in many other respects. The system, for example, does not age: the behavior is on the average the same wherever (and therefore—whenever) one starts.

order one, an integro-differential operator with nice mathematical properties, with D_α being the generalized diffusion coefficient.

Let us note that the regime of the anomalous diffusion persists indefinitely (in an unbounded medium) only if the mean waiting time for a step diverges, *i.e.* when the corresponding waiting times are not bounded from above. In our initial models this implies an infinite hierarchy of binding energies⁸ or a presence of indefinitely long dangling ends. In the case of finite hierarchies (as it is always the case in real systems) the final regime will be normal diffusion⁸ with the diffusion coefficient governed by the sojourn time in the deepest traps, and the anomalous regime appears as a transient describing the crossover between the short-time behavior and the long-time diffusion with small enough terminal diffusion coefficient.³⁸ If this regime is long enough one may speak about an *intermediate asymptotic behavior* over a finite time domain;³⁹ in our models we abstract from this fact, and consider the regime as a true asymptotic behavior. Experimentally it is however not always easy to distinguish between the intermediate asymptotic regime of anomalous diffusion and crossovers appearing for other reasons, especially if the data cover only a couple of orders of magnitude in time. Such a distinction may be achieved by performing different, independent experiments aimed at elucidation of the nature of behavior, as discussed in.⁴⁰ The same reservation has to be made in the cases corresponding to other models of anomalous diffusion.⁴¹

3.2 Labyrinthine environments

Another class of models corresponds to motion in labyrinthine environments.† Imagine that the crowded interior of the cell only left narrow, tortuous channels, in which the motion is possible. One of the examples of such a structure is an incipient percolation cluster.⁴² A labyrinthine model does not have to be percolation at all, and can be another fractal system, *i.e.* the one showing scale invariance and no translational symmetry. The nature of anomalous diffusion in percolation systems is well understood, and is common for many other labyrinthine models⁴² which can be quite realistic in many cases.^{12,43–45} Labyrinthine models are often invoked for explanation of anomalous diffusion in crowded systems and are eagerly simulated. Relatively low popularity of such models among “pure” theorists working on cellular diffusion is due to the fact that there are no closed equations which allow for the back-of-an-envelope exact solution. A rare example of an exactly solvable labyrinthine model is a random walk on a random walk (RWRW) by Kutner and Kehr,⁴⁶ Fig. 1, playing in this case the same role of a simply understandable conceptual model that the comb one plays for trapping. The interesting property of RWRW and of a comb is that they are “twins”, *i.e.* share the same PDF in an unbounded domain (which stresses the fact that the PDF is the least interesting property of the process), but are different in many other respects.⁴⁷ Thus, while the PDF in the RWRW model in an unbounded domain may be considered as given by the same FDE as for a comb, the solutions to FDE in bounded domains, which

give correct first passage times and other characteristics for a comb model, fail to reproduce the RWRW behavior.

3.3 Viscoelastic systems

The first two classes of models correspond to a single particle which moves in a fixed potential landscape which is either rough (in genuine trap models with energetic disorder) or consists of flat valleys surrounded by high ridges (in labyrinthine ones). Another class of models corresponds to the case when the tagged particle is part of a complex interacting system showing viscoelastic behavior,^{48,49} so that the motion of the system’s parts has to take place in a concerted way, as it is the case when the particle considered is part of a polymer molecule or of a polymer network. The corresponding situation physically seems to be much more involved than previously considered two classes, but it is often simpler to describe. In many cases the adequate description is given by a mathematical model called fractional Brownian motion (fBm), which we discuss in Section 5, a Gaussian process whose correlation properties are chosen to mimic the situation at hand.

An instrument of choice here are the generalized Langevin equations (GLEs) where the friction term now contains an integral expression describing intrinsic memory of the environment, for example,⁵⁰ see also ref. 51 and 52 where the instrument is used to describe subdiffusion within a single protein molecule (as an alternative to trapping assumptions^{53,54}),

$$m\dot{v} = -\gamma \int_0^t \Gamma(t-t')v(t')dt' + f + \xi(t) \quad (8)$$

with the power-law kernel $\Gamma(t) \propto t^{-\beta}$, and with the Gaussian noise $\xi(t)$ which may or may not (depending on the exact setting) satisfy the fluctuation–dissipation theorem $\langle \xi(t)\xi(t') \rangle = k_B T \Gamma(t-t')$. Such equations appear quite naturally when reducing the Markovian multiparticle dynamics of a complex system to the behavior of few relevant coordinates,²⁶ but often are simply postulated as a reasonable phenomenological description. The exact relation between the memory exponent β and the one of the anomalous diffusion α depends on our assumptions about the noise. Also overdamped variants of such equations are in use: these ones follow closely the fBm model, which otherwise appears only as a long time limit of the GLE, *c.f.* ref. 50. Interestingly enough, multiparticle viscoelastic models share many common properties with labyrinthine ones, and indeed the Rouse model of a polymer (or a single-file diffusion model) is a close relative of the RWRW, which was introduced as a quenched model thereof, see Fig. 2. Both these classes have much more in common than each of them has with trap models.

3.4 Time-dependent diffusion coefficient

Yet another popular model has to be mentioned; this is essentially not a physical model but a fitting means. It has to be taken seriously because it is often used. If the experimental curves, *e.g.* the ones from FRAP (fluorescence recovery after photobleaching), cannot be fitted by expressions obtained by solving a diffusion equation with a constant diffusion coefficient D , one assumes that the effective diffusion coefficient depends on the

† The expression “labyrinthine environment” stems from Katja Lindenberg.

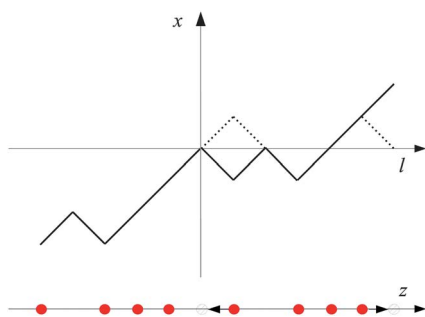


Fig. 2 Upper panel: the kink-jump (Orwoll–Stockmeyer) lattice model of polymer dynamics, here in one dimension. The allowed motions correspond to jumps (in 1d: flipping) of the kinks of the chain bringing the monomer performing the move to one of the allowed sites on the lattice. The monomers at the ends can always jump. A kink allowed to move is chosen at random at each time step. The monomer at a position corresponding to a long rectilinear segment without kinks cannot move. The configurations resulting from flipping are shown by dotted lines. At longer times the model leads to Rouse dynamics. Note that the RWRW model (c) in Fig. 1 corresponds to a situation when only one kink is allowed to move, while the rest of the configuration is frozen. Lower panel: a lattice model of a single file diffusion. At each time step, a particle, chosen at random, can move to a neighboring site, if it is empty. The model is equivalent to the previous one (but the observable differs: note that the coordinate z of the particle corresponds to the contour length variable l , not to the coordinate x of a monomer). To see the equivalence, associate the empty site in the lower picture with the bond showing down in the upper picture. The site occupied by a particle corresponds to a bond showing up. Allowed moves (shown by arrows) are associated with flipping the kinks or moving the end monomers.

time scale, and tries to fit the data using essentially the same expressions now containing a time-dependent diffusion coefficient $D(t)$ instead.⁴⁵ One often finds that at longer times $D(t)$ decays as a power-law $D(t) \propto t^{\alpha-1}$. Although the displacement PDF in this model is exactly the same as in the fBm (which it is often and erroneously used as a model of), the models have little in common except for this PDF,⁵⁵ *i.e.* the two models are also “twins”. Essentially, the $D(t)$ -model (“scaled Brownian motion”, sBm) is a close relative of CTRW.

4 Normal and anomalous diffusion

The discussion pertinent to this section can be conducted using the discrete-time random walk picture, or the CTRW picture, both based on steps, or using continuous picture based on velocities (parallel to the Langevin’s). The details of the discussion differ depending on what of three pictures is accepted, but the results are the same, and the translation between the pictures is possible at any time. In the discrete random walk description we start from eqn (3); now however we do not assume steps to be independent anymore. The CTRW case can either be translated into the discrete time picture, where the τ_0 -intervals in which no displacement takes place are assigned $s_i = 0$, and only the intervals containing jumps are assigned nonzero jump lengths, or considered as it is, *i.e.* with independent steps following at random times. Note that although in the first picture the displacements in different steps for the CTRW with power-law waiting times are no more independent (it is easy to show that the

zero displacement follows with the higher probability after another zero one) they are still uncorrelated, $\langle s_i s_j \rangle = 0$ for $i \neq j$. The continuous (Taylor–Kubo) description follows when considering the limiting case of the step description for $\tau_0 \rightarrow 0$ (and abandoning the request that different steps have to be independent). In our discussion here we adopt the velocity description of the motion which is always a correct microscopic description, and translate the results into the language of steps at the end of the section. We restart from our eqn (6):

$$\langle x^2(t) \rangle = 2 \int_0^t dt' \int_0^{t-t'} C_{vv}(t'; \tau) d\tau \quad (9)$$

For a particle in a contact with equilibrium bath, like discussed in Section 2, and for other processes with stationary increments $C_{vv}(t'; \tau)$ depends only on the time lag and not on the initial time t' , since the properties of the system do not change. If the dependence on t does not vanish, there are some physical changes in the system (*e.g.* aging). Then the velocity is given by a non-stationary random process and the coordinate is not a process with stationary increments.

Let us now consider the integral $I(t-t', t') = \int_0^{t-t'} C_{vv}(t'; \tau) d\tau$. In processes with stationary increments the dependence of $C_{vv}(t'; \tau)$ on t' is suppressed so that $I(t) = \int_0^t C_{vv}(\tau) d\tau$ depends only on the upper limit of integration. If this integral tends to a finite value $D = \lim_{t \rightarrow \infty} I(t)$, then

$$\langle x^2(t) \rangle = 2 \int_0^t dt' I(t-t') \rightarrow 2Dt, \quad (10)$$

and we have to do with normal diffusion with $D = \int_0^\infty C_{vv}(\tau) d\tau$. If we take $C_{vv}(\tau) = \langle v^2 \rangle f(\tau)$ (where $f(\tau) = C_{vv}(\tau)/C_{vv}(0) \equiv C_{vv}(\tau)/\langle v^2 \rangle$) then $D = \langle v^2 \rangle \tau_{\text{corr}}$ where $\tau_{\text{corr}} = \int_0^\infty f(\tau) d\tau$ is the correlation time of the process. If the corresponding $\lim_{t \rightarrow \infty} I(t)$ diverges (*i.e.* $\langle x^2(t) \rangle$ grows faster than the first power of time), one has to do with superdiffusion. Since this corresponds to $\tau_{\text{corr}} \rightarrow \infty$, the process is strongly *persistent*. Such persistence⁵⁶ leads for example to the fact that diffusion behavior in model two-dimensional fluids differs strongly from the prediction of the Einstein’s and Langevin’s approaches, as first observed in ref. 57 and 58. If the corresponding limit vanishes, we have to do with subdiffusion. Note that since $C_{vv}(0) = \langle v^2 \rangle > 0$ and since $C_{vv}(\tau)$ is typically a continuous function of τ , it has to change sign at least once in order to get the integral vanishing. This means that a period of motion, say, with positive velocity is typically followed by a period of motion with negative velocity, and the motion is *antipersistent*.^{59,60} We note that C_{vv} is amenable to direct measurements.⁹ Both the motion of a monomer in a polymer chain, and the motion of a particle in a labyrinth are antipersistent, albeit on different reasons: in the first case, the monomer trying to go too far is pulled back by its neighbors, in the other case, the particle encountering a wall has to return, and makes a step in the opposite direction.

Although one can formally define the time-dependent diffusion coefficient to match the behavior of $\langle x^2(t) \rangle$ in eqn (10) by taking $D(t) = \frac{d}{dt} \langle x^2(t) \rangle$, the usefulness of such a quantity is quite restricted on the reasons discussed at the end of Section 6.1.

Let us now consider the case when the velocity process is not stationary, and $C_{vv}(t';\tau)$ depends on its both arguments. It can happen, that the limit $t \rightarrow \infty$ of the integral $D(t') = \int_0^t C_{vv}(t', \tau) d\tau$ converges for any particular t' , but depends on this t' . In this case we may have to do with a truly time-dependent diffusion coefficient $D(t')$, and our eqn (10) now is changed for $\langle x^2(t) \rangle = 2 \int_0^t D(t') dt'$ (note that the process doesn't yet have to be a simple Fickian diffusion). Vanishing of the corresponding $D(t)$ at long times leads to subdiffusion, its divergence to a superdiffusive behavior. The nature of these sub- and superdiffusive processes is however vastly different from the ones previously discussed.

The translation between the continuous picture and fixed-time random walk follows by changing integrals for corresponding sums and velocity–velocity correlation functions for step–step ones. We see that for antipersistent random walks the steps in one direction are typically followed by the steps in the opposite one, while in CTRW-like situations steps are uncorrelated, and either the mean squared step length, or stepping rate, or both, change with time.

5 Position–position correlation function

Let us now concentrate on the particle's position. The MSD from the initial position gives us only the minimum of information on the diffusive properties. More information is given by the position–position correlation function at two different times t and s :

$$\phi(t, s) = \langle x(t)x(s) \rangle \quad (11)$$

with $\langle x^2(t) \rangle = \phi(t, t)$. From this the MSD during some time interval follows:

$$\langle [x(t) - x(s)]^2 \rangle = \langle x^2(t) \rangle + \langle x^2(s) \rangle - 2\phi(t, s). \quad (12)$$

Thus, the position–position correlation function contains information on MSD during time intervals not starting at $t = 0$. For processes with stationary increments $\langle [x(t) - x(s)]^2 \rangle = \langle x^2(t - s) \rangle$ and therefore

$$\phi(t, s) = \frac{1}{2} [\langle x^2(t) \rangle + \langle x^2(s) \rangle - \langle x^2(t - s) \rangle]. \quad (13)$$

If the corresponding process belongs to the class of anomalous diffusions, then

$$\langle [x(t) - x(s)]^2 \rangle = \langle x^2(t - s) \rangle = K(t - s)^\alpha \quad (14)$$

with K being some constant (we assume $t > s$). The celebrated fractional Brownian motion (fBm) model of Mandelbrot and van Ness⁶¹ (essentially introduced by Kolmogorov in 1940 (ref. 62)) is exactly the model of this class. Taking $\langle x^2(t) \rangle = Kt^\alpha$ and $\langle [x(t) - x(s)]^2 \rangle$ as given by eqn (14) we get

$$\phi(t, s) = \frac{K}{2} (t^\alpha + s^\alpha - |t - s|^\alpha). \quad (15)$$

In addition the model assumes that the PDF of displacements is Gaussian. There are at least two physical models generating such kind of behavior: the single file diffusion and the Rouse model of a polymer chain,⁶³ both corresponding to $\alpha = 1/2$. Of course, as always in physical systems, the behavior is bounded to

a finite time domain which (in the case of the polymer) stretches between the time of the order of the time a monomer needs to diffuse over the Kuhn's length of the chain and the time the chain as a whole needs to diffuse over its own size. Since these two are separated by a factor of the order of N^2 (where N is the number of monomers in the chain) this time domain can be very large. We note that single file diffusion (self-diffusion of particles organized in one-dimensional arrays, where individual particles are not allowed to change the order of their arrangement) is a relevant model for description of experimental findings in zeolites⁶⁴ and other nanoporous systems and as such has also found much theoretical attention, see *e.g.* ref. 65–67. The single-file models may explain some properties of conductivity in ion channels.^{68,69} The behavior of subdiffusion as an intermediate asymptotic regime in single file systems is discussed in:⁷⁰ the crossover time to terminal normal diffusion grows proportionally to the square of the channel's length.

The popularity of Gaussian models in the physical community is partly due to the fact that Gaussian distributions appear universally when considering fluctuations of extensive thermodynamical variables in situations close to equilibrium. In the case of diffusion, the variable we are looking at is not an extensive thermodynamical one, there is no special reason for it to be Gaussian, and realistic situations can be quite involved, see *e.g.* ref. 71 and 72 for the simulation of the intramolecular diffusion in peptides. However, the exact form of the PDF (*i.e.* higher moments) seldom plays a role in applications, and a Gaussian approximation (*i.e.* using fBm as a model) can be quite safe.

Let us now consider a process whose increments in the forthcoming time intervals are not correlated with ones at previous ones (as it is the case in CTRW). Taking $t > s$ we can put $\phi(t, s) = \langle x(t)x(s) \rangle = \langle [x(s) + \Delta x(s, t - s)]x(s) \rangle$ where $\Delta x(s, t - s)$ is the displacement of particle during the time interval of duration $t - s$ starting at s . The mean $\langle \Delta x(s, t - s)x(s) \rangle$ vanishes because the increments at times which are larger than s are symmetrically distributed and uncorrelated with those comprising $x(s)$, so that $\phi(t, s) = \langle x(t)x(s) \rangle = \langle x^2(s) \rangle$ and therefore

$$\langle [x(t) - x(s)]^2 \rangle = \langle x^2(t) \rangle + \langle x^2(s) \rangle - 2\langle x^2(s) \rangle = \langle x^2(t) \rangle - \langle x^2(s) \rangle. \quad (16)$$

For $\langle x^2(t) \rangle = Kt^\alpha$ we get

$$\langle [x(t) - x(s)]^2 \rangle = K(t^\alpha - s^\alpha). \quad (17)$$

Note that the only case when two equations, eqn (14) and (17), are fulfilled simultaneously corresponds to $\alpha = 1$, *i.e.* to normal diffusion.

6 Aging and ergodicity breaking

6.1 Aging

Let us assume that our system was prepared in its present state at some time t_0 , while our measurement started at some later instant of time. For example, in the experiments on dispersive transport in disordered semiconductors which served as a motivation for formulating the CTRW scheme with power-law waiting times,⁷³ charge carriers were absent in the system before they were created by the light flash, and therefore the time t_0 was well-defined.

Whenever we start our measurement on a process with stationary increments, the result of this measurement only depends on the time-lag between the measurement points. There is no chance, performing a measurement in a time interval between t_1 and t_2 to tell, what was the time instant t_0 when the system was prepared:

$$\langle [x(t_2 - t_0) - x(t_1 - t_0)]^2 \rangle = \langle x^2(t_2 - t_0 - t_1 + t_0) \rangle = K(t_2 - t_1)^\alpha. \quad (18)$$

Therefore our process possesses no *age* (and, respectively, does not age). In the case of a process with uncorrelated increments different from simple diffusion the situation is vastly different. Let our measurement start at time t_1 and monitor the mean squared displacement for different t_2 :

$$\langle [x(t_2 - t_0) - x(t_1 - t_0)]^2 \rangle = K[(t_2 - t_0)^\alpha - (t_1 - t_0)^\alpha]. \quad (19)$$

If enough data points are collected, we can estimate all parameters of the motion including t_0 , (as long as $\alpha \neq 1$, in which case the dependence on t_0 cancels out), *i.e.* obtain the age of the system. In this case, the process possesses age and continuously ages.

The corresponding behavior can be expressed as a function of the age of the system at the beginning of observation $t_a = t_1 - t_0$ and of the observation time $t_{\text{obs}} = t_2 - t_a$:

$$\langle x^2(t_{\text{obs}}, t_a) \rangle = K[(t_{\text{obs}} + t_1)^\alpha - t_a^\alpha] = K t_a^\alpha \left[\left(\frac{t_{\text{obs}}}{t_a} + 1 \right)^\alpha - 1 \right]. \quad (20)$$

The dependence on t_{obs} (for fixed t_a) is described by the dimensionless scaled variable $\theta = t_{\text{obs}}/t_a$ and corresponds to a *pure*, or *full* aging. Also more complicated forms of aging are known (in different models, *e.g.* for a one-dimensional trap model^{76,77}): if one can represent the data as a function of $\theta = t_{\text{obs}}/t_a^\mu$ with $\mu \neq 1$ one speaks about subaging if $\mu < 1$ and about superaging if $\mu > 1$.

Note that if $t_{\text{obs}} \ll t_a$, we can expand the expression in brackets in eqn (20), and see that in this case

$$\langle x^2(t_{\text{obs}}, t_a) \rangle \approx K \alpha t_a^{\alpha-1} t_{\text{obs}}, \quad (21)$$

i.e. it grows proportionally to the observation time and therefore exhibits *apparently normal diffusion* with an age-dependent diffusion coefficient.^{74,75}

6.2 Moving time averages

The linear growth of the mean squared displacement at observation times smaller than aging time leads to another property of systems exhibiting ongoing aging: the discrepancy between the ensemble means and the moving-time averages over a single long trajectory given by

$$\langle x^2(t) \rangle_{\text{MTA}} = \frac{1}{T-t} \int_0^{T-t} [x(t'+t) - x(t')]^2 dt'. \quad (22)$$

Since in CTRW and related models such an average still may not converge to a sharp value even for $T \rightarrow \infty$ (which in fact will

be discussed in Section 6.4), theoretically it is easier to discuss a double average over the time and over the ensemble of different trajectories,

$$\langle \langle x^2(t) \rangle \rangle = \frac{1}{T-t} \int_0^{T-t} \langle [x(t'+t) - x(t')]^2 dt' \rangle, \quad (23)$$

which then goes as

$$\langle \langle x^2(t) \rangle \rangle \propto T^{\alpha-1} t, \quad (24)$$

i.e. again shows *normal diffusion*.^{78,79} The strong discrepancy between the ensemble and moving time averages (implying non-ergodicity of such systems) may serve as a test which allows us to distinguish between the trap models and models with stationary increments, as labyrinthine and viscoelastic ones.⁸⁰ Other tests of ergodicity,⁸¹ or tests for temporal homogeneity (like the p -variation test⁸²) can also reliably serve the purpose on the single trajectory level.^{83,84} In ref. 85 the p -variation test reliably distinguished between the predictions of CTRW and fBm, but was not able to discriminate between the fBm and GLE models fitted to data.

One can also have to do with more complex situations, *e.g.* when a particle moves in a percolation structure, or in a tortuous channel, or is a part of the large molecule, and may get trapped. Such situations lead to subdiffusion of mixed origins,⁸⁶ which are indeed observed experimentally.⁸⁷⁻⁸⁹ In this case the MSD in aged diffusion or in the moving-time (or double) average does not have to follow a normal diffusion pattern, but there are still large discrepancies between the behavior of the “young” and the aged system or between the ensemble and the moving-time averages, and the test based on the comparison of the both is still decisive.

Note, that if we take seriously a model of diffusion with time-dependent diffusion coefficient, $D(t) \propto (t - t_0)^{\alpha-1}$, with

$$\frac{\partial p}{\partial t} = D(t) \frac{\partial^2 p}{\partial t^2} \quad (25)$$

and calculate the mean squared displacement in the interval between t_1 and t_2 , we get exactly eqn (17), and both its consequences, eqn (21) and (24) still hold. This is a reason why using the time-dependent diffusion coefficient may give an adequate description for a process with uncorrelated increments, but is not safe for the one with stationary ones. Indeed, the model based on the diffusion equation with time dependent diffusion coefficient, eqn (25) is a close relative of CTRW but not of fBm or of diffusion on a percolation cluster. It can be considered as a Gaussian approximation for CTRW, and its nature as a mean-field CTRW model gets evident, if we consider a cloud of random walkers performing traditional CTRW, and concentrate on the behavior of its center of mass (*i.e.* on the average position over many walkers starting all in the same place but having different step times and directions): this one is exactly described by eqn (25). We note that both CTRW and sBm models can be considered as models subordinated to normal Brownian motion (*i.e.* obtained *via* time transformation of such a motion). In CTRW this time transformation is random, while in sBm it is given by a deterministic function, which describes the decaying rate of steps.

6.3 Aging and equilibration

So far we discussed the mathematical roots of aging. Let us discuss physics behind it. A single particle (a point mass with three degrees of freedom) can neither be in nor out of equilibrium with its environment constituting a heat bath: the notion of thermodynamical equilibrium implies a large system or an ensemble of small ones. In the last case it is a statistical distribution in the ensemble which may (or may not) be in equilibrium with the bath. The situation is the same if the state of the bath is not an equilibrium but a stationary one (with the only unpleasant difference that we often do not know, what set of macroscopic variables is sufficient to characterize it).

With this respect, two kinds of experiments on diffusion have to be distinguished. An experiment of the first type starts at $t = t_0$ with placing a particle into the system, and then following it with our measurement appliance. Another experiment corresponds to a different situation: the system was prepared long ago, and we tag particles already preexisting in the system. In this case the initial particle positions are sampled with probabilities they would have in an equilibrium (or stationary) or at least in a strongly aged state. While this second situation corresponds to the behavior in the vicinity of equilibrium (or stationary) state, the first one may or may not be close to equilibrium (or stationary) depending on how far the equilibrium distribution in the system is from the one corresponding to the (typically only poorly controlled) initial one.

Physical models showing aging start far from equilibrium or stationarity: in the potential trap model the homogeneous distribution of initial positions does not correspond to the Boltzmann distribution over traps of different depth which is an equilibrium one. In the diffusion on a comb, starting on a spine (as is assumed in the standard model) does not correspond to equilibrium, in which case most of the particles sit in the teeth. After equilibration, the anomalous diffusion in the system either comes to a halt (all particles sitting in deepest traps, or getting lost in the teeth) or crosses over to the normal one (if the depth of the traps is bounded, or the length of the teeth is finite). On the contrary, considering the particle's diffusion on the infinite cluster of the percolation system, we see that its initial homogeneous distribution over the cluster corresponds to the equilibrium distribution, and no aging is possible. This physical reason for aging as resulting from starting extremely far from the equilibrium is not obvious when only considering reduced models (*e.g.* renewal CTRW, where it is mirrored by the deviance of the waiting time distribution for the first step from all other waiting time densities²⁸), but can be easily understood when redoing the corresponding derivations (*e.g.* starting from the time-dependent rate model of ref. 90 or ref. 91) leading from the physical to the mathematical model.

If our system is close to equilibrium or stationarity, *i.e.* if we have waited long enough before starting the measurement, or have censored a considerable part of our numerical trajectory, it is highly improbable that the diffusion anomalies are solely due to traps and can be adequately captured by CTRW models. Using fractional diffusion equations for data fitting in this case is not physically motivated. The reason for anomaly in the case must lay in the existence of some underlying (subordinated) process with stationary increments (diffusion on a fractal,

viscoelastic motion, *etc.*), although its properties might be modified by the existence of traps, leading to the subdiffusion of mixed origins.

6.4 Lack of self-averaging

There is another consequence of the (weak) ergodicity breaking in CTRW-like systems connected with their time-inhomogeneity.⁹² A single (however long) trajectory of a CTRW even confined to a small domain does not fill this domain homogeneously; the homogeneity only appears on the average. Here situations in which CTRW is an exact model (like for a comb) and in which CTRW appear when averaging over many realizations of the random potential, differ. In the last case this inhomogeneous distribution essentially mimics the strongly inhomogeneous Boltzmann distributions in different realizations of traps.⁹³ CTRWs in finite domains possess many other quite peculiar properties, see *e.g.* ref. 95 and 96 which we do not consider here in detail.

If not confined, each of the trajectories leads to its own value of the effective diffusion coefficient obtained *via* a moving-time averaging procedure, eqn (22), and these values do not converge to a single, sharp value even in the limit of infinitely long trajectories^{78,79} (as also observed experimentally⁹⁴), but the *probability distribution* of diffusivities tends to a universal form. Therefore, CTRW models exhibit universal fluctuation behavior. A similar lack of self-averaging and strong fluctuations (now not connected with non-stationarity, *i.e.* lack of translational invariance in time, but with the lack of translational invariance in space) can be observed in labyrinthine systems:⁴⁵ here different realizations of the structure (or behaviors of trajectories starting at distant points of the same structure) may be strongly different; also more involved situations are observed.⁹⁷ On the other hand, the fBm and the sBm models do not lead to large and universal fluctuations (although in the fBm case the convergence can be rather slow⁹⁸). Fractional Brownian motion is not a good candidate model if experiments hint towards strong inhomogeneity of data.

7 Summary

Let us summarize our discussion. A particle's motion in crowded cellular environments often exhibits anomalous diffusion. The nature of this anomaly can differ for different types of particles and cells, and for different experimental conditions. The assumptions on this nature give rise to different physical models: thus the environments in which the motion takes place may contain trapping sites, labyrinthine paths, or maybe viscoelastic structures which the particles observed are attached to. Each of these physical assumptions can be translated into a mathematical model by assuming some additional details, abstracting from some other ones, or by releasing some physical restrictions (*e.g.* assuming that a process which is observed in a confined time window may proceed indefinitely). Thus, trapping under corresponding conditions can be mapped on continuous time random walks, a general labyrinthine structure can be modeled by Bernoulli percolation, and the motion of a monomer in a polymer chain be approximated by a fractional Brownian motion. Some mathematical models come with nice mathematical instruments

for their description (CTRW with fractional diffusion equations, fBm with fractional Langevin ones). The beauty of the instrument sometimes seduces an investigator to use it without any connection to the corresponding mathematical model, let alone the physical one. The author hopes that a discussion above will reduce the danger of such inappropriate use.

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