The Hitchhiker model for Laplace diffusion processes in the cell environment

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Aggregation and fragmentation of single molecules in the cell environment lead to a spectrum of diffusivities and to statistical laws of movement very different from typical Brownian motion. Current models of intracellular transport do not explain at a microscopical level the emergence of these deviations. Employing a many body approach, which we call the Hitchhiker model, we elucidate how the widely observed exponential tails in the particle spreading, i.e. the Laplace distribution and the modulations of the diffusivities, are controlled by size fluctuations of single molecules. By means of numerical simulations Laplace distributions are obtained whether we track one molecule or many molecules in parallel. However, we show that the diffusivity varies significantly depending on which tracking protocol is applied. Using a renewal process in the space of sizes, we quantify to what extent the average diffusivity in the single molecule technique is decreased compared with the ensemble average.

I. INTRODUCTION

Single molecule tracking in the cell environment sheds light on the dynamics of molecules making life possible [1,4]. A repeating theme is the observation of deviations from simple Gaussian Brownian diffusion [5–9]. Theoretical stochastic frameworks investigating these anomalies are based on a picture of a single particle coupled to a complex environment [5,7]. Usually the anomalies of the diffusion processes are related to the dense heterogeneous environment of the cell and to active transport [5,7]. In many cases the diffusion constant of the tracked particle will randomly vary in time and this leads to deviation from normal behavior [10–22].

Clever experimental techniques, capable of tracking the merging of individual molecules, or relate between the intensity of emitted light (a proxy for size) and diffusivity indicate that diffusion processes in the cell are controlled by aggregation processes [11,13,17,23,24]. Following Heller et al. [13] in Fig. 1 we show schematically such a process where two diffusing monomers merge to create a dimer, thus modifying the diffusivity of the tracked particle. Another example is the work of Thompson et al. [11], in this case mRNP are tagged and these are comprised of conglomeration of mRNA molecules, ribosomes, and other molecules, thus a wide variety of particle sizes and thus a variety of diffusion coefficients is found. This indicates that we must treat the diffusion of particles in the cell as a many body process, where sticking of one molecule to the other may lead to time dependent stochastic diffusivity.

Thus our work is motivated by a set of new experiments which led already to a paradigm shift on the way we view diffusion processes in the cell environment. From them we make two observations, the first is statistical and the second correlates between fluctuations of sizes of tracked molecules and their diffusivity. Next we discuss these observations, but first we mention that the latter together with previous theoretical works on aggregation processes [25,26] motivate us later to consider what we call the Hitchhiker model. This is a simple many body approach. In a nutshell, we know that single molecules in the cell attach and detach to and from other particles, so roughly speaking we view the cell as a metropolis where a single hitchhiker mimicking the tracked molecule can attach and detach to different diffusing objects hence the
diffusivity of the single molecule fluctuates in time similar to what is observed in many experiments. How to make this picture quantitative and in agreement with observations is the topic of this article.

Let us mention the statistical observations. In an increasing number of experiments the diffusion of the tracer particles is shown to be linear, namely the mean square displacement (MSD) is

\[ \langle x^2 \rangle = 2Dt, \]  

hence according to Einstein’s theory of Brownian motion one would expect that this normal behavior will come hand in hand with a Gaussian packet of spreading particles

\[ P(x,t) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}}. \]

Instead, in many cases as reported in [10, 12, 14, 17, 23, 27], the tails of the density decay exponentially and this is modelled with the Laplace density

\[ P(x,t) = \frac{1}{\sqrt{4\pi D(t)}} e^{-\frac{|x|}{\sqrt{4D(t)}}}, \]

with \( \langle D \rangle \) the average diffusivity of the system. Other experiments [13, 14, 17] record the spectrum of diffusion constants, and find the distribution of the diffusivities, which is broad and peaked close to the minimum of the recorded diffusivity, for example an exponential distribution

\[ P(D) = e^{-\frac{D}{\langle D \rangle}} \text{ for } D > 0. \]

In other experiments a group of confined particles with \( D = 0 \) is found, this subclass of motionless particles (within the error of the experiment) is typically excluded from the diffusion analysis [11], see also [28, 29]. As shown in [10, 18, 30] if we assume locally a Gaussian diffusive process Eq. (2) then averaging over the diffusivities using Eq. (4) we get the Laplace probability density function (PDF) Eq. (3). Beyond the departure of these behaviors from Einstein’s theory of diffusion, note that the exponential tails are by far broader if compared to the Gaussian packet, and this has important consequences for search in the cell environment and for biochemical interactions [31, 32]. Further, exponential tails are not limited to dynamics in the cell environment, they are found in glassy systems as well and in that sense are universal [33].

The second observation is related to new tracking capabilities that as mentioned imply that the fluctuations of diffusivity is due, at least partially, to the role of size fluctuations. This leads also to the second theme of our work, which is the influence of the tagging method on the statistical estimation of diffusivity in the cell (see Fig. 2). Nowadays single molecule tracking techniques allow experimentalist to view many particles in parallel and follow a proxy for the size of the molecules. That in turn reveals that the increase in the size of the molecule implies that it slows down. Given these advances we explore theoretically two tagging methods, one which follows all the complexes in the system, and the other where we have one light emitting particle (the Hitchhiker) which can be attached to different size complexes see Fig. 2. If all the particles are Brownian and identical the two approaches give the same estimation for the diffusivity. However, we advance here the hypothesis that in the cell these methods give different results due to the many body nature of the process. Roughly speaking, imagine we parachute a hitchhiker on a metropolis, it then has a greater likelihood to attach to a large train if compared to a small rickshaw, and since size correlates with diffusivity this will impact the statistical analysis of diffusivity. Below we quantify this effect using the Hitchhiker model. Thus the amount of labeling, and the method of tracking can modify the diffusivity recorded in the laboratory, and hence the reported diffusion fields become a matter for interpretation.

II. PHENOMENOLOGICAL ARGUMENTS

As mentioned our working hypothesis is that diffusivity of a tracked particle \( D \) depends on the size of the macromolecule to which it is attached. Following Heller et al. [13] we consider as a basic unit a monomer, that through a process of diffusion, aggregation and breaking, made more specific soon, is attached and detached from other monomers in the system, creating dimers, trimers and more generally \( N \)-mers. The diffusivity of the tagged particle \( D(N(t)) \) is fluctuating in time, since the number of monomers in the macromolecule \( N(t) \) is stochastically modified. We note that in general \( N(t) \) could represent the number of attached particles, each one composed of
many monomers, so the term monomer is used here as a basic unit of a large object. In turn \( N(t) \) is related to the size of the particle using Flory’s arguments (see below). The processes are all diffusive, which is motivated by the observation of a normal \( \text{MSD} \), and hence we assume that locally we have Gaussian statistics \([10, 18, 30]\). This means that the propagator for short times can be expressed as

\[
P(x, t) = \int_0^\infty \frac{e^{-\frac{x^2}{4\pi D(N)t}}}{\sqrt{4\pi D(N)t}} P(N) dN,
\]

This approach in its generality is sometimes called superstatistics \([34]\) and \( P(N) \) is the distribution of the sizes. Our first question is phenomenological, given a diffusive law \( D(N) \) what is the PDF \( P(N) \) that yields the observed Laplace distribution Eq. \([3]\)?

### A. Stokes-Einstein-Flory approach

In general a molecular complex can be treated as a diffusing polymer chain with a hydrodynamic radius \( R \). These systems exhibit a scaling of the radius with the number of monomers in the chain as: \( R = bN^\nu \), where \( \nu \) is the Flory exponent, and \( b \) the Kuhn length. Hence using the Stokes-Einstein equation \([35]\)

\[
D = \frac{k_B T}{6\pi\eta_b N^\nu},
\]

clearly larger complexes are slowed down compared to a monomer. The value of the Flory exponent, depends on the interactions among the monomers in the chain and with the solvent. Typical values are: \( \nu = 1/3 \) (Stokes original law, the polymer is effectively a solid sphere), \( \nu = 1 \) the Rouse chain \([36]\), while Zimm chain gives \( \nu = 3/5 \) \([37]\). Using the Stokes-Einstein-Flory law, in order to obtain the Laplace distribution Eq. \([3]\) via Eq. \([5]\), we have to employ (see Appendix \(A\) for details)

\[
P(N) = \frac{\nu k_B T}{6\pi\eta_b\langle D \rangle} N^{-\nu-1} e^{-\frac{k_B T}{6\pi\eta_b\langle D \rangle}},
\]

which has the form of a generalized inverse gamma distribution \([38]\). This means that the distribution of sizes is fat tailed, in fact scale free in the sense that the mean of \( N \) diverges when \( \nu < 1 \). In practice, in the model we study below, the power law tail must be cutoff due to finite size effects, still this law may capture the dynamics on some time scales as demonstrated below with the Hitchhiker model. Further in Appendix \(A\) we show how the exponential tails in \( P(x, t) \) are preserved in the presence of a cut off size in the large size regime. In single molecule experiments there is already some evidence that distribution of fluorescence intensities (which are proportional to sizes) are far from Gaussian, and rather broad \([11, 13, 39, 40]\), and there is some evidence for Rouse dynamics \( \nu = 1 \) \([13]\). Interestingly, distribution of size of rocks in Saturn follows a power law with a cutoff \([41]\), and several models of aggregation of particles predict such heavy tail statistics \([26, 42]\).

### B. Arrhenius law

Given the dense environment of the cell, deviations from the Stokes-Einstein-Flory model are expected at least in some cases. This is found in diffusion of proteins in polymer solutions, where an Arrhenius activation mechanism is known \([43, 44]\). Here we have \( D = D_0 e^{-\frac{E_A}{k_B T}} \) where \( E_A \) is an activation energy. This activation energy depends on the size \( N \) of the complex like \( E_A = \epsilon bN^\nu \), with \( \nu \) a scaling exponent \([43]\). This gives

\[
D = D_0 e^{-cN^\nu},
\]

with \( c = \epsilon b/k_B T \). In this case the underlying assumption of a Laplace distribution for the spreading of particles Eq. \([3]\) leads to the PDF of sizes

\[
P(N) = \frac{cD_0 e^{N^{\nu-1}}}{\langle D \rangle} e^{-\left(\frac{cD_0}{\langle D \rangle} e^{-cN^\nu} + cN^\nu\right)},
\]

so now \( N \) follows a doubly exponential distribution. Particularly if \( \nu = 1 \) we get

\[
P(N) = \frac{c D_0}{\langle D \rangle} e^{-\left(\frac{cD_0}{\langle D \rangle} + cN\right)},
\]

which is the density of the Gumbel distribution from extreme value statistics. Importantly, these type of distributions are peaked and narrow. We conclude that due to the exponential sensitivity of the diffusivity on \( N \) small changes in \( N \) are sufficient to create large modification in \( D \), hence we get here a behavior very different from the power law statistics found in the Stokes-Einstein-Flory approach.

These observations can in principle be detected in the laboratory. Measuring the size dependency of diffusivity, then estimating \( P(N) \) one may predict the spreading of the packet of particles, which then can be measured directly. Our phenomenological theory shows how to obtain the Laplace distribution from \( P(N) \), we now turn to a microscopical approach.

### III. THE HITCHHIKER MODEL

Inspired by the experiments \([11, 13, 17]\) the Hitchhiker model consists of an ensemble of particles performing random walks on a one dimensional lattice with size \( L \) and with periodic boundary conditions. We start placing a monomer \( (N = 1) \) in each lattice site. When particles meet they may merge creating multi-meres, whose size is \( N(t) \) \([23, 20, 42]\). Particles may also break in a binary way, with a rate \( w \). Here we have chosen binary breaking...
for the sake of simplicity but other breaking mechanisms like random scission or chipping give similar results (see Appendix 1). Such a model was considered by Rajesh et al. 20 where the focus was on dense systems, while here we allow for single molecule tracking, which means we work in the small rate of breaking regime, allowing for particles to diffuse freely for some time before they break or merge see Fig. 1 for a graphic representation of its dynamics see Fig. 3.

The diffusivity of the complex is $D(N)$, in each case of interest is defined by Eq. (6) or Eq. (7). As usual $D$ determines the frequency of jumps given by a cluster of monomers, in our model we consider that an aggregate of particles can either walk on a lattice to the left or right or it can remain on its site. We achieve this by considering a rate of diffusion $d(N)$ which comprises the physical relation between $D$ and $N$ as following: $d(N) = 1/N^\nu$ for the Stokes-Einstein-Flory model and $d(N) = e^{-N/\nu}$ for the Arrhenius case. The rate of diffusion $d(N)$ is defined more precisely in Eq. (B1) below. The diffusion coefficient and the rate of diffusion are related by $D(N) = d(N)/2\Delta$, with $\Delta = t_i - t_{i-1}$ the time increment (note that here the lattice spacing is set to one). A detailed description of the model is given in Appendix B.

IV. SIMULATIONS RESULTS

Simulating the model we now check: what is the distribution of the $P(N)$? how do the diffusion laws modify $P(N)$? and does the model give us the Laplace distribution? In this case $P(N)$ is the molecule size distribution for the FT tagging method. The first result presented in Fig. 4 shows clearly that modifying the microscopic law of diffusion has a strong impact on the distribution of $P(N)$. For Stokes-Einstein-Flory models i.e. with diffusion rates given by $d(N) = 1/N$ for the Rouse model with $\nu = 1$ and $d(N) = 1/N^2$ for the Zimm model with $\nu = 3/5$, we obtain visually broad distributions of $P(N)$ well fitted by Eq. (7) while for the Arrhenius model, $d(N) = e^{-N}$ with $\nu = 1$, we find a very narrow distribution well fitted with Eq. (10). Of course since our system is finite, and we work in the sparse limit of the model after reaching the steady state (in the sense that most lattice points are in fact empty, otherwise free diffusion is not defined) we have a finite cutoff and the largest particles we find are of size 32 for the Rouse model, 68 for the Zimm model and 8 for the Arrhenius one. In this way the sample average molecule sizes for the Zimm, Rouse and Arrhenius models satisfy the ordering $\langle N_Z \rangle = 9.93 > \langle N_R \rangle = 5.77 > \langle N_A \rangle = 2.48$. In reality and in simulations particles much larger than a monomer will be totally stuck on the finite time scale of observation 45. Mathematically this means that in the observed distribution of diffusivities we have a delta function on $D = 0$. For example in experimental measurements in 11 13% of particles are sub-threshold and one cannot determine their diffusivity.

One of our main observations is that for three models of $D(N)$, i.e. Rouse, Zimm, and Arrhenius, the packet of particles exhibits a transition from Laplace distribution to a Gaussian behavior. In Fig. 5 we show $P(x,t)$ in semi-log scale for a system following the Rouse model of diffusion rates and in the bottom of Fig. 5 we show the corresponding for the Arrhenius law. This transition was observed previously is some experiments 23 and using single particle Langevin dynamics with an added stochastic diffusivity 18, 30, 92. For short times, relative to the breaking and merging rate, we observe different particles of different sizes, whose distribution is $P(N)$. Then to find the displacement we average the Gaussian propagator which depends on $D(N)$ over the respective distribu-
FIG. 5. (Color online) Top: $P(x,t)$ in semi-log scale, obtained from the Hitchhiker model with Rouse dynamics. For short times we show the comparison with their respective Laplace distribution Eq. (3) (solid lines). $P(x,t)$ for large times are well described by Gaussian statistics Eq. (2) (dashed lines). Bottom: the same as above but for a system following Arrhenius diffusion rates, exhibiting the same transition towards Gaussianity, but within a longer time scale. For both cases the simulations were done for an ensemble of 10000 tracked molecules with a rate of breaking $w = 0.005$ and in the molecule size steady state regime. The particles were tracked by the FT method.

V. TRACKING IN A MANY BODY SCENARIO

As mentioned in the introduction one of the main goals of single molecule tracking is to evaluate the distribution of diffusivities and the non-Gaussian spreading. As we showed here this is related to the fluctuations in the sizes of the molecules. However these recorded observables depend on the measurement protocol. We consider two protocols of measurements, both applicable in single molecule experiments. In the first we label all the monomers/molecules estimating the distribution of diffusivity after they reached a stationary state, we call this method full tagging (FT), see bottom of Fig. 2. Results of Fig. 4 and Fig. 5 are based on the FT technique. In the single molecule (SM) we tag one light emitting unit (see top of Fig. 2). This monomer attaches and detaches to and from other molecules in the environment, which are not visualized in the laboratory.

Here for both mentioned methods we compare the respective distributions of sizes and the average diffusivities. Unlike free Brownian motion, the two procedures will give different results. In the second approach, the single emitter is statistically more likely to be found as part of a large $N$-mer.

To quantify the difference in the diffusivity arising from the usage of distinct tagging methods we use tools from renewal theory [46–48]. Typical phenomena described by this framework are: arrival times of particles to a detector, or a bus arriving to a station. It is assumed that the time intervals between events (called renewals) are mutually independent and identically distributed random variables. A classical problem is the calculation of the distribution of the time interval straddling, i.e. the statistics of the time interval defined by the first event after some observation time and the one just before it [46–48].

Next we implement these ideas in space of sizes.

As mentioned in the SM protocol, at the beginning of the experiment we pick randomly one and only one monomer, and this is the tracked particle. At a given moment we have in the system complexes with different sizes: $N_1, N_2, \ldots$, etc. Placing all these complexes on the line, see Fig. 6, we then ask what is the distribution of the size of the complex on which the tagged monomer is residing (called $z$)? This mathematically is the same as defining some large $\tilde{N}$ (much larger than the average size) and asking where this $\tilde{N}$ will fall, then the straddling size $z$ is defined by the interval around $\tilde{N}$ as in Fig. 6. Repeating this procedure many times we can obtain the distribution of $z$. In [46–48] it was found that it satisfies

$$P(z) \sim \frac{NP(N)|_{N=z}}{\langle N \rangle}.$$  \hspace{1cm} (11)
Here $P(N)$ is the distribution of sizes of molecules in our system which we have investigated already, i.e. employing the FT method and shown in Fig. 3. Eq. (11) shows how larger molecules are more likely to be sampled, as we multiply $P(N)$ with $N$. To gain insights we now recover Eq. (11) using simple arguments. Expressing $P(z)$ as

$$P(z) = \frac{\# \text{ of monomers in complexes with size } z}{\text{total number of monomers in the system}} \cdot \frac{z \cdot \# \text{ of complexes of size } z}{\sum_i \# \text{ of complexes of size } i \cdot \langle N \rangle}.$$

The last line of Eq. (12) is the same as Eq. (11), since by definition the empirical probability of the # of complexes of size $z$ divided by the sum of # of complexes of size $i$ is simply $P(N)_{N=1}$.

Using the Rouse model, we proceeded to make simulations with the Hitchhiker model following a single molecule until time $t$. In the top of Fig. 7 we present the molecule size distribution in the SM protocol (blue boxes) by acquiring the value of $z$ and we compare it with $P(N)$ in the FT protocol (red boxes). As one can see the PDF of $z$ is shifted to the right, namely large particles are sampled in agreement with Eq. (11). The value of the sample mean of the molecule size obtained from our simulations was $\langle N \rangle = 5.77$ and its peak (or the mode) is located at $N_{\text{max}} = 3$. In the case of the single Hitchhiker we have a sample mean $\langle z \rangle = 7.75$ and $z_{\text{max}} = 5$, so $\langle z \rangle > \langle N \rangle$ as expected. Another interesting feature of $P(z)$ is that, in the large size regime, it has a fatter tail in comparison with the one of $P(N)$.

In the bottom of Fig. 7 we observe that $P(z)$ (blue boxes) agrees with the analytical formula Eq. (11) extracted by the simulation data using the FT method (green boxes).

Eq. (11) allows us to go from one measurement protocol to another, and to make predictions of the diffusivity and the spreading of packets. For example the diffusivity in equilibrium, in the single particle approach is $D(z)$ when we follow all the molecules we have $D(N)$. The general trend is that in the single molecule approach we sample large complexes, and hence the diffusion is slowed down compared with the full tagging approach since statistically $D_{\text{SM}}(z) < D_{\text{FT}}(N)$.

The difference between the two tagging methods is quantified using the relation between the two average diffusivities. As we show in the Appendix D employing Eq. (11) and the Stokes-Einstein-Flory model Eq. (6), we find that the ratio of the diffusivities meets

$$\frac{\langle D_{\text{FT}} \rangle}{\langle D_{\text{SM}} \rangle} = \frac{\langle N \rangle}{\langle N^{1-\nu} \rangle} \left( \frac{1}{N^\nu} \right) \geq 1.$$

Here the averages on the right hand side are with respect to the distribution of sizes $P(N)$. This ratio is unity only if $P(N)$ is very narrow, i.e. it is delta peaked, or if $\nu = 0$ namely the diffusivity does not depend on size which is non-physical.

We now test Eq. (13) following the example of the Rouse model, in this case the ratio given by Eq. (13) is $\langle D_{\text{FT}} \rangle/\langle D_{\text{SM}} \rangle = \langle N \rangle/\langle 1/N \rangle$. From the data extracted in the simulations of the Rouse model for the FT protocol we have $\langle N \rangle = 5.77$ and $\langle 1/N \rangle = 0.25$, defining a ratio of $\langle D_{\text{FT}} \rangle/\langle D_{\text{SM}} \rangle = 1.44$. A direct measurement of average diffusivities by the MSD gives $\langle D_{\text{FT}} \rangle/\langle D_{\text{SM}} \rangle = 1.45$, see details in Appendix E. Finally in Fig. 8 we compare the distribution of displacements showing that the tracked particles in the FT protocol are visually faster, and FT and SM tagging methods exhibit at short times a Laplace like behavior. Clearly the tagging technique matters, and hence the estimation of the diffusivity field is non-trivial without using Eq. (13).

VI. DISCUSSION

The exponential decay of the distribution of displacements, Eq. (3), is found for all the observed range of $x$, in some single molecule experiments such as [14, 17]. Nevertheless in some other experiments e.g. [12, 27], the exponential decay is found in the tails of the distribution. The Laplace distribution Eq. (3) in the full range of $x$ is recovered by Eq. (5) for very specific distributions of diffusivities $P(D)$ and therefore distribution of molecule sizes $P(N)$. Hence we ask, how robust is the exponential decay in the distribution of displacements for pertinent modifications on $P(N)$ and $P(D)$?
In the majority of experiments, due to finiteness of the cell, the distribution of molecule sizes (or the distribution of intensities) exhibits a cut off at the large size regime \[ P(x,t) \xrightarrow{t \to \infty} \delta(x-x_0) \] Then it is reasonable to modify \[ P(N) \] obtained with the phenomenological model Eq. (7) by adding an exponential cut off term for the large size regime, see Eq. (11) below. We find that even for different values of the cut off size, \[ P(x,t) \] via Eq. (3) still displays an exponential decay in the large \( x \) regime. For small \( x \) we have a Gaussian like behavior in \( P(x,t) \).

In some other experiments with aggregation and breaking of polymers as in \[ \text{[49]} \], the distribution of cluster sizes was fitted with the log-normal distribution. Compared with the distributions found by phenomenological arguments Eq. (7) and Eq. (9) the log-normal distribution, for a wide range of its parameters, shares with them qualitative similarities. Furthermore in sedimentation of particles \[ \text{[50]} \] the log-normal distribution arises as an effective predictive model. The log-normal distribution for particle sizes was suggested by Kolmogorov using central limit theorem arguments \[ \text{[51]} \]. By averaging a Gaussian propagator for the displacements with a log-normal distribution, for \( x \) a narrow distribution of molecule sizes can lead to a relative large fluctuation in \( D \). Still in all cases we find in the short time regime Laplace distributions for \( P(x,t) \), see Fig. 5.

The second main result was that the protocol of tagging molecules matters. Briefly when one single molecule is tagged its average diffusivity is smaller compared with the diffusivity obtained via the full tagging protocol. From the experimental point of view the difference between average diffusivities Eq. (13) is important since the estimation of diffusivity can be made in several ways. As long as the experiment time is shorter than the mixing time the method of tagging is crucial. Importantly we believe this is the typical situation in the cell, as otherwise one would observe simple Gaussian diffusion and very narrow distribution of diffusivities.

Previous work \[ \text{[5]} \] showed that diffusion in disordered systems, like the cell may exhibit weak ergodicity breaking. This points out a difference between time and ensemble averages. Theoretically it is found due to the divergences in the average waiting time in continuous time random walk models, this phenomenon is observed together with anomalous diffusion. In the case of the Hitchhiker model the processes are perfectly normal and ergodic, still different tagging protocols surrender average diffusivities which vary depending on the chosen protocol of tagging. Since diffusivity yields estimates of biochemical reaction rates, our work could help clarifying better the basic meaning of diffusion fields within the cell.

We used two approaches to describe the problem the first phenomenological and the second microscopical. The first approach is useful as it applies for any dimension, and in that sense it is operational. Further its predictions can be tested in the laboratory, as a measurement of the distribution of sizes which gives the distri-
bution of diffusivities (in practice other effects may contribute to the distribution of diffusivities, the claim here is that a considerable contribution comes from the distribution of sizes).

The microscopic method developed here has the advantage that it can be adjusted to different dynamics that happen in the cellular media, i.e. different diffusion laws, mechanisms of breaking, even active transport. Besides its extension to higher dimensions like 2D or 3D is plausible. Nonetheless we believe that the change of dimension in the system won’t modify the results dramatically, since the fluctuations in sizes still will be within a broad range of values, inducing a non-Gaussian distribution of displacements. Further, the key observation is that the Hitchhiker model in any dimension will exhibit a normal distribution in the system won’t modify the results dramatically, since the fluctuations in sizes still will be within a broad possible. Nonetheless we believe that the change of dimension to higher dimensions like 2D or 3D is plausible. Therefore we believe that the model is elastic, though of course more work is needed on the exact conditions for exponential tails.

Appendix A: Deduction of the distribution of sizes

We are searching the distribution of sizes \( P(N) \) which by means of Eq. (5), satisfies the Laplace distribution Eq. (3). By changing variables as \( N \rightarrow D \), now Eq. (5) is given by

\[
\frac{e^{-\frac{|X|}{\sqrt{4Dt}}}}{\sqrt{4\pi Dt}} = \int_0^\infty e^{-\frac{x^2}{4Dt}} P(D) dD. \tag{A1}
\]

with \( P(D) = (P(N)|\frac{dN}{dD}|)_{N=N(D)} \) and \( N(D) \) the inverse of Eq. (6) or Eq. (8). As mentioned in the introduction the distribution of diffusivities must be exponential in order to obtain the Laplace law Eq. (5). For the specific diffusion model the change of variables \( D \rightarrow N \) defines \( P(N) \). In the Stokes-Einstein-Flory diffusivity model Eq. (6) the molecule size distribution is equal to Eq. (7). In the case of the Arrhenius model Eq. (8), the corresponding molecule size distribution is defined by Eq. (9).

Appendix B: Dynamics of the Hitchhiker model

**Diffusion.** In the Hitchhiker model depending on their size the molecules have different probabilities of walking, such that the probability of hopping decreases with its respective size. Let \( \{X_i(N)\}_{t \in \mathbb{Z}^+} \) be the position of a random walker with size \( N \) at time \( t \). We employ a size dependent diffusion rate \( d(N) \), which is related with the diffusion coefficient \( D \) see Eq. (B3), defined in each case by the models Eq. (6) or Eq. (8). For the Rouse model we have \( d(N) = 1/N \), in the Zimm model \( d(N) = 1/N^\frac{3}{2} \) and for the Arrhenius case \( d(N) = e^{-N} \). Thus the corresponding transition probabilities from site \( i \) to site \( j \) in one step of time are given by

\[
P(X_t = j | X_{t-1} = i) = \begin{cases} \frac{d(N)}{2} & \text{if } j = i + 1, \\ \frac{d(N)}{2} & \text{if } j = i - 1, \\ 1 - d(N) & \text{if } j = i, \\ 0 & \text{otherwise.} \end{cases} \tag{B1}
\]

For a molecule with size \( N \) the first/second row in Eq. (B1) defines the probability to give a step to the right/left on the lattice. The third entry represents the probability of remaining at the same site. Thus the displacement of a random walker with size \( N \), is defined by \( \Delta X_t(N) = X_t(N) - X_{t-1}(N) \), such that \( \Delta X_t(N) \in \{-1,0,1\} \). We consider two different sorts of interactions between particles: breaking and aggregation.

**Breaking.** We assume a spontaneous binary breaking of molecules, see Fig. 3. Namely, if a molecule is composed of an even number of monomers it breaks into two equal parts of size \( N_i/2 \). When a molecule is composed by an odd number of monomers, it splits into two parts \( (N_i - 1)/2 \) and \( N_i - \frac{2N_i - 1}{2} \). In both cases the remaining clusters are placed randomly at the immediate neighboring sites, leaving empty the site of breaking. The rate of breaking is \( w \) (see more details below in simulations methods).

**Aggregation.** In the two cases of breaking, aggregation happens when the remaining parts are placed randomly and add up with the molecules at their respective neighboring sites \( j \in \{i-1,i+1\} \), leaving the site \( i \) empty. For the diffusion of particles at site \( i \), the corresponding aggregation takes place when the molecule jumps and adds up to the molecule at \( i + 1 \) or at \( i - 1 \), see Fig. 3 and Fig. 4.

The variance in the Hitchhiker model in a simple step, which is defined by the displacements \( \Delta X_t(N) \in \{-1,0,1\} \) and the transition probabilities Eq. (B1), is equal to

\[
\mathbb{E}[\Delta X_t^2(N)] = d(N). \tag{B2}
\]

Substituting Eq. (B2) in Eq. (1) the diffusion coefficient \( D \) and the diffusion rate \( d(N) \) in the Hitchhiker model are related by

\[
D = \frac{d(N)}{2\Delta}, \tag{B3}
\]

with \( \Delta = t_i - t_{i-1} \), here we used lattice spacing equal to one, in all of the cases the corresponding parameters in \( D \) are set to one i.e. \( k_B T / 6 \pi \eta b = 1 \), \( D_o = 1 \) and \( c = 1 \).

Appendix C: Simulations

The simulations of the Hitchhiker model were made by the following algorithm. At the initial time every site
in the lattice is occupied by one monomer \((N_i = 1)\), given this at every update one non-empty site is chosen randomly, then either with probability \(d(N)/[w + d(N)]\) we do diffusion and the corresponding aggregation; or with probability \(w/[d(N) + w]\) we perform a breaking event and its corresponding aggregation. We consider that after \(M\) updates a Monte Carlo step is achieved. The value of \(M\) is defined by the average number on non-empty sites in the lattice, 1000 for the Rouse Model, 500 for the Zimm and 2000 for the Arrhenius one.

We use a fixed rate of breaking \(w = 0.005\) and a lattice with 6000 sites. And the range of diffusion \(d(N)\) depends on the size of each diffusing molecule via the Rouse, Zimm (Stokes-Einstein) Eq. (7) or Arrhenius Eq. (9). The distributions of \(P(x,t)\) for all the cases were obtained within the steady state regime for the molecule size distribution. This means that first we relax the system, letting it reach equilibrium.

We implemented the tagging protocols as following, for the FT method after a relaxation time all the different size molecules are labeled and then tracked. For the SM method starting from the initial configuration, one monomer is marked and then it is traced.

**Appendix D: Average diffusivity in the FT and SM tracking protocols**

Following the Stokes-Einstein-Flory theory employing the diffusion rate \(d(N) = 1/N^\nu\), by Eq. (13), the diffusion coefficient is \(D(N) = 1/(2N^\nu \Delta)\). In this way the average diffusivity in the FT method is given by

\[
\langle D \rangle_{FT} = \int_0^\infty D(N)p(N)dN = \frac{1}{2\Delta} \left( \frac{1}{N} \right). \tag{D1}
\]

On the other hand in the SM protocol we have \(D(z) = 1/(2z^\nu \Delta)\). In this case the average diffusivity by Eq. (11) is given by

\[
\langle D \rangle_{SM} = \left( \int_0^\infty \frac{Np(N)}{\langle N \rangle} dN \right) \left| \frac{N}{N} \right|_{N=z} = \frac{1}{2\Delta} \left( \frac{N^{1-\nu}}{\langle N \rangle} \right). \tag{D2}
\]

Both Eq. (D1) and Eq. (D2) define the ratio Eq. (13).

**Appendix E: Average diffusivity in the Rouse model**

We corroborate this difference in the diffusivities for the Rouse model using simulations of the Hitchhiker model and within the Laplace regime for \(P(x,t)\), in Fig. 8 in the main text we show the difference in the particle spreading generated by \(D_{SP}(z) < D_{FT}(N)\). When the SM tagging method is used the maximum length in the displacements (blue circles) reached by the tracked particles is lower than the one obtained with the FT protocol (red circles). In each case we show in solid color lines the corresponding fitting with the Laplace distribution Eq. (3). From the data of \(X_i\) we computed the ratio between diffusivities by the variance of each data set since \(\langle x^2 \rangle_{FT} = 2(D)_{FT}t\) and \(\langle x^2 \rangle_{SM} = 2(D)_{SM}t\), having a value of \(\langle D \rangle_{FT}/\langle D \rangle_{SM} = 1.4550\).

**Appendix F: Cut off size and the distribution of displacements**

A power law distribution for the molecule sizes must have a cut off in the large size region, we call the cut off scale \(N^*\). In this way the PDF of \(N\) in Eq. (7) can be modified as

\[
P(N) = \tilde{C}N^{-\nu-1}e^{-\frac{N}{\nu}} e^{-\frac{N}{N^*}}, \tag{F1}
\]

with \(\tilde{C}\) the normalization constant, \(c > 0\) and \(c\exp(-N/N^*)\) a term representing an exponential cut off in the large size regime. Now we can ask ourselves how this cut off size influences the distribution of displacements?

Following the super-statistics approach and assuming the Stokes-Einstein-Flory diffusivity as \(D(N) = D_0/N^\nu\), with \(D_0 > 0\) then distribution of the displacements is given by

\[
P(x,t) = \int_0^\infty \tilde{C}N^{-\nu-1}e^{-\frac{N}{\nu}} e^{-\frac{N}{N^*}} e^{\frac{N^*}{2D_0t}} dN,
\]

\[
\frac{\sqrt{\frac{\pi}{4\nu}}}{C} P(x,t) = \int_0^\infty e^{-I(N)} dN, \tag{F2}
\]

with \(I(N) = \frac{N}{\nu} + \frac{N}{N^*} + N^\nu \chi^2 - \left( \frac{\nu}{2} - \nu - 1 \right) \ln N\) and \(\chi^2 = x^2/4D_0t\). Considering the scaling \(N = \chi^2\), taking into account the leading terms for \(\chi \to \infty\) then \(P(x,t)\) can be approximated by the steepest descent method as

\[
\frac{\sqrt{\frac{\pi}{4\nu}}}{C} P(x,t) \approx \sqrt{\frac{2\pi}{2\chi^2 - \frac{2}{\nu} \chi^2}} e^{-(1+c)|x| - \frac{|x|^2}{2\nu} - (\frac{\nu}{2} + 1) \ln |x| - \frac{\nu}{2}}. \tag{F3}
\]

This shows that for the large \(x\) regime \(P(x,t)\) exhibits exponential tails even for a power law distribution with a cut off Eq. (F1). As an example we work with the Rouse model \(D(N) = D_0/N\), in Fig. 9 the solution of Eq. (F2) is shown in semi-log scale for different values of \(N^*\in\{10,30,100\}\) (red, blue and green solid lines respectively). As we can see for the three cases, in the large \(x\) regime, \(P(x,t)\) has an exponential decay. In the inset of Fig. 9 we show the respective molecule size distribution in log-log scale with the respective exponential cut off in \(N \to \infty\). Physically large \(N\) implies small diffusivities, and this influence the statistics of \(P(x,t)\) when \(x\) is small thus the cut off at \(N^*\) is not important for the large \(x\) regime.
FIG. 9. (Color online) Distribution of displacements Eq. (F2) in semi-log scale, for molecule size distribution with an exponential cut off Eq. (F1) with \( c = 1 \) and for \( N^* = 10 \) red solid line, \( N^* = 30 \) in blue solid line and \( N^* = 100 \) in green solid line. For \( \chi = |x|/\sqrt{4D_0t} \) in the limit \( \chi \to \infty \) all the distributions have exponential tails collapsing in one straight line. In each case the approximated solution Eq. (F3) is shown in dashed color line. In the inset we show the corresponding molecule size distribution Eq. (F1) in log-log scale.

FIG. 10. (Color online) Molecule size distributions obtained for simulations for the Rouse (red circles), Zimm (blue circles) and Arrhenius (black circles) models. The respective fitting with Eq. (7) and Eq. (10) is shown in color solid lines. In each case a fitting with the log-normal distribution Eq. (G1) is displayed in dashed yellow lines, demonstrating that widely used log-normal distribution is a valid model. The simulations parameters are the same as in Fig. 4.

Appendix G: Fitting the log-normal distribution for the molecule sizes

The log-normal distribution is given by

\[
P(N) = \frac{e^{-(\ln N - \mu)^2/2\sigma^2}}{N\sigma\sqrt{2\pi}}, \tag{G1}
\]

with \( \mu \) the mean value and \( \sigma \) the standard deviation. As mentioned in the Discussion this distribution has been used as a model for the distribution of sizes in breaking/aggregation phenomena.

In Fig. 10 we show \( P(N) \) obtained from simulations of the Hitchhiker model for different diffusion rate models (color circles) with the respective fitting with the log-normal distribution given by Eq. (G1) (yellow dashed line). As we can see the log-normal distribution fits in a good way, as well Eq. (7) and Eq. (10) (solid color lines), to the molecule size distributions in the Hitchhiker model. It immediately follows that widely used log-normal distributions can be used to predict exponential tails of \( P(x,t) \) as we now demonstrate.

Using Eq. (5) we found \( P(x,t) \) by averaging a Gaussian packet with a log-normal distribution obtained by the fitting of the molecule size distribution extracted via simulations of the Hitchhiker model. So we proceeded to solve Eq. (5) with \( P(N) \) following the log-normal distribution Eq. (G1) with \( \mu = 1.61 \) and \( \sigma = 0.41 \), see green solid line in Fig. 11. For this case \( P(x,t) \) has exponential tails for large \( x \), though when \( x \approx 0 \) the curvature of \( P(x,t) \) is more Gaussian like. The Laplace distribution Eq. (6) is non-analytical on \( x = 0 \) but this is not observed in this case. At the same time in Fig. 11 we compare the latter distribution of displacements with \( P(x,t) \) obtained from the numerical solution of Eq. (5) with \( P(N) \) given by the fitting of the molecule size distribution in the simulations with Eq. (7) (magenta solid line). As we can see both cases exhibit exponential tails and fit satisfactorily the simulation data for \( P(x,t) \) (red circles).

Appendix H: Exponential tails in \( P(x,t) \)

As mentioned while some experiments and stochastic frameworks promote the modelling of data with the Laplace distribution, at least in the short time limit of the diffusive process, others observe the exponential decay of the distribution of displacements only in the tails of the packet \[27\]. To understand this better consider an empirical distribution of diffusivities, fitted with a finite sum of exponentials

\[
P(D) = \sum_{i=1}^{k} \frac{a_i}{D_i} \exp(-D/D_i). \tag{H1}
\]

Using

\[
\int_0^\infty \frac{\exp(-D/D_i)}{\sqrt{4\pi D_i t}} \frac{dD}{\sqrt{4D_i t}} = \frac{\exp(-|x|/\sqrt{D_i t})}{\sqrt{4D_i t}} \tag{H2}
\]
the super-statistics principle gives

\[ P(x, t) = \sum_{i=1}^{k} a_i \exp \left( -\frac{|x|}{\sqrt{4D_i t}} \right). \quad (H3) \]

Thus the propagator is a weighted sum of Laplace distributions. If \( k = 1 \), namely an exponential distribution of diffusivities, we have only one term in the sum. In the general case we arrange \( D_1 < D_2 \ldots < D_k \) so \( D_k = D_{\text{max}} \). Then we focus on the large \( x \) tail of the packet of particles and find

\[ P(x, t) \simeq \frac{a_k}{\sqrt{4D_{\text{max}} t}} \exp \left( -\frac{|x|}{\sqrt{4D_{\text{max}} t}} \right). \quad (H4) \]

As a simple example consider a sum of two exponentials \( P(D) = N[\exp(-D) - \exp(-\lambda D)] \) with \( \lambda > 1 \), so here \( P(0) = 0 \) unlike the case discussed in text with a maximum on \( D = 0 \), see Eq. (1). In experiments it is common to present the distribution of displacements on a log-linear scale to emphasize the exponential decay of the data, hence we do the same

\[ \ln \left[ \sqrt{4t}P(x, t) \frac{\lambda - 1}{\lambda} \right] = -\xi + \ln \left\{ 1 - \frac{1}{\sqrt{\lambda}} e^{-\xi(\sqrt{\lambda} - 1)} \right\} \quad (H5) \]

where \( \xi = |x|/\sqrt{4D_{\text{max}}} \) and now we set \( D_{\text{max}} = 1 \). We see that when either \( \lambda \) or \( \xi \) are large we may neglect the second term on the right and find a linear function. Large \( \lambda \) means that the ratio of the two diffusivities in the model, \( D_{\text{max}}/D_{\text{min}} = \lambda \) is large. Specifically

\[ \ln \left[ \sqrt{4t}P(x, t) \frac{\lambda - 1}{\lambda} \right] = \begin{cases} -\sqrt{\lambda} \xi^2/2 & \text{if } \xi \ll 1 \\ -\xi & \text{if } \xi \gg 1. \end{cases} \quad (H6) \]

Hence for small \( \xi \) we find a Gaussian behavior. In Fig. 12 we show Eq. (H5) for different values of \( \lambda \in \{2, 5, 50\} \). As we can see in all the cases for large \( \xi \) the distribution of displacements exhibit exponential tails. In the inset of Fig. 12 we show the small \( \xi \) limit, for which the logarithm of \( P(X, t) \) shows a parabolic decay characteristic of the Gaussian distribution.

The transition between these asymptotic behaviors takes place when \( \xi \simeq 2/\sqrt{\lambda} \) so as we increase the diffusivity ratio \( \lambda \) the transition from Gaussian for small \( \xi \) to Laplace for large \( \xi \), is pushed to smaller values of \( \xi \). We note that the average diffusivity in the model is \( \langle D \rangle = \sum_{i=1}^{k} a_i D_i \), and only when \( k = 1 \) we have \( \langle D \rangle = D_{\text{max}} \) hence in generality the average diffusivity does not give the exponential tail of the packet of particles which is determined by \( D_{\text{max}} \).

**Appendix I: Other breaking mechanisms**

**Random scission**

Instead of doing an equal binary breaking here we present the distribution for molecule sizes \( P(N) \) and displacements \( P(x, t) \) for the Hitchhiker model, but for a random fission mechanism. For this case a breaking event happens at a constant rate \( w \), although now the cluster of particles with size \( N_i \) is divided into two random parts \( N_i - F \) and \( F \). With \( F \) a discrete uniform random variable, such that \( F \in [1, N_i - 1] \). In this way a monomer or a bigger sub-aggregate (less than \( N - 1 \)) can be ripped out from the cluster. The remaining two parts are placed randomly at the neighboring sites, leaving empty the site of breaking. The corresponding aggregation takes place when the mentioned fractions are add up at the neighboring sites \( \{i - 1, i + 1\} \).

In the top of Fig. 13 we show in purple circles the molecule size distribution obtained from simulations of the Hitchhiker model with random binary fragmentation and Rouse dynamics. As we can see \( P(N) \) qualitatively has the same shape as in the case of equal binary breaking (red circles), but they differ in the peak height and the latter is shifted to the right. Then is reasonable assuming that \( P(N) \) still has the same functional form but now with different parameters. This is shown in Fig. 13 by the purple solid line, which represents the corresponding fitting with an inverse gamma distribution like model given by

\[ P(N) = CN^{-\beta}e^{-N/\delta}. \quad (I1) \]

The parameters relative to the powers of \( N \) in Eq. (I1) are \( \beta = 2.83 \) and \( \delta = 0.37 \). In the middle of Fig. 13 we observe that the displacements for short times follow a Laplace distribution Eq. (3), recovering Gaussian statistics Eq. (2) in the long run. By changing the breaking mechanism for a more general one, we see that the distribution of sizes qualitatively remains equal and the displacements still exhibit an exponential decay in the short run.

**Chipping**

Finally we implement a single molecule breaking, also
we show a hiker model with Rouse dynamics. In the top of Fig. 13 we used chipping of particles in the Hitchhiker with Rouse dynamics. In the inset we show the same but in log-log scale, as we can see the power law model just follows a transition from exponential in the low density regime to a power law distribution in the high density limit. In our case, since the density is given by $\rho = \text{Total mass}/L = 1$, it is not clear which distribution should follow $P(N)$. In Fig. 13 we show a power law fitting (solid black line) with the simulation data of the Hitchhiker with chipping, as we can see in the inset plot the power law $P(N) \sim N^{-\tau}$ with $\tau = 1.15$ fits well just for the range of small values of $N$. But in the large size regime this model does not describe anymore the behavior of $P(N)$. What does it hold with this dynamics, that the displacements also exhibit an exponential decay for the short time regime, see bottom of Fig. 13 and Gaussian statistics are recovered for the large time regime.

**High density regime**

As mentioned above working in the high density limit $\rho >> 1$, for similar aggregation models with chipping and molecule size dependent diffusion rates [26], power law distributions for $P(N)$ have appeared. In Fig. 14 we show $P(N)$ for the Hitchhiker model with chipping and for different levels of density in the system $\rho \in \{0.2, 10, 20\}$. A fitting with a power law with exponent $\tau = 1.15$ is shown in solid black line. We observe that for the low density regime $\rho = 0.2$ (red diamonds) $P(N)$ decays exponentially and for systems with a higher density $\rho = 10$ (blue triangles) and $\rho = 20$ (black squares) $P(N)$ follows a power law except for large values of $N$.

**Note added:** After the submission of this manuscript several related works on the topic have been posted on the arXiv [56–58].
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