Superdiffusion in a Model for Diffusion in a Molecularly Crowded Environment

Dietrich Stauffer · Christian Schulze ·
Dieter W. Heermann

Received: 11 June 2007 / Accepted: 9 April 2008 / Published online: 6 June 2008
© Springer Science + Business Media B.V. 2008

Abstract We present a model for diffusion in a molecularly crowded environment. The model consists of random barriers in a percolation network. Random walks in the presence of slowly moving barriers show normal diffusion for long times but anomalous diffusion at intermediate times. The effective exponents for square distance vs time usually are below one at these intermediate times, but they can also be larger than one for high barrier concentrations. Thus, we observe sub- and superdiffusion in a crowded environment.

Keywords Anomalous diffusion · Effective exponents · Random walk

1 Introduction

One of the important issues in biology is to understand how diffusion is affected by the environment. This understanding is needed to correctly describe passive intracellular transport, as this process may regulate important cellular properties: signal transduction [1], gene transcription [2], reaction kinetics [3], and regulation of cell polarization [4].

The interior of biological cells [5] represents a very dense and crowded environment with a specific molecular mobility. Intracellular diffusion is hindered by barriers consisting of large molecules, sometimes even immobile, tethered large molecules, and binding and collisional interactions. One way of interpreting such a system is to view it as a disordered

D. Stauffer · C. Schulze
Institut für Theoretische Physik, Universität zu Köln,
50923 Köln, Germany

D. Stauffer
e-mail: stauffer@thp.uni-koeln.de

D. W. Heermann (✉)
Institut für Theoretische Physik, Universität Heidelberg,
Philosophenweg 19, 69120 Heidelberg, Germany
e-mail: heermann@tphys.uni-heidelberg.de

system. In general, for random walks [6] in media with disordered microscopic substructures, one expects anomalous diffusion [7–9] where the mean-square displacement $\langle \Delta \mathbf{r}(t)^2 \rangle$ is no longer proportional to the time t :

$$\langle \Delta \mathbf{r}(t)^2 \rangle = C_\alpha t^\alpha \quad (1)$$

with $C_\alpha > 0$. If $0 < \alpha < 1$, then we call the diffusion subdiffusive, and, if $\alpha > 1$, superdiffusive; normal diffusion has $\alpha = 1$. In biological systems, as well as in models of biological systems, so far, only subdiffusive behavior has been observed [9, 10], except if the transport is facilitated or restricted. For example, if the diffusion is directed by a motor protein, nonrandom superdiffusion can be observed, but not for free diffusion. However, superdiffusion has been observed in a two-dimensional complex plasma [11] and in two-dimensional Yukawa liquids [12]. Thus, superdiffusion does exist and its existence in the cell needs to be discussed.

Subdiffusion occurs if the mobility of a diffusing particle or molecule is impaired by obstacles (mobile and immobile) or attractive forces. Under these premises, it seems unlikely to find superdiffusion.

From a physical point of view, the disorder in the cell has a characteristic time scale. If the diffusing particle has diffused long enough such that the time scale has been explored, one expects normal diffusion [10]. If there is no characteristic time (in fractal media), then the diffusion is always anomalous [7]. However, this picture does not take into account the (im)mobility, collision, attractive forces, etc. To study the effects produced by immobile and mobile barriers, we have developed a model mimicking the molecularly crowded environment with mobile and immobile barriers, taking into account particular length scales.

2 The Model

In percolation theory [13], each site on a large lattice is randomly either occupied, with probability p , or empty, with probability $1 - p$. For percolative diffusion, a random walk starts on an occupied site, and then, at each time step, randomly selects a direction to move to. It moves one distance unit (lattice constant) in this direction if that selected neighbor site is occupied. Empty sites are prohibited for the walker. For $p < p_c$, the walk can extend only over the finite cluster in which it started, while for $p > p_c$, it can diffuse towards infinity if it started on the infinite cluster. At $p = p_c$, anomalous diffusion takes place with a mean square distance increasing to infinity, but with an exponent $\alpha < 1$ [13].

In biological applications, the prohibited sites may be more or less mobile biomolecules. Their effect can be taken into account approximately by also assuming that a prohibited site i allows the walker to move through it, with some probability q_i . The reciprocal probability $1/q_i$ then can be interpreted as the lifetime of the barrier, in the sense that about once during that lifetime the barrier moves away for one time step before returning to that site. Thus, we still have quenched disorder; with annealed disorder, where all lifetimes are the same, we have normal diffusion, with squared distance proportional to time, and with a diffusivity reduced by the (slowly) moving barriers. We now assume that the probability distribution function $f(q)$ for the q_i is a power law,

$$f(q) \propto 1/q^a \quad (2)$$

with some exponent a between zero and infinity. More quantitatively, for each prohibited site, we determine when it is visited for the first time by the walker, a random number r , homogeneously distributed between 0 and 1, and then fix q_i for that site i as

$$q_i = A r^{1/(1-a)} \quad (3)$$

with some free parameter A .

Apart from the barriers, our methods have been standard for decades: periodic boundary conditions were used in one direction and helical ones in the remaining direction(s). Walkers can, and sometimes do, travel over distances larger than the lattice because we add up how often the walker went left, right, up or down, and calculated the distance from these sums. Typically, 8,000 walkers were put into one sample one after the other; our last figure will show the statistical errors by a comparison with 32,000 walkers. No interaction between different walkers takes place and a random initial position on the lattice is selected, thus

Fig. 1 Illustration in small square lattice: Tried (a) and visited (b) sites after one million time steps

Fig. 2 Effective exponent for 8,000 walks on $7,001 \times 7,001$, $d = 2$, $a = 0.5$, $A = 0.01$. The concentration p of allowed sites decreases from top to bottom: $p_c - p = 0$ (plus signs), 0.1 (crosses), 0.2 (stars), 0.3 (open squares), 0.4 (filled squares), 0.5 (circles)

also sampling the initial condition whether the walker starts on a finite cluster, the infinite cluster, or on a blocked lattice site. For each walker, a different set of barriers was simulated, and each sample averaged over thousands of walks. Exponents were determined as slopes between consecutive pairs of distances at times differing by a factor of two.

Fig. 3 Effective exponent for 8000 walks on $401 \times 401 \times 401$ (part a, symbols as in Fig. 2) and 7001×7001 , (part b); $a = 1/2$, $A = 0.01$

3 Results

Figure 1 illustrates, for two dimensions, at $p = p_c - 0.5 = 0.0927$ and exponent $a = 1/2$ the results of one walk after one million time steps. Figure 1a shows the set of sites that have been tried at least once, and Fig. 1b shows those sites that have actually been visited in spite of the barriers. After eight million steps, all sites were tried, and after 64 million steps, all sites were visited. One can get anywhere, provided one has enough time.

For $7,001 \times 7,001$ square lattices, where $p_c \simeq 0.593$, our simulations show for $A = 0.01$ and 0.0001 that the squared distance is a complicated function of the time. (For $A = 1$ and $a > 1$, the q_i are larger than one, which makes little sense, and for $a = 0$ and 0.5 at $A = 1$, the squared distances are close to $t/2$; not shown.) We thus look for smaller A in the slopes in the log–log plots, i.e., at the effective exponents

$$\alpha_{\text{eff}} = d \ln \langle \Delta \mathbf{r}(t)^2 \rangle / dt. \quad (4)$$

In each case, we simulate $p = p_c$, $p_c - 0.1$, $p_c - 0.2$, ... down to $p_c - 0.5 \simeq 0.093$. We see, for short times, different slopes in our log–log plots, but for long times, the effective slopes approach unity: normal diffusion with mean squared distance proportional to time. For $a = 2$, for an exponentially decaying distribution $f(q)$, and for a Weibull distribution

Fig. 4 Test of superdiffusion at intermediate times, showing two sets with ten samples each, in three dimensions and with $p = 0.0116$ and $L = 401$. We see that the scattering does not increase with time, and the standard deviation is of the order of what can be inferred from the irregularities in the curves for single samples. Figure **a** compares 8000 (x symbols) with 30,000 (+ symbols) walkers in three dimensions. **b** Due to the rather extreme values of our parameters, even after one billion time steps, the mean squared distance is only 117, giving a root mean square (RMS) distance of less than 11. This RMS distance is much smaller than our linear lattice dimension $L = 401$; thus, most particles do not traverse the whole lattice even once. This can be seen in **b** showing results for $L = 101$ (+ symbols) and 701 (x symbols), to be compared with $L = 401$ in **a**. It shows no significant finite-size effects

Fig. 5 Effective exponents with $A = 0.0001$, $p - p_c = 0.3$, and $L = 401$. Exponents are shown for 8000 (x symbols) and 30,000 (+ symbols) walkers. As in Fig. 3 but $A = 0.0001$ and with better statistics or longer times

(stretched exponential), the time variations of the effective exponents were similar but less pronounced.

Experimentally more relevant are three instead of two dimensions, and some results are shown in Fig. 3a, rather similar to two dimensions in Fig. 2. Now, $p_c = 0.3116$. For very small $p = 0.0116$, squares in Fig. 3, we see an overshooting with an effective exponent α_{eff} above unity at intermediate times; this is not a statistical fluctuation and appears in all 20 simulated samples, as shown in Fig. 4. It also was seen in two dimensions at very low p , Fig. 3b. One may call this effect superdiffusion because, for more than one order of magnitude, the exponent is above unity.

Basically, the positive probability of each barrier to move away and to let through the random walker means that, for sufficiently long times, we always get normal diffusion, $\alpha = 1$. For times that are not long enough to see this moving-away of the barriers, but long enough for the walker to explore the whole finite cluster for $p < p_c$ on which it started, we have $\alpha = 0$. For our moderately small $A = 0.01$, these different regimes cannot be reliably separated; this works better for much less mobile barriers such as $A = 0.0001$ as shown in Fig. 5. There, the effective exponents are about zero for $t \sim 10^2$, show a maximum but no longer overshooting below $t \sim 10^5$, and approach unity above $t \sim 10^8$.

4 Discussion

In summary, we see a nonmonotonic variation of the effective exponents with time, showing both subdiffusive and superdiffusive behavior. Asymptotically, however, the exponent always seems to approach unity for $t \rightarrow \infty$. In experiments with more limited variation of times, this variation of α_{eff} with time could wrongly be interpreted as asymptotic subdiffusion or asymptotic superdiffusion; long times [14] are needed.

If the apparent superdiffusivity were a statistical fluctuation only, being present or absent completely randomly, then it would be present in all of a finite set m of samples, and absent in none of them, with a probability $1/n^m \simeq 1/10^6$, which is very small. Carrying out a set of 20 samples, we confirmed this picture (see Fig. 4). Thus, most likely, the effect is not due to randomness; of course, it could be due to unknown systematic errors, as in all complicated simulations.

It should be noted that superdiffusion was seen only for some parameter combinations and not for all. We see no reason why this should make our results less reliable; rather, it may explain why our superdiffusion was not found earlier by others. Whether the small range of concentrations where our superdiffusion was observed fails to make the effect pertinent to biological systems remains to be seen. Our model is not realistic enough to identify our concentration quantitatively with biological porosities. For the same reason, we refrain from identifying our simulated times with real biological times; different models of the same type should be investigated to check for differences before any of them are compared quantitatively with reality.

In general, however, such overshooting is not entirely uncommon. If any quantity X approaches, as a function of time t , an asymptotic value Y , then it may do so following a law $X(t) = Y + A/t + B/t^2 + \dots$ (or with more complicated powers of time). Now, if the coefficient A is positive and B is negative, while the higher-order terms are negligible, then for $t < -B/A$, the $X(t)$ is below its asymptotic value Y , while for longer times it is above this asymptotic value, reaches a maximum, and then decays downwards towards Y . There is no special physical reason for this behavior, which is just a consequence of the differing signs of the leading corrections to scaling. This is roughly the behavior we have observed for the effective exponent as a function of the logarithm of time.

More importantly, because we use a probability distribution of mobilities, allowing for arbitrarily long times until a barrier allows the penetration of a diffuser, it is not, even now, unit clear to us that normal diffusion is to be expected asymptotically. Only with a cutoff for the mobilities would we expect normal asymptotic behavior without any confirming simulation. We would not be surprised if, in some modification of our model, one would find anomalous diffusion even asymptotically. Indeed, Saxton [10] stated that if a particle diffuses in a suitable infinite hierarchy of binding sites, diffusion is well known to be anomalous at all times.

Acknowledgements One of us (DWH) thanks M. Weiss for discussions.

References

1. Pederson, T.: Diffusional protein transport within the nucleus: a message in the medium. *Nat. Cell Biol.* **2**, E73–E74 (2000)
2. Guthold, M., Zhu, X., Rivetti, C., Yang, G., Thomson, N., Kasas, S., Hansma, H., Smith, B., Hansma, P., Bustamante, C.: Direct observation of one-dimensional diffusion and transcription by *Escherichia coli* RNA polymerase. *Biophys. J.* **77**, 2284–2294 (1999)
3. Berry, H.: Monte Carlo simulations of enzyme reactions in two dimensions: fractal kinetics and spatial segregation. *Biophys. J.* **83**, 1891–1901 (2002)
4. Valdez-Taubas, J., Pelham, H.: Slow diffusion of proteins in the yeast plasma membrane allows polarity to be maintained by endocytic cycling. *Curr. Biol.* **13**, 1636–1640 (2003)
5. Weiss, M., Elsner, M., Kartberg, F., Nilsson, T.: Anomalous subdiffusion is a measure for cytoplasmic crowding in living cells. *Biophys. J.* **87**, 3518 (2004)
6. Binder, K., Heermann, D.W.: *Monte Carlo Simulation in Statistical Physics: An Introduction*, 4th edn. Springer, Heidelberg (2002)
7. Bouchaud, J.P., Georges, A.: Anomalous diffusion in disordered media: statistical mechanisms, models and physical applications. *Phys. Rep.* **195**, 127 (1990)
8. Frey, E., Kroy, K.: Brownian motion: a paradigm of soft matter and biological physics. *Ann. Phys. (Leipzig)* **14**, 20 (2005)
9. Lindenberg, K., Oshanin, G., Tachiya, M.: Chemical kinetics beyond the textbook: fluctuations, many-particle effects and anomalous dynamics. *J. Phys. Condens. Mat.* **19**, 060301 (2007)
10. Saxton, M.J.: A biological interpretation of transient anomalous subdiffusion. *Biophys. J.* **92**, 1178–1191 (2007)

11. Ratynskaia, S., Rypdal, K., Knapek, C., Khrapak, S., Milovanov, A.V., Ivlev, A., Rasmussen, J.J., Morfill, G.E.: Superdiffusion and Viscoelastic Vortex Flows in a Two-Dimensional Complex Plasma. *Phys. Rev. Lett.* **96**, 105010 (2006)
12. Liu, B., Goree, J.: Superdiffusion in two-dimensional Yukawa liquids. *Phys. Rev. E* **75**, 016405 (2007)
13. Stauffer, D., Aharony, A.: *Introduction to Percolation Theory*. Taylor & Francis, London (1992)
14. Ruiz-Lorenzo, J.J., Yuste, S.B., Lindenberg, K.: Simulations for trapping reactions with subdiffusive traps and subdiffusive particles. *J. Phys. Condens. Mat.* **19**, 065120 (2007)