Two Coupled Mechanisms Produce Fickian, yet non-Gaussian Diffusion in Heterogeneous Media

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(Dated: September 27, 2019)

Fickian yet non-Gaussian diffusion has been observed in several biological and soft matter systems, but the underlying reasons behind the emergence of non-Gaussianity while simultaneously retaining the linear nature of the mean square displacement remain speculative. Here, we perform a set of controlled experiments that quantitatively explore the effect of spatial heterogeneities on the appearance of non-Gaussianity in Fickian diffusion. We study the diffusion of fluorescent colloidal particles in a matrix of micropillars having a range of structural configurations: from completely ordered to completely random. Structural randomness and density are found to be the two most important factors in making diffusion non-Gaussian. We show that non-Gaussianity emerges as a direct consequence of two coupled factors. First, individual particle diffusivities become spatially dependent in a heterogeneous environment. Second, the spatial distribution of the particles varies significantly in heterogeneous environments, which further influences the diffusivity of a single particle. As a result, we find that considerable non-Gaussianity appears even for weak disorder in the arrangement of the micropillars. A simple simulation validates our hypothesis that non-Gaussian yet Fickian diffusion in our system arises from the superstatistical behavior of the ensemble in a structurally heterogeneous environment. The two mechanisms identified here are relevant for many systems of crowded heterogeneous environments where non-Gaussian diffusion is frequently observed, for example in biological systems, polymers, gels and porous materials.

PACS numbers: 82.70.Dd, 05.40.-a, 47.56.+r

Einsteins theory of Brownian motion shows that for colloidal particles diffusing in two-dimensions in a homogeneous, Newtonian fluid, the mean square displacement (\textit{MSD}) is given by \textit{MSD} = 4D\tau where \textit{D} is the diffusion coefficient and \textit{\tau} is the lag time. The solution of the diffusion equation is obtained as a Gaussian probability distribution of displacements (\textit{G(\Delta x)}) as is expected for random, independent displacements. However, in many systems including granular materials \cite{1}, turbulent flow \cite{2}, active gels \cite{3}, glassy materials \cite{4}, porous materials \cite{5,6}, nanoparticles diffusing in polymer melt \cite{7}, log-return of stock prices \cite{8} and biological systems \cite{9–13}, a non-Gaussian \textit{G(\Delta x)} has been observed. In many of these systems the non-Gaussian nature of \textit{G(\Delta x)} is related to a process of anomalous diffusion. In such cases the \textit{MSD} itself is non-linear in time and given by \textit{MSD} = 4D\tau^{n}, \textit{n} being the diffusion exponent with a value < 1 for subdiffusion and > 1 for superdiffusion. However, in several very surprising cases, diffusion has been observed to be Fickian, that is the \textit{MSD} remains linear in time, but counter-intuitively \textit{G(\Delta x)} is non-Gaussian. This peculiar behavior has been referred to as ‘Anomalous, yet Brownian’ or ‘Fickian yet non-Gaussian’ diffusion (FNG), and has been observed in a wide variety of systems ranging from tracer colloids diffusing in suspensions of swimming microorganisms \cite{14}, colloidal particles diffusing on phospholipid tubules and entangled actin filaments \cite{10}, liposomes diffusing in nematic solutions of F-actin filaments \cite{15}, peptide coated gold nanoparticles weakly interacting with peptide coated surfaces \cite{16}, polymer chains diffusing on a surface \cite{17,18}, colloidal particles diffusing among swimming cells \cite{19}, colloidal spheres in a matrix of larger colloidal spheres \cite{20} and quasi 2D colloidal hard sphere fluids \cite{21}. Several theories have been put forward to explain such behavior which include the diffusing diffusivity model \cite{22–25} that considers dynamic heterogeneities experienced by each colloidal particle in a changing environment. A second suggestion \cite{10,15,20,22} is that such motion arises from the superstatistical behavior of an ensemble with each member having different diffusive parameters in a spatially varying environment. Guan \textit{et al.} \cite{20} observed FNG diffusion even in hard spheres—a system of probe colloidal particles diffusing in a static matrix of densely packed bigger particles. It was postulated that the differences in the local configurations of the larger matrix particles led to the observed Fickian yet non Gaussian diffusion. However, since the configuration of the matrix particles could not be controlled experimentally, it was not possible to quantitatively estimate the effect of the spatial heterogeneities on the non-Gaussian nature of the diffusion.

Here we perform a controlled experiment elucidating the emergence of non-Gaussianity from the superstatistical behavior of an ensemble in a spatially varying environment. More importantly, we quantitatively estimate the percentage of environmental randomness that results in a given degree of non-Gaussianity in a system. This is achieved by fabricating arrays of micropillars with different degrees of randomness using photolithography and...
tracking the motion of colloidal particles through them. We find that even a small degree of randomness leads to extensive non-Gaussianity due to two coupled mechanisms arising directly from the randomness in the arrangement of the micropillar arrays. Our experiment establishes the paramount importance of structural disorder in FNG diffusion.

Our samples consist of micropillars (cylindrical cross-section with diameter = 6 µm, height = 6 µm) made of the photoresist SU8 using standard photolithography techniques on glass cover slips. Samples with different areal densities and degrees of randomness were fabricated by designing corresponding masks in MATLAB. A flat glass control was made by exposing and developing an SU8 coated cover-slip without introducing any mask. Fluorescent polystyrene particles (4.19 ± 0.27 µm in diameter) obtained from Bangs Laboratories Inc. were injected onto the micropillar arrays and covered with a top glass plate. A weight of about 10 g was put on the top glass plate and the sample was sealed with UV-curable adhesive. The diffusion of the probe particles was imaged with an Olympus IX-71 inverted microscope with a 40X objective in both bright field and fluorescence modes. Videos of the particle motion were recorded at 50 fps and the trajectories of the particles were obtained using Trackpy 3.0 [26], a Python based implementation of the Crocker-Grier algorithm [27]. We performed two sets of experiments to probe the effects of density and structural order of the micropillar arrays on the diffusion of the probe colloidal particles.

Initially we consider two cases of randomly arranged arrays of micropillars along with a control sample of polystyrene spheres diffusing in 2D on a planar glass surface (Fig. 1(a)). In the first sample the micropillars have an areal density of ≈ 20% referred to as ‘dilute random’ (Fig. 1(b)) while in the second case, the areal density is ≈ 72% referred to as ‘dense random’ (Fig. 1(c)). It should be noted that in the dense random case, the randomly placed micropillars were so close to each other that many of them were connected. This led to the formation of pockets separated by rigid walls in which particles could get trapped. The large polystyrene particles sedimented onto the glass floor of the samples and could diffuse in the spaces in between the pillars. The MSD of the particles in all three cases was observed to be clearly linear over a time scale spanning three decades (Fig. 1(d)), thereby giving n = 1. However, G(Δx) showed a completely different picture (Fig. 1(e) and (f)). Whereas in the case of free 2D diffusion, a Gaussian behavior was observed as expected, for the dilute random case the distribution was markedly non-Gaussian with a small peak centered at zero, and the whole distribution curve tapering off at longer lag times. For the dense random case, G(Δx) was even more dramatic, having a clear exponential appearance. It should be noted here that at sufficiently long time intervals (lag time > 5 s), the dense random sample showed n = 0.8 instead of 1, indicating a caging effect at these time scales. However, in the time scale in which the diffusion is Fickian, G(Δx) clearly exhibits an exponential behavior. This indicates that an increase in areal density of the micropillars leads to greater non-Gaussianity.

To explore the effect of the structural heterogeneity of the micropillars on the diffusion of the probe polystyrene spheres, we made a series of five samples each having 20% areal coverage of the micropillars (referred to as ‘dilute random’) (c) in a matrix containing 72% density of randomly placed micropillars (referred to as ‘dense random’). The brighter circles are the fluorescent particles and the bigger circles or irregular fused structures are the micropillars as seen from the top in transmission mode. The time ensemble averaged MSD plots are shown in (d) while inset shows the log-log plots for the same systems indicating clear Fickian diffusion with n = 1. G(Δx) plots are shown for lag times (e) τ = 0.06 s and (f) τ = 0.6 s. Note the distinct exponential behavior of the system with the dense random micropillars while the MSD is still clearly linear in time.

FIG. 1: Increase in density of the micropillars makes diffusion Fickian yet non-Gaussian. Top-view microscope images show fluorescent polystyrene particles diffusing on (a) a glass surface (b) in a matrix containing 20% density of randomly placed micropillars (referred to as ‘dilute random’) (c) in a matrix containing 72% density of randomly placed micropillars (referred to as ‘dense random’). The brighter circles are the fluorescent particles and the bigger circles or irregular fused structures are the micropillars as seen from the top in transmission mode. The time ensemble averaged MSD plots are shown in (d) while inset shows the log-log plots for the same systems indicating clear Fickian diffusion with n = 1. G(Δx) plots are shown for lag times (e) τ = 0.06 s and (f) τ = 0.6 s. Note the distinct exponential behavior of the system with the dense random micropillars while the MSD is still clearly linear in time.
Given percentage of the micropillars randomly and then shifting them by a random amount from their positions in the perfectly ordered structure while designing the mask. This essentially is equivalent to the introduction of a given percentage of ‘defects’ in an ordered structure. Diffusion in all the samples was again observed to be Fickian (Fig. 2(d)), with the slope of the MSD plots (thereby the average diffusion constant) increasing progressively with increasing randomness in the structure. However, $G(\Delta x)$ showed a clear tendency towards greater non-Gaussianity while going from complete order to complete randomness (Fig. 2(c) and (f)). It is also to be noted that even with an inclusion of only 10% randomness in the structure, the $G(\Delta x)$ plots are very similar to the case for the 100% random structure, indicating very high sensitivity of the system to even a dilute concentration of ‘defects’. This behavior is also reflected in the non-Gaussian parameter $\alpha$ [20], where $\alpha(t) = \frac{\langle (\Delta x^2(t)) \rangle}{\langle (\Delta x^2(t))^2 \rangle} - 1$ (Fig. 3(a)). $\alpha$ is very close to zero for the free 2D diffusion case, while it is $\approx 1.2$ times higher than that of the ordered micropillars for the 2% and 5% samples, and is nearly the same as for the 10% and 100% disordered samples. Notably, $\alpha$ remains nearly constant over several lag times for most cases. For the dense random case $\alpha$ is $\approx 5$ times that of the ordered case, indicating a very high degree of non-Gaussianity. We also verified the exponential nature of $G(\Delta x)$ for the dense random case [10] by fitting the equation $G(\Delta x) = Ae^{-\frac{\lambda^2}{\Delta}}$ to $G(\Delta x)$ plots over several different lag times and calculated the corresponding values of $\lambda$. From Fig. 3(b) we see that indeed $\lambda^2 \sim \tau$, confirming the Fickian, yet exponential behavior.

From our observations, we come to the conclusion that an increase in both the structural randomness and density of the random structures leads to higher non-Gaussianity in otherwise Fickian diffusion. To understand the reason behind this, we looked more closely into the probability distribution of the diffusion constants $P(D)$ over the ensemble for the seven systems: free 2D, ‘dilute random’ samples with randomness of 0%, 2%, 5%, 10% and 100%, and the dense random case (Fig. 4(a)). Here we see that even though the free 2D and the ordered micropillar systems have a near Gaussian distribution of the diffusion constants, for all the samples with different degrees of randomness there are two notable features in $P(D)$: a) there is a second peak at lower values of the diffusion constant $(D)$, indicating that a portion of the ensemble move very slowly b) there is an extended tail at higher values of $D$ indicating again that a portion of the ensemble move faster than the average. With the dense random, the distribution looks almost exponential. In spite of such wide differences in the $P(D)$ distributions, probability distribution of $n$ values for the individual particles of the ensemble $P(n)$ peaks at $n = 1.0$ for all the seven cases, indicating pure Fickian diffusion on the single particle level for the great majority of the particles (Fig. 4(b)).

The explicit difference in $P(D)$ for the random and ordered micropillars therefore points to the fact that the local spatial heterogeneities in the random structure result in the ensemble having subgroups of particles that see different local environments and consequently diffuse differently. In a random structure there are more open areas...
FIG. 4: (a) Probability distribution $P(D)$ of the diffusion constants ($D$) for the seven cases: free 2D, 0%, 2%, 5%, 10% and 100% randomness and dense random respectively. Note the existence of two populations in the $P(D)$ plots for the dilute random samples with different degrees of randomness while the dense random sample shows a near-exponential behavior. (b) Probability distribution $P(n)$ of the diffusion exponents ($n$) calculated from the linear fits of log-log MSD plots for each individual particle. Note that the distribution peaks about $n = 1.0$, indicating predominantly normal diffusion for the majority of the particles for all the cases.

FIG. 5: 2D color maps representing the $D$ values of colloids for (a) 0% random, (b) 10% random and (c) 100% random micropillars. Note the higher $D$ values for particles in open spaces and lower $D$ values for particles close to a wall or other particles for the random sample. Pair correlation function $g(r)$ of the (d) micropillars and (e) particles for the 0% random, 10% random and 100% random cases.

and narrow cavities as compared to an ordered structure. A particle can get trapped in the cavities surrounded by the micropillar walls on one hand, while on the other hand it might happen to be in a location which is far off from any micropillar wall. While the former leads to a slower motion or even a caged diffusion, in the later, the particle can diffuse unhindered resembling a free particle. From Fig. 5(a)-(c) which shows us the $D$ values of the particles as 2D color maps, we see that for the random samples, the particles trapped in cavities have on average lower values of $D$ whereas particles far from any walls have generally higher values. A second cause is the spatial distribution of the probe particles themselves, which in a random structure is very different compared to that in an ordered one. While in the ordered structure the particles are distributed throughout the sample with a certain periodicity, in the random structure the particles are more prone to clustering in some locations and being more sparsely distributed in others. As a result, the diffusion of a particle entrapped in the crowded regions gets slowed down while diffusion is faster in regions with very few particles. Comparing the 2D pair correlation function $g(r)$ for both the micropillars (Fig. 5(d)) and the particles (Fig. 5(e)) we see that for the ordered sample, $g(r)$ for the particles resembles that of the micropillars. In contrast, $g(r)$ for the 100% random case saturates very fast to 1.0, indicating a wide distribution of the nearest neighbor distances. Also the peak at 6 $\mu$m is the highest for the particles in the random structure as compared to the very small peak in the ordered structure (Fig. 5(e)), indicating the presence of particles at very close distances to other particles or very crowded regions for the random arrangement. The amplified effect of the two coupled factors - the location dependence of the diffusivity values in a spatially heterogeneous structure, and slowing or speeding up of diffusion near crowded or free regions, produces the extensive non-Gaussian response even at a dilute concentration of defects. The non-Gaussianity persists at both short and long time scales as seen from the nearly constant behavior of the non-Gaussian parameter over more than two decades of lag time (where the smallest time interval is 0.02 s). This is because each individual particle does not move appreciably from its location within our experimental time frame, and does not experience the whole set of environments in the sample. In contrast, in the ‘diffusing diffusivity’ model, each individual particle experiences a slowly fluctuating environment over their trajectory and the non-Gaussian behavior is seen for each particle. In this model, at longer time scales the diffusion of a single particle transitions to Gaussian behavior [10, 22].

To verify our hypothesis, we did a simple calcula-
tion. Assuming $G(\Delta x)$ for each individual particle to be purely Gaussian, we took the weights of the different diffusion constant values from our measurements (Fig. 4(a)) and summed over the individual displacements using $G(\Delta x, t) = \sum_{i=1}^{N} \frac{w_i}{\sqrt{4\pi D_{\text{eff}}t}} e^{-\frac{\Delta x^2}{4D_{\text{eff}}t}}$ where $w_i$ is the weight of each given value of the diffusion constant $D_i$. Our calculation results at a lag time of 0.6 s (see Supplemental Material Fig. S1(a)-(b)) [28] agree well with our $G(\Delta x)$ measurements (Fig. 1(f) and Fig. 2(f)), indicating that indeed the spread in the diffusion constants arising from the local spatial heterogeneities in a random structure is the reason behind the FNG diffusion in these systems. This is in essence superstatistical behavior where the fast, random motion of the colloidal particles is superposed with the variations in the environment with specific areas having higher and lower diffusivity values [22]. Previously, a diffusion constant distribution of the form $P(D) = \frac{1}{D} e^{-\frac{D}{D_0}}$ where $D$ is the mean diffusion constant was shown to produce an exponential $G(\Delta x)$ [23, 29]. In our system, this is observed in the dense random case.

In conclusion we experimentally showed that the existence of spatial heterogeneities is a profoundly important factor behind the emergence of non-Gaussianity in Fickian diffusion. Both the areal density and structural randomness of the heterogeneities contribute directly to increasing the non-Gaussianity culminating in exponential displacement distributions in extreme cases. Even weak disorder in the system (10%) can produce an extensive deviation from Gaussianity. This extreme sensitivity to randomness in the structure originates from the amplified contributions of two coupled effects. First, due to the presence of cavities and open spaces in the random structure, the diffusivities of each individual particle in the ensemble becomes a function of its spatial location. Second, the structural randomness itself produces crowded and sparser regions of particles where a probe particle experiences slower or faster diffusion, respectively. The combined effect of these two factors results in an ensemble having a wide range of diffusivities and produces the superstatistical non-Gaussian behavior for Fickian diffusion. The importance of our study lies in the fact that it is the first controlled experiment quantitatively examining the effect of environmental heterogeneities on the nature of diffusion of colloidal particles. We expect this work to be an important addition in the endeavor to understand non-conventional diffusive behaviors in complex systems including biological environments and porous materials.

This research was supported by the Israel Science Foundation (grant No. 988/17) and the PBC Postdoctoral fellowship of the Council for Higher education, Israel.

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FIG. 1: Simulated probability distribution of displacements at lag time $= 0.6$ s by assuming each individual particle having Gaussian displacement distribution and summing over the ensemble with the given weights taken from the measured diffusion constant distributions. (a) $G(\Delta x)$ for free 2D, dilute and dense random cases and (b) $G(\Delta x)$ for the 0%, 2%, 5%, 10% and 100% random samples. Note the very good match with the experimentally obtained $G(\Delta x)$ in Figs. 1(f) and 2(f) of the paper.