



# Active transport in complex media: Relationship between persistence and superdiffusion

Marcelo A. Despósito<sup>a,c,\*</sup>, Carla Pallavicini<sup>a</sup>, Valeria Levi<sup>b,c</sup>, Luciana Bruno<sup>a,c</sup>

<sup>a</sup> Departamento de Física, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 1428 Buenos Aires, Argentina

<sup>b</sup> Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 1428 Buenos Aires, Argentina

<sup>c</sup> Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina

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## ABSTRACT

We study the relationship between anomalous diffusion and persistent motion of micron-sized particles moving in a viscoelastic environment and subjected to an external noise. In the framework of a generalized Langevin equation, we compare the analytical expressions of the mean square displacement and the mean cosine of the turning angle. Both magnitudes can be easily computed from the particles trajectories, and allow us to investigate the different anomalous regimes typically obtained, for instance, in single particle tracking experiments within living cells. Finally, we analyze the directional changes occurring during the motion of pigment organelles driven by molecular motors in *Xenopus laevis* melanocytes, as an example of application of our model.

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## 1. Introduction

In a viscous fluid where a particle freely diffuse, the mean-square displacement (MSD) of the particle is proportional to time. In contrast, diffusion through complex media with viscoelastic properties (such as polymers, colloids, and biological materials) exhibits an anomalous regime characterized by the occurrence of a MSD which deviates from the linear Brownian dependence on time.

Anomalous diffusion has been observed in a wide variety of complex systems [1]. When the system is only driven by thermal fluctuations, typically subdiffusive regimes are recovered [2–4]. However, in the presence of nonthermal active processes, such as the action of molecular motors in living cells, the system can also exhibit superdiffusion. Transitions between different anomalous regimes have been observed in many experimental conditions [5–13].

One of the commonly used techniques to characterize the viscoelastic properties of complex media is microrheological experiments where the motion of a small tracer particles is analyzed [14–20]. Typically, trajectories are recovered with millisecond temporal resolution and nanometer precision by means of single particle tracking (SPT) techniques (see e.g. Ref. [21]).

Microrheology is based on the generalized Langevin equation (GLE) for the particle vector position  $\vec{X}(t)$

$$m \frac{d^2 \vec{X}(t)}{dt^2} + \int_0^t dt' \gamma(t-t') \frac{d\vec{X}(t')}{dt'} = \bar{\xi}(t) + \bar{f}_e(t), \quad (1)$$

where the dissipative memory kernel  $\gamma(t)$  characterizes the viscoelastic properties of the medium,  $\bar{\xi}(t)$  is the *internal* noise due to thermal activity and  $\bar{f}_e(t)$  is an external force.

\* Corresponding author at: Departamento de Física, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 1428 Buenos Aires, Argentina.  
E-mail address: [mad@df.uba.ar](mailto:mad@df.uba.ar) (M.A. Despósito).

Trajectories are often characterized through the statistical behaviour of the MSD as a function of the time lag  $\tau$ , which allows determining the different diffusive regimes (see e.g. Refs. [2,22,11,23]).

Alternative information about the observed behaviour can be extracted from the turning angles between successive segments, so the directionality or persistence aspects of the motion can be studied. The study of the turning angle of particles trajectories has started to be used since it allows retrieving further information than the obtained from the MSD analysis. Examples of this approach can be found in cytoskeleton remodeling [12,8,9], endosomes dynamics [4], animal [24] and cell [25] searches strategies.

For instance, a subdiffusive process can be the consequence of trapping or caging, and the analysis of the turning angle can help to favor one over the other hypothesis. As an example, Lenormand et al. have shown that caged dynamics regulates cytoskeleton remodeling at short time scales based on the antipersistent motion of microbeads bound to the cytoskeleton [12]. On the other hand, Refs. [12,8,9] have provided evidence of directional memory in the remodeling of the cytoskeleton at long time lags due to active transport. In that system, the MSD undergoes a transition from subdiffusive to superdiffusive behaviour with time, which is associated with changes of the turning angle distribution from antipersistence to persistence, suggesting that superdiffusion is strongly associated with persistent behaviour.

However, no formal theory has been proposed to relate the microscopical aspects of forces acting over the particle to the observed anomalous behaviour and its association with persistence.

So, in this paper we investigate the relationship between anomalous diffusion and motion persistence of a particle moving through a complex environment and actively driven by external fluctuations. Also, we explore if active transport will always result in a superdiffusive outcome and how the viscoelastic properties of the medium condition the final dynamics. To answer these questions, we base our study on a very general theoretical framework starting from a GLE introduced in Ref. [23]. We consider that the motion of particles is strongly damped as is observed in many experimental systems such as the intracellular media [26]. In this condition, the inertial term in the GLE (1) can be neglected.

To model the action of active forces we add an external noise. Assuming a power law correlation function for the external noise, we explore the connection between persistence-superdiffusion and antipersistence-subdiffusion. Our approach also recovers the experimentally observed transition between different anomalous regimes [23,12,8].

In the next section, we present the model and explicit expressions for the two-time dynamics are computed as a function of time and time lag. Then, we calculate the analytical expression for the MSD and the mean cosine of the turning angle, and compare the behaviour at the long time limit.

To test our results, in Section 3 we analyze the actin-based transport of *Xenopus laevis* melanosomes driven by myosin-V motors using this framework. From the analysis of the data, we conclude that a bound value for the exponent of the motor forces correlation is required in order to recover the persistent and superdiffusive regimes.

Finally, a summary of our results is given in Section 4.

## 2. The model

In what follows we consider the GLE proposed in Ref. [23] in which  $\bar{f}_e(t) = \bar{\chi}(t)$  is a fluctuating force representing the action exerted by an external energy source. This contribution stems from sequences of active directed movements into random directions and can originate a transition from a subdiffusive to a superdiffusive regime [23]. Thus, the total random force  $\bar{\xi}(t) + \bar{\chi}(t)$  is assumed to be the sum of two uncorrelated contributions. The internal thermal noise  $\bar{\xi}(t)$  is related to the memory kernel  $\gamma(t)$  via the fluctuation-dissipation theorem (FDT) [27]:

$$C(t) = k_B T \gamma(t), \quad (2)$$

where  $C(t)$  is the corresponding autocorrelation function,  $T$  is the absolute temperature and  $k_B$  is the Boltzmann constant. However, the presence of the external fluctuating force  $\bar{\chi}(t)$  implies that an overall FDT is no longer valid because a relation between friction and the total noise correlation does not hold.

In what follows we consider that the typical damping time constant is too short to be appreciable experimentally and thus the effect of inertia can be neglected in (1). Assuming that  $\bar{X}(t=0) = 0$ , the evolution of the position mean value can be written from (1) as

$$\bar{X}(t) = \int_0^t dt' G(t-t') (\bar{\xi}(t') + \bar{\chi}(t')), \quad (3)$$

where the relaxation function  $G(t)$  is the inverse form of the Laplace transform:

$$\widehat{G}(s) = \frac{1}{s\widehat{\gamma}(s)}, \quad (4)$$

being  $\widehat{\gamma}(s)$  the Laplace transform of the dissipative memory kernel.

Then, from Eq. (3) and using the previous results given in Ref. [23], one can demonstrate that

$$\langle \bar{X}(t+\tau) \cdot \bar{X}(t) \rangle = 2k_B T [I(t) + I(t+\tau) - I(\tau)] + 2E(t, \tau), \quad (5)$$

where

$$I(t) = \int_0^t dt' G(t'), \quad (6)$$

and

$$E(t, \tau) = \int_0^t dt_1 [G(t_1)H(t_1 + \tau) + G(t_1 + \tau)H(t_1)] \quad (7)$$

is the contribution of the external noise, being

$$H(t) = \int_0^t dt_1 G(t_1) \Lambda(t - t_1), \quad (8)$$

the convolution of the kernel  $G(t)$  with the external noise correlation function.

The internal noise  $\xi(t)$ , responsible for the passive motion, is a zero-centered and stationary random force with correlation function  $\langle \xi(t)\xi(t') \rangle = C(|t - t'|)$ . Pure power-law correlation functions are usually employed to model subdiffusive processes in viscoelastic media [28–30]. Then, we assume that the Laplace transform of the noise autocorrelation function  $C(t)$  can be chosen as

$$\widehat{C}(s) = C_0 s^{\lambda-1}, \quad (9)$$

where  $0 < \lambda \leq 1$  and  $C_0$  is a proportionality coefficient. When  $0 < \lambda < 1$ , the noise autocorrelation function exhibits a power-law time decay

$$C(t) = \frac{C_0}{\Gamma(1 - \lambda)} t^{-\lambda}, \quad (10)$$

corresponding to a subdiffusive regime due to the long-time tail of the noise. On the other hand, for  $\lambda = 1$  one gets  $C(t) = C_0 \delta(t)$ , corresponding to a white noise, non-retarded friction, which gives rise to a normal diffusion.

The force autocorrelation  $\Lambda(|t - t'|) = \langle \chi(t)\chi(t') \rangle$ , is assumed to be given by the inverse Laplace transform of

$$\widehat{\Lambda}(s) = \Lambda_0 s^{\alpha-1}, \quad (11)$$

being  $\Lambda_0$  a proportionality coefficient and  $0 < \alpha \leq 1$ . The limit  $\alpha \rightarrow 1$  corresponds to a series of instantaneous infinite force pulses (white noise limit) while  $\alpha \rightarrow 0$  corresponds to the indefinitely large memory case, i.e., the so-called strong memory limit [31]. Then, an intermediate value of  $\alpha$  should correspond to a smoothing of discontinuities in instantaneous force pulses.

Using the autocorrelation functions given by (9) and (11), the kernels  $I(t)$ ,  $G(t)$ ,  $H(t)$  can be written as [23]

$$I(t) = \frac{k_B T}{C_0} \frac{1}{\Gamma(\lambda + 1)} t^\lambda, \quad (12)$$

$$G(t) = \frac{k_B T}{C_0} \frac{1}{\Gamma(\lambda)} t^{\lambda-1}, \quad (13)$$

$$H(t) = \varepsilon k_B T \frac{1}{\Gamma(\lambda - \alpha + 1)} t^{\lambda-\alpha}, \quad (14)$$

where  $\varepsilon = \Lambda_0/C_0$  and  $\Gamma(z)$  is the gamma function.

On the other hand, the integral term (7) can be explicitly evaluated when  $2\lambda - \alpha > 0$ . Using (13) and (14) we get

$$E(t, \tau) = \varepsilon \frac{k_B T}{\gamma_0} \frac{1}{\Gamma(\lambda)} \frac{1}{\Gamma(\lambda - \alpha + 1)} \tau^{2\lambda-\alpha} \left[ (-1)^{-\lambda} B_{-\frac{\tau}{t}}(\lambda, \lambda - \alpha + 1) - (-1)^{\lambda+\alpha} B_{-\frac{t}{\tau}}(\lambda - \alpha + 1, \lambda) \right], \quad (15)$$

where  $B_x(a, b)$  is the incomplete beta function [32].

Then, expressions (12) and (15) fully determine the dynamics of the correlation function (5).

## 2.1. Mean-square displacement

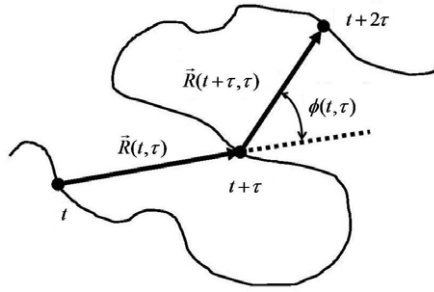
Typically, a 2D particle trajectory is quantitatively analyzed in terms of the MSD, which is calculated as  $\langle (\bar{X}(t + \tau) - \bar{X}(t))^2 \rangle$  where  $|\bar{X}(t + \tau) - \bar{X}(t)|$  is the particle displacement between two time points,  $t$  denotes the *absolute time* while  $\tau$  is the so-called *lag time*.

In Ref. [23], the MSD was calculated using the correlation (5) given by (9) and (11). In particular, it can be demonstrated that the MSD long time limit

$$\rho(\tau) = \lim_{t \rightarrow \infty} \langle (\bar{X}(t + \tau) - \bar{X}(t))^2 \rangle \quad (16)$$

can be written as

$$\rho(\tau) = \frac{4k_B T}{\gamma_0} \left\{ \frac{1}{\Gamma(\lambda + 1)} \tau^\lambda + \varepsilon K_{\lambda, \alpha} \tau^{2\lambda-\alpha} \right\}, \quad (17)$$



**Fig. A.1.** Schematic trajectory, illustrating the turning angle  $\phi(t, \tau)$  and the vectors  $\bar{R}(t + \tau, \tau)$  and  $\bar{R}(t, \tau)$ , being  $t$  the absolute time and  $\tau$  the lag time.

where

$$K_{\lambda, \alpha} = \Gamma(\alpha - 2\lambda) \frac{\sin(\pi(\lambda - \alpha)) - \sin(\pi\lambda)}{\pi} \tag{18}$$

is the positive constant defined in Ref. [23],  $\gamma_0 = C_0/kT$  and  $\varepsilon = \Lambda_0/C_0$  is a dimensionless parameter that measures the relative intensity among the external fluctuating force and the thermal random force.

### 2.2. Turning angle

Given a 2D trajectory, we define the turning angle  $\phi(t, \tau)$  as the internal angle between successive segments of duration  $\tau$ . From Fig. A.1, one can realize that  $\cos \phi(t, \tau)$  can be computed as

$$\cos \phi(t, \tau) = \frac{\bar{R}(t + \tau, \tau) \cdot \bar{R}(t, \tau)}{\|\bar{R}(t + \tau, \tau)\| \|\bar{R}(t, \tau)\|}, \tag{19}$$

where the vector

$$\bar{R}(t, \tau) = \bar{X}(t + \tau) - \bar{X}(t) \tag{20}$$

defines the displacement between two successive points of the two-dimensional particle trajectory and  $\|\bar{R}(t, \tau)\|$  represents the modulus of the displacement vector.

Then, the correlation function  $\langle \bar{R}(t + \tau, \tau) \cdot \bar{R}(t, \tau) \rangle$  can be written as

$$\begin{aligned} \langle \bar{R}(t + \tau, \tau) \cdot \bar{R}(t, \tau) \rangle &= \langle \bar{X}(t + 2\tau) \cdot \bar{X}(t + \tau) \rangle + \langle \bar{X}(t + \tau) \cdot \bar{X}(t) \rangle \\ &\quad - \langle \bar{X}(t + 2\tau) \cdot \bar{X}(t) \rangle - \langle \bar{X}(t + \tau) \cdot \bar{X}(t + \tau) \rangle. \end{aligned} \tag{21}$$

Note that this magnitude coincides with the displacement correlation function recently introduced in Ref. [33] to characterize a confined motion in the subdiffusive domain.

An explicit expression for the correlation  $\langle \bar{R}(t + \tau, \tau) \cdot \bar{R}(t, \tau) \rangle$  can be obtained from Eq. (21) inserting (12) and (15) into (5). After some algebra and using the asymptotic expansions for the incomplete beta function [32], one gets

$$\lim_{t \rightarrow \infty} \langle \bar{R}(t + \tau, \tau) \cdot \bar{R}(t, \tau) \rangle = \frac{2k_B T}{\gamma_0} \left\{ \frac{(2^\lambda - 2)}{\Gamma(\lambda + 1)} \tau^\lambda + \varepsilon(2^{2\lambda - \alpha} - 2)K_{\lambda, \alpha} \tau^{2\lambda - \alpha} \right\}. \tag{22}$$

The first term of (22) represents the contribution originated in the viscoelastic properties of the environment while the second one represents the contribution due to the external active processes.

On the other hand, one can realize that

$$\lim_{t \rightarrow \infty} \langle \|\bar{R}(t + \tau, \tau)\| \|\bar{R}(t, \tau)\| \rangle = \rho(\tau). \tag{23}$$

Finally, using (22) and (17), we get

$$\langle \cos \phi(\tau) \rangle = \frac{1}{2} \frac{\frac{(2^\lambda - 2)}{\Gamma(\lambda + 1)} \tau^\lambda + \varepsilon(2^{2\lambda - \alpha} - 2)K_{\lambda, \alpha} \tau^{2\lambda - \alpha}}{\frac{1}{\Gamma(\lambda + 1)} \tau^\lambda + \varepsilon K_{\lambda, \alpha} \tau^{2\lambda - \alpha}}. \tag{24}$$

Expression (24) is one of the main results of our work and gives the mean cosine turning angle in terms of few parameters.

A close observation of expressions (17) and (24) shows that the anomalous diffusion regimes are strongly related with the persistence condition of the motion. In both cases, the scaling behaviour is regulated by  $\lambda$  and  $2\lambda - \alpha$ , which involves the two exponents of the autocorrelation functions of the noises.

In a purely diffusive motion, where the turning angle is randomly selected, it would be expected that  $\langle \cos \phi(\tau) \rangle = 0$ . A negative value of  $\langle \cos \phi(\tau) \rangle$  implies that the motion is antipersistent, favoring backwards steps, which will give rise to subdiffusive behaviour. On the other hand, a positive  $\langle \cos \phi(\tau) \rangle$  means forward steps, which will result in superdiffusion.

The reader may notice that the mean cosine of the turning angle (24) exhibits a crossover from a antipersistent to a persistent regime, since for short time lags, (24) leads to

$$\langle \cos \phi(\tau) \rangle = \frac{(2^\lambda - 2)}{2} < 0, \quad (25)$$

while for large time lags expression (24) reads

$$\langle \cos \phi(\tau) \rangle = \frac{(2^{2\lambda-\alpha} - 2)}{2} > 0. \quad (26)$$

Since the same kind of behaviour is obtained for the MSD, a transition from antipersistent to persistent motion is directly linked to a transition from a subdiffusive to a superdiffusive regime.

Particularly, in the purely viscous case ( $\lambda = 1$ ) and strong memory limit ( $\alpha = 0$ ), Eq. (24) for large time lags leads to  $\langle \cos \phi(\tau) \rangle = 1$ . Accordingly, from (17) one can realize that the corresponding local slope of the MSD is  $\frac{\partial \ln \rho(\tau)}{\partial \ln \tau} = 2$ , indicative of a ballistic regime.

An interesting remark is that the active transport is a necessary but not sufficient condition in order to develop superdiffusion. In other words, external energy input is needed to pull the system out of equilibrium; however, this input may not be sufficient to give rise to a persistent (though superdiffusive) motion. This can be seen in the interdependence of  $\lambda$  and  $\alpha$  in the long time limit regime: except in the pure viscous case where any exponent of the correlation function (11) gives a superdiffusive-persistent behaviour, in the more general viscoelastic environment, the external noise need to have some degree of correlation to develop a superdiffusive regime.

### 3. Motor-driven transport in melanophore cells

We now apply the previous results to the analysis of experimental trajectories of melanosomes in *Xenopus laevis* melanophores cells, reported in two previous works [23,34]. Melanosomes are black pigment organelles with sizes around 500 nm, that move along the cytoskeleton filaments in response to hormone stimuli. Their transport involves the action of molecular motors kinesin II, cytoplasmic dynein and myosin-V, which convert the chemical energy released during the hydrolysis of ATP into directed motion of the cargoes [35]. When motors activity is impaired, the organelles motion is only regulated by the viscoelastic properties of the intracellular environment, typically developing subdiffusive or almost diffusive behaviour [3,36–38].

In the experiments, cells were treated with nocodazole to depolymerize microtubules, so the active transport of melanosomes is driven by the F-actin-dependent motor myosin-V [39]. The experimental data were split into two groups: one set was obtained using wild-type (WT) cells in which melanosomes are driven by myosin-V motor proteins, while the other set was obtained using mutant cells that have a dominant-negative inhibition of myosin-V driven melanosome transport. Consequently, we are able to analyze the motion of melanosomes in the presence and the absence of active motors.

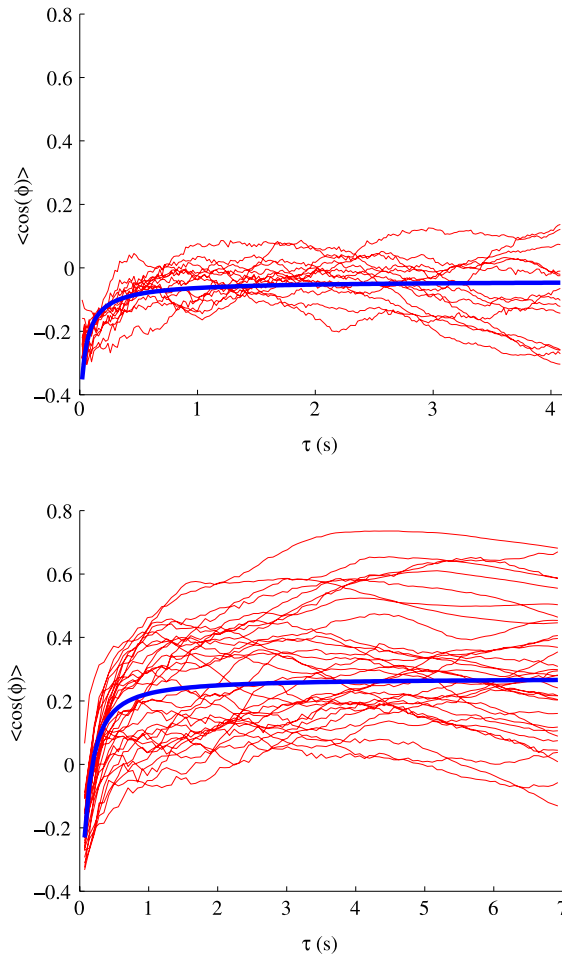
To compare the analytical expression (24) with the experimental data obtained using SPT techniques, it is necessary to take into account the error on the particle position determination (see Appendix).

In Fig. A.2(A) we show the behaviour of  $\langle \cos \phi \rangle$  as a function of the time lag for different experimental trajectories corresponding to mutant cells. To compute this magnitude, we calculate the turning angle  $\phi(t, \tau)$  between successive segments of duration  $\tau$  (see Fig. A.1) and perform the time average of  $\cos \phi(t, \tau)$ . The solid line in Fig. A.2(A) corresponds to the fitting of the ensemble averaged data using the analytical expression given by (A.3). Although the curves are noisy, all of them become flat for lags larger than 1s. The values of the plateau determined as the average of  $\langle \cos(\phi) \rangle$  values for  $\tau > 1$ s are between  $-0.2$  and  $0$ . According to (A.3) this implies that  $\lambda$  takes values between  $0.7$  and  $1$ , which means that mutant cells develop a subdiffusive behaviour in most of the cases, as shown in Refs. [23,34]. From the fitting, we obtained a value of  $\lambda = 0.94 \pm 0.06$ . The values of the subdiffusive exponent in the range  $0.6 - 1$  were also obtained for beads moving in intracellular environment [2], in highly concentrated polymer solutions [40] and in reconstituted actin cytoskeleton [41]. In other words, for impaired motor activity, the intracellular medium develops a variety of behaviours with different degrees of viscoelasticities, given by the range of  $\lambda$  values obtained.

The Fig. A.2(B) displays the results obtained for WT cells. The solid line represents a fitting of the ensemble average using Eq. (A.1), with  $\lambda = 0.92 \pm 0.07$  and  $\alpha = 0.48 \pm 0.16$ . These values are in agreement with those obtained in Ref. [23] via the analysis of the MSD. WT cells reach average asymptotic values of  $\langle \cos(\phi) \rangle$  in the range  $[0, 0.6]$ , which means, following (26), that  $2\lambda - \alpha$  ranges from  $1$  to  $1.7$ . Since  $2\lambda - \alpha$  is the local slope of the MSD for large time lags [23], these values range means that the melanosome motion is superdiffusive for large time lags. However, none of the trajectories developed a clearly ballistic behaviour with  $\langle \cos(\phi) \rangle \sim 1$ . This implies that a constant force is not a good model for the forces exerted by myosin-V motors. On the other hand, a range of  $\alpha$  values around  $0.5$  means that the motors forces cannot be seen as instantaneous and uncorrelated pulses, but that there is a degree of memory or correlation between the pulses. This agrees with the well-accepted picture of molecular motors moving in a step-like manner on microtubules or actin filaments [42–44].

### 4. Summary

In this work we obtained an analytical expression for the mean cosine of the turning angle of a small particle immersed in a viscoelastic environment and in the presence of external fluctuating forces. We have shown that this system can



**Fig. A.2.** (Color online) Evolution of  $\langle \cos(\phi) \rangle$  for (A) mutant cells ( $n = 14$ ) and (B) WT cells ( $n = 33$ ). Solid lines represent a fitting of the ensemble averaged data.

exhibit a crossover between antipersistent to persistent behaviour, depending on the competition between the passive and active contributions. Furthermore, we have demonstrated that a persistent motion is directly related to a superdiffusion. Importantly, the presence of active transport does not implicate a persistent or superdiffusive behaviour.

We have applied our results to the analysis of the directional changes occurring during the motion of motor-driven melanosomes along actin *in vivo*. We have shown that the model predicts the observed crossover from an antipersistent to a persistent regime, which are directly related with the subdiffusive and superdiffusive regimes, respectively. This crossover depends essentially on the interplay of two parameters  $\lambda$  and  $\alpha$ , which characterize the effects of the intrinsic random forces within the intracellular environment [45,46] and the directed motor forces [22,11,23], respectively. By fitting the experimental data with our model, we were able to determine limit bounds for the values of the exponent of the external noise correlation. We believe that our theoretical model provides a solid framework to analyze the motion of micron-sized particles within complex environments and allows the quantification of the microscopical properties that govern its behaviour.

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### Appendix. Expressions in the presence of experimental noise

As established in Refs. [47,7], the effect of an uncorrelated noise of variance  $\eta^2$ , generated by measurement errors in particle location or by biological activity, introduces an additive term  $4\eta^2$  in the expression of the MSD (17). Similarly, and

taking into account (21), a term equal to  $-2\eta^2$  must be added in the expression (22). Then, the expression (24) modifies as

$$\langle \cos \phi(\tau) \rangle = \frac{1}{2} \frac{\left\{ \frac{(2^\lambda - 2)}{\Gamma(\lambda + 1)} \tau^\lambda + \varepsilon (2^{2\lambda - \alpha} - 2) K_{\lambda, \alpha} \tau^{2\lambda - \alpha} \right\} - \delta}{\frac{1}{\Gamma(\lambda + 1)} \tau^\lambda + \varepsilon K_{\lambda, \alpha} \tau^{2\lambda - \alpha} + \delta}, \quad (\text{A.1})$$

where

$$\delta = \gamma_0 \frac{\eta^2}{k_B T}. \quad (\text{A.2})$$

It is worth pointing out that the presence of noise with the mentioned characteristics, leads to a unique value equal to  $-1/2$  at  $\tau \rightarrow 0$ .

In the absence of activity of motor proteins, i.e.  $\varepsilon = 0$  in Eq. (A.1), the expression for  $\langle \cos \phi(\tau) \rangle$  is

$$\langle \cos \phi(\tau) \rangle = \frac{1}{2} \frac{\left\{ \frac{(2^\lambda - 2)}{\Gamma(\lambda + 1)} \tau^\lambda \right\} - \delta}{\frac{1}{\Gamma(\lambda + 1)} \tau^\lambda + \delta} \quad (\text{A.3})$$

with an asymptotic value given by (25).

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