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Thermodynamic Uncertainty Relation Bounds the Extent of Anomalous Diffusion

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In a finite system driven out of equilibrium by a constant external force the thermodynamic uncertainty relation (TUR) bounds the variance of the conjugate current variable by the thermodynamic cost of maintaining the nonequilibrium stationary state. Here we highlight a new facet of the TUR by showing that it also bounds the timescale on which a finite system can exhibit anomalous kinetics. In particular, we demonstrate that the TUR bounds subdiffusion in a single file confined to a ring as well as a dragged Gaussian polymer chain even when detailed balance is satisfied. Conversely, the TUR bounds the onset of superdiffusion in the active comb model. Remarkably, the fluctuations in a comb model evolving from a steady state behave anomalously as soon as detailed balance is broken. Our work establishes a link between stochastic thermodynamics and the field of anomalous dynamics that will fertilize further investigations of thermodynamic consistency of anomalous diffusion models.

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Imagine an overdamped random walker (e.g., a molecular motor) moving a distance x_t in a time t. If driven into a nonequilibrium steady state [1] the walker's mean displacement grows linearly in time, $\langle x_t \rangle = vt$ with velocity v, whereas the variance $\sigma_x^2(t) \equiv \langle x_t^2 \rangle - \langle x_t \rangle^2$ may exhibit anomalous diffusion [2–6] with

$$\sigma_x^2(t) \simeq K_\alpha t^\alpha \tag{1}$$

with anomalous exponent $\alpha \neq 1$ and generalized diffusion coefficient K_α having units $\mathrm{m^2 s^{-\alpha}}$. When $\alpha > 1$ one speaks of superdiffusion, which was observed, for example, in active intracellular transport [7], optically controlled active media [8], and in evolving cell colonies during tumor invasion [9] to name but a few. Conversely, the situation $\alpha < 1$ is referred to as subdiffusion and in a biophysical context was found in observations of particles confined to actin networks [10,11], polymers [12], denaturation bubbles in DNA [13], lipid granules in yeast [14], and cytoplasmic RNA proteins [15]. In these systems subdiffusion is often thought to be a result of macromolecular crowding [16–18], where obstacles hinder the motion of a tracer particle.

A paradigmatic example of anomalous diffusion is the motion of a tracer particle in a single file depicted in Fig. 1(a) where hard-core interacting particles are confined to a one-dimensional ring and block each others passage effecting the well-known $\alpha = 1/2$ subdiffusive scaling [19–29] that was corroborated experimentally [30–32]. Subdiffusion in single file systems emerges more generally in the presence of any repulsive interaction [20] such as, e.g., in polymer chains [27,33,34] [see Fig. 1(b)]. More recently out-of-equilibrium anomalous transport was studied in the context of single file diffusion in the presence of a nonequilibrium bias ($v \neq 0$) [35–38] and in active comb models [see Fig. 1(c)] that were shown, quite surprisingly, to display accelerated diffusion [39] in stark contrast to passive combs (see, e.g., Refs. [40–44]).

The span of anomalous diffusion in physical systems is naturally bound to finite (albeit potentially very long) timescales [45] as a result of the necessarily finite range of correlations in a finite system that eventually ensure the emergence of the central limit theorem [17].

We throughout consider a walker (e.g., a molecular motor) that operates in a (nonequilibrium) steady state [1], which means that the walker's displacement x_t is weakly ergodic. That is, the centralized displacement $x_t - vt$ is unbiased with vanishing "ergodicity breaking parameter" [46] (see also Refs. [47,48]), i.e., as long as trajectories are sufficiently long, ensemble- and time-average observables, such as the centralized time averaged square mean displacement (TAMSD) [49], coincide.

At sufficiently long times where diffusion becomes normal, $\sigma_x^2(t) \propto t$, the thermodynamic uncertainty relation (TUR) [50,51] bounds the walker's variance by [52]

$$\sigma_x^2(t) \geq \frac{2k_\mathrm{B} T v^2}{\dot{W}_\mathrm{ss}} t \equiv Ct, \tag{2}$$

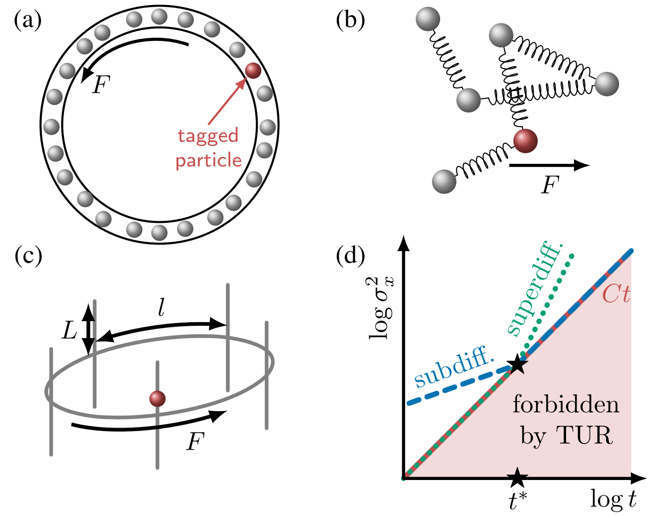

FIG. 1. Anomalous diffusion in finite systems. (a) Single file on a ring driven by a force F. (b) Tagged-particle diffusion in a harmonic chain. (c) Biased diffusion in a finite (periodic) comb. The experimental observable is the unbounded displacement x_t in the direction of the force F. (d) The TUR, $\sigma_x^2(t) \geq Ct$, delivers a threshold time t^* that imposes an upper bound on the duration of subdiffusion (dashed blue line) or the earliest possible onset of superdiffusion (dotted green line). The star denotes $K_\alpha(t^*)^\alpha = Ct^*$ in Eq. (3).

where $\dot{W}_{\rm ss}$ is the power dissipated by the walker, $k_B T$ is the thermal energy, and in the last step we have defined the constant C. Equation (2) is derived by assuming that the underlying (full) system's dynamics follows a Markovian time evolution. The TUR was originally shown to hold in the long time limit "$t \to \infty$" [50,51] and later on also at any finite time for a walker's position evolving from a nonequilibrium steady state [53,54]. Using aspects of information geometry [55–57] Eq. (2) was recently shown to hold for any initial condition [58]. Subsequent studies have applied Eq. (2) to bound the efficiency of molecular motors [59] and heat engines [60,61], and extended the TUR to periodically driven systems [62–66], discrete time processes [67], and open quantum systems [68]. For a broader perspective see Refs. [1,69–71].

Main result.—We now show how the TUR (2) may be used to obtain a thermodynamic bound on the duration of anomalous diffusion. We first consider subdiffusion ($\alpha < 1$) and estimate the largest time t^*, where Eq. (1) must cease to hold as a result of thermodynamic consistency. Namely, according to Eq. (2) subdiffusion in Eq. (1) with constant exponent $\alpha < 1$ cannot persist beyond

$$t^* \simeq \left(\frac{K_\alpha}{C}\right)^{1/(1-\alpha)}, \qquad (3)$$

see intersecting point in Fig. 1(d). Conversely, superdiffusion with an exponent $\alpha > 1$ in Eq. (1) cannot emerge *before* t^* [see Fig. 1(d)]. Equation (3) thus bounds the extent of both sub- and superdiffusion. The bridge between anomalous diffusion and stochastic thermodynamics embodied in Eq. (3) is the main result of this Letter. We note that the bound t^* follows directly from the inequality (2) and in general *cannot* be deduced from the long time diffusion behavior (for an explicit counterexample see Supplemental Material [72]). In the following we use the three paradigmatic physical models depicted in Fig. 1 to illustrate how to apply the bound (3).

Driven single file on a ring.—We first consider a single file of N impenetrable Brownian particles with diameter d and a diffusion coefficient D *all* dragged with a constant force F described by the Langevin equation $\dot{x}_i(t) = \gamma^{-1}F + \xi_i(t)$ for $i = 1, \ldots N$, where the friction coefficient obeys the fluctuation-dissipation relation $\gamma = k_B T/D$ and $\xi_i(t)$ represents Gaussian white noise with zero mean and covariance $\langle \xi_i(t)\xi_j(t')\rangle = 2D\delta_{ij}\delta(t-t')$. The hardcore interaction imposes internal boundary conditions $x_i < x_{i+1} + d$ and the confinement to a ring with circumference l [see Fig. 1(a)] additionally imposes $x_N - x_1 \leq l - d$, i.e., the first particle blocks the passage of the last one. We refer to this setting as "pseudo nonequilibrium" since the transformation to a coordinate system rotating with velocity $v = \gamma^{-1}F$ virtually restores equilibrium dynamics with vanishing current [72]. Nevertheless, the power required to drag the N particles with velocity $v = \gamma^{-1}F$ against the friction force is $\dot{W}^{\rm ss} = N \times Fv$ and Eq. (2) in turn yields $C = 2k_{\rm B}T/\gamma N$, a result independent of F (see also Ref. [77]).

It is well known that a tracer particle in a dense single-file ($1 \ll N < \infty$) exhibits transient subdiffusion according to Eq. (1) with exponent $\alpha \simeq 1/2$ and generalized diffusion constant $K_\alpha \simeq 2N^{-1}\Omega\sqrt{D/\pi}$ (see, e.g., Refs. [19,21–29] and experiments in Refs. [30–32]), where $\Omega \equiv l - Nd$ is the free volume on a ring with circumference l. Therefore, the inequality (2) implies that subdiffusion can persist at most until a time $t^* = (K_\alpha/C)^{1/(1-\alpha)} \simeq \Omega^2/(D\pi)$ [see vertical line in Fig. 2(a) and Eq. (3)].

Thermodynamic consistency limits the extent of subdiffusion to timescales $t \lesssim t^*$. To test the bound in Fig. 2(a) we determined the centralized TAMSD (see symbols) of a tracer particle from a single trajectory of length $\tau = 10^3 \times (D/\Omega)$ generated by a Brownian dynamics simulation with time increment $dt = 10^{-6} \times (D/\Omega)$, and independently deduced σ_x^2 also from a mapping inspired by Jepsen [78] (see lines, Supplemental Material [72] as well as Refs. [79,80]). The results confirm that the TUR sharply bounds the duration of subdiffusion terminating at time t^* (see intersection of the TUR bound and vertical line). If we were to allow particles to overtake the long-time asymptotics would not saturate at the dashed line [see Figs. 10(a)–10(c) in Ref. [81]]—in this scenario subdiffusion may terminate before t^*.

Active single file.—A "genuinely" nonequilibrium steady state is generated by pulling only the tagged particle

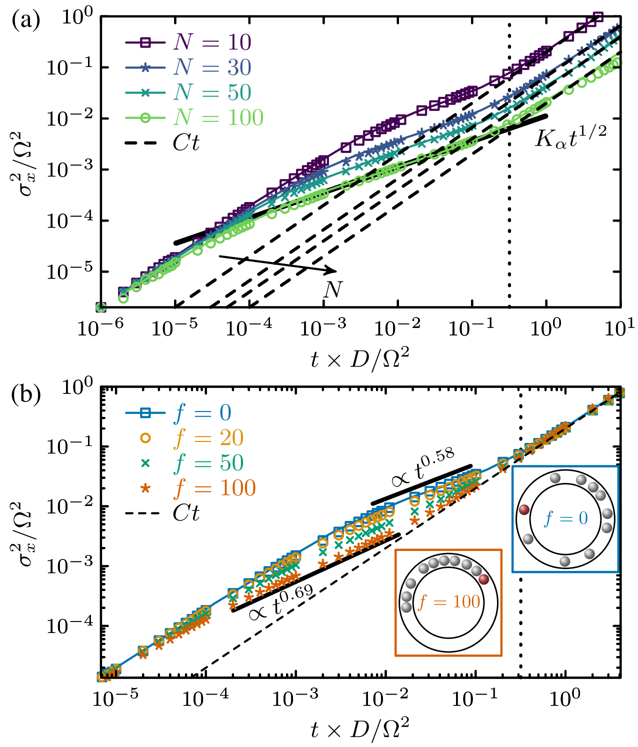

FIG. 2. Variance of particle-displacement in a single file on a ring [see Fig. 1(a)]. (a) All N particles are pulled by a force F (here $F = 0$); (b) only the tagged particle is pulled by a force $F\Omega \equiv f \times k_B T$ (the inset depicts the effect of F) with $N = 10$. Symbols represent the centralized TAMSD [49] extracted from a long trajectory $\tau = 10^3 \times D/\Omega^2$ for each N. The lines are deduced from a modified Jepsen mapping (see Supplemental Material [72]). Parameters: $D = k_B T = \Omega = 1$ and $d = 0$, i.e., time is measured in units of D/Ω^2 and displacements in units of $\Omega = l - Nd$.

with a force F. The tagged-particle diffusion quantified by $\sigma_x^2(t)$ is shown in Fig. 2(b). Here the nonequilibrium driving force $f \equiv F \times \Omega/k_B T$ increases the anomalous exponent from $\alpha \approx 0.58$ to $\alpha \approx 0.69$. Nevertheless, the TUR (dashed line) still tightly bounds the time subdiffusion terminates. Moreover, the onset of subdiffusion is shifted towards shorter times which may be explained as follows. A strongly driven particle "pushes" the nonactive particles thereby locally increasing density which in turn shifts the onset of subdiffusion. The effect increases with the strength of the driving [see inset "$f = 100$" in Fig. 2(b)]. This result seemingly contradicts previous findings on active lattice models at *high density* showing that all even cumulants (incl. the variance) remain unaffected by the driving f [35] (see also Ref. [36]). The contradiction is only apparent—single file diffusion for any number of particles in fact corresponds to the *low density* limit of lattice exclusion models.

Gaussian chain (Rouse model).—We now consider a harmonic chain with N beads [see Fig. 1(b)]. The equations of motion (for the time being in absence of a pulling force) correspond to Refs. [82–84] $\dot{x}_k(t) = -D\sum_l H_{kl}x_l(t) + \xi_k(t)$ where $(\mathbf{H})_{kl} = H_{kl}$ is the Hessian of $U = \sum_{i=2}^N (x_i - x_{i-1})^2/2$. We set $\gamma^{-1} = D$, i.e., $k_B T \equiv 1$. The variance of the kth bead's position reads (see, e.g., Ref. [85])

$$\sigma_x^2(t) = \frac{2}{N}\left[Dt + \sum_{p=1}^{N-1} \cos^2\left(\frac{\pi p(2k-1)}{2N}\right)\frac{1 - e^{-2D\lambda_p t}}{\lambda_p}\right], \tag{4}$$

where $\lambda_p = 4\sin^2(\pi p/2N)$ [82–84]. The first term in Eq. (4) corresponds to the center-of-mass diffusion.

Suppose now that we drag *all* particles with a constant force F. In this case the force affects only the mean displacements but *not* the variance [72]. In other words, the left-hand side of Eq. (2) is not affected by F, whereas the right-hand side becomes $C = 2D/N$ since $\dot{W}_{\rm ss} = v \times NF$ with $v = \gamma^{-1}F = DF$. By inspecting Eq. (4) directly [note that all terms in Eq. (4) are non-negative] one can verify that the TUR indeed bounds the diffusion of the kth particle by $\sigma_x^2(t) \geq 2Dt/N$ at any time t.

In Fig. 3(a) we inspect the sharpness of the bound. For example, tagging the 10th bead in a polymer with $N = 100$ we observe subdiffusion with an exponent $\alpha \approx 0.508$ (see thick black line) that terminates at $t < t^*$ (see vertical arrow), i.e., faster than predicted by the TUR (see green rectangle). Interestingly, the scaling of $\sigma_x^2(t)$ at this point does not become normal with $\alpha = 1$ but instead turns to a second, slightly larger anomalous exponent. Normal diffusion is in fact observed at much longer times. This example highlights that subdiffusion with an (initial) exponent α cannot extend beyond t^*. However, this does *not* imply that t^* necessarily corresponds to the onset of normal diffusion. Conversely, if we tag the first particle of the chain [see Fig. 3(b)] the TUR bounds the overall duration of subdiffusion quite tightly. According to Eq. (3) the longest time subdiffusion can persist increases with N as $t^* \propto C^{-2} \propto N^2$ [see symbols in Fig. 3(b) as well as Ref. [17]].

Superdiffusion in the active comb model.—So far we have discussed only systems exhibiting subdiffusion. To address superdiffusion we consider the "active comb model" depicted in Fig. 1(c) corresponding to diffusion on a ring with side branches with a *finite* length L oriented perpendicularly to the ring at positions separated by l. Within the ring (but not in the side branches) the particle is dragged with a constant force F. For simplicity we assume the diffusion constant D to be the same in the ring and along the side branches. The probability density and flux are assumed to be continuous at the intersecting nodes such that the steady state probability to find the particle in the ring (i.e., in a "mobile state") corresponds to $\phi_m = l/(l + 2L)$

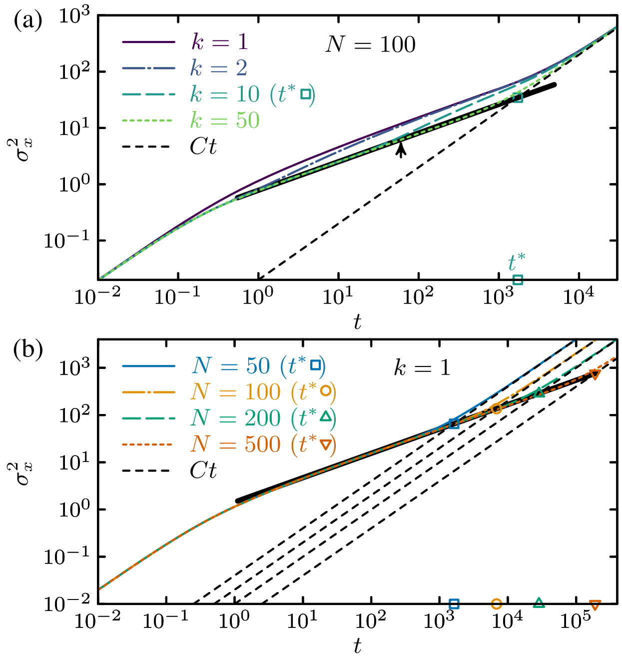

FIG. 3. (a) $\sigma_x^2(t)$ from Eq. (4) for a dragged Gaussian chain with $N = 100$ beads, where we tag the kth particle ($k = 1, 2, 10, 50$). The TUR bound is shown as the dashed black line. Taking, e.g., $k = 10$ we find transient subdiffusion $\sigma_x^2(t) \simeq K_\alpha t^\alpha$ (solid black line) in the vicinity of $t \sim t_{\rm ref} \equiv 10^1$; using Eq. (4) yields the exponent $\alpha \equiv t\partial_t \ln \sigma^2(t)|_{t=t_{\rm ref}} \approx 0.508$ with $K_\alpha \equiv t_{\rm ref}^{-\alpha}\sigma^2(t_{\rm ref})$. The rectangle denotes the upper bound on the extent of subdiffusion t^* while the vertical arrow highlights the actual time at which the subdiffusive regime for $k = 10$ terminates. (b) $\sigma_x^2(t)$ of the first bead ($k = 1$) for increasing N. Symbols denote the TUR bound.

yielding a mean drift velocity $v = \beta DF\phi_m$. Using $\dot{W}_{\rm ss} = Fv$ alongside the TUR [Eq. (2)] we immediately obtain $\sigma_x^2(t) \geq 2\phi_m Dt$. It is known that infinite side branches "$L = \infty$" in the passive comb model (i.e., $F = 0$) break ergodicity. That is, a nonequilibrium steady state ceases to exist and subdiffusion with exponent $\alpha = 1/2$ persists for any fixed initial condition and time t (e.g., see Refs. [40–42]). Conversely, a bias $F \neq 0$ in a finite comb ($L < \infty$) was found, quite counterintuitively, to enhance the long time diffusion [39], which leads to transient superdiffusion as discussed below.

The particle's position along the ring does not change while it is in a side branch. Therefore, only the (random) "occupation time in the mobile phase" [86,87], $\tau_m(t) \leq t$, is relevant. Its fraction is referred to as the "empirical density" [87,88] since $\langle \tau_m(t) \rangle = \phi_m t$.

The particle drifts with velocity βDF and diffuses with diffusion constant D during the time $\tau_m(t)$ it spends in the ring. This implies a displacement distributed according to $x_t \sim \beta DF\tau_m(t) + \sqrt{2D\tau_m(t)}\mathcal{N}$, where $\mathcal{N}$ is a standard normal random number, which eventually leads to (for an alternative derivation see Ref. [39])

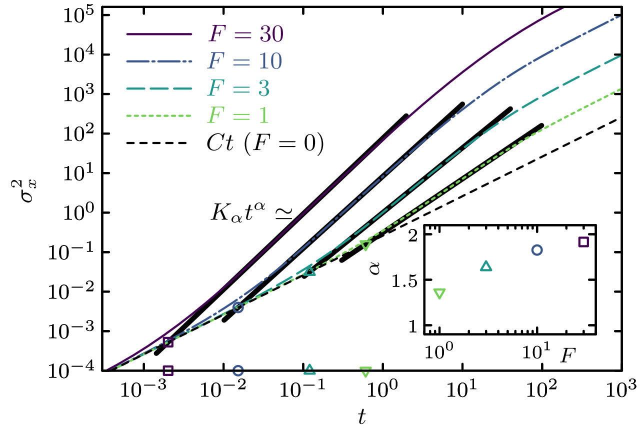

FIG. 4. σ_x^2 in the driven comb model [see Fig. 1(d)]. We consider various driving forces F and side branches with length $L = 10$ separated by a distance $l = 3$ yielding a steady state probability in the ring $\phi_m = l/(l + 2L) = 3/23 \approx 0.13$ with $D = \beta = 1$. The force-free case $F = 0$ coincides with the bound Ct in Eq. (2). The thick lines correspond to $K_\alpha t^\alpha$ with the maximal exponent $\alpha \equiv \max_t t\partial_t \ln \sigma_x^2(t)$ depicted in the inset. Symbols denote the time t^* in Eq. (3), where $K_\alpha t^\alpha$ and Ct intersect. Long times $t \to \infty$ and strong driving $\beta Fl \gg 1$ yield $\sigma_x^2 \simeq 2D\phi_m t + (\beta Fl)^2(1 - \phi_m)^3 t/6$.

$$\sigma_x^2(t) = 2D\phi_m t + (\beta DF)^2\sigma_\tau^2(t), \tag{5}$$

where we used $\langle \mathcal{N}^2 \rangle = 1$, $\langle \mathcal{N} \rangle = 0$, $\langle \tau_m(t) \rangle = \phi_m t$ and defined $\sigma_\tau^2(t) \equiv \langle \tau_m(t)^2 \rangle - \langle \tau_m(t) \rangle^2$. To deduce $\sigma_\tau^2(t)$ we translated the equation of motion into a Markov jump system according to Ref. [89] and used a spectral expansion [87] which alongside Eq. (5) yields $\sigma_x^2(t)$. The result for $l = 3$ and $L = 10$ [72] is shown in Fig. 4. The thick lines denote power laws with a "maximal exponent" $\alpha = \max_t t\partial_t \ln \sigma_x^2(t)$ (see inset for the respective values). At equilibrium ($F = 0$) the diffusion is normal at all times. The presence of a force causes transient superdiffusion with an exponent approaching the ballistic regime $\alpha \approx 2$ upon increasing F. Note that here the TUR bounds the *time of initiation* of superdiffusion (see symbols) and *not* the termination.

To explain this we must understand when $\sigma_\tau^2(t)$ increases nonlinearly with t. One can show that for sufficiently small times $t \to 0$ the particle is found with high probability either only in the ring or only in one of the side branches which yields a vanishing variance $\sigma_\tau^2(t) = \mathcal{O}(t)$. Conversely, we have recently found [87] that the dispersion of the fraction of occupation time at long times, $\mathcal{D} \equiv \lim_{t\to\infty} \sigma_\tau^2(t)/t$, is entirely encoded in the (steady state) joint return probability, $P(m, t, m)$, i.e., the probability to be in the mobile region m initially and again at time t

$$\mathcal{D} = 2\int_0^\infty [P(m, t, m) - \phi_m^2]\mathrm{d}t = \frac{4lL^2[(\beta F)^2 lL + 3\beta Fl\coth(\beta Fl/2) - 6]}{3D(\beta F)^2(l + 2L)^3}, \tag{6}$$

where the first line is shown in Ref. [87], and the second line is derived in Ref. [72] (a similar result is found in Ref. [39]). At strong driving $\beta Fl \gg 1$ we find $\mathcal{D} \simeq l^2(1-\phi_m)^3/6$ which interestingly enhances diffusion $\propto (\beta Fl)^2(1-\phi_m)^3$ by a magnitude that increases with the likelihood to reside immobile. Superdiffusion thus arises from an interplay between effectively "ballistic" transport in the ring and pausing in the side branches, and becomes pronounced at strong driving $\beta Fl \gg 1$ and in the presence of long side branches $L \gg l$, yielding $1-\phi_m \approx 1$. A similar effect gives rise to the so-called Taylor dispersion [90] that occurs in diffusion in a flow field [91–93].

Conclusion.—We established a bridge between anomalous diffusion and the TUR by explaining how the latter can be utilized to (sharply) bound the temporal extent of anomalous diffusion in finite systems driven out of equilibrium. We used the TUR to demonstrate that a nonequilibrium driving may in fact be required for anomalous dynamics to occur such as e.g., in the comb model. We have shown that the TUR can also bound the duration of anomalous diffusion in systems obeying detailed balance if we are able to construct a fictitious non-equilibrium system with the same dynamics, which we demonstrated by means of the passive and driven single file and the Rouse polymer. In this context it will be useful to deepen the connection between the TUR [94] and anomalous transport [95,96] close to equilibrium, growing interfaces [97,98], and to bound subdiffusion in flexible gel networks [99].

Finally, we point out that the TUR [Eq. (2)] and therefore our results apply to overdamped systems (i.e., when momenta relax "instantaneously"). If we include momenta or consider the presence of magnetic fields the TUR requires modifications [100,101]. Such extensions will allow to bound the extent of anomalous diffusion in underdamped systems [102–106]. Finally, the recent generalization of the TUR [58,66,107] will allow applying the TUR to anomalous diffusion and anomalous displacements arising from nonstationary and nonergodic infinite systems [35].

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[1] U. Seifert, Physica (Amsterdam) **504A**, 176 (2018).
[2] R. Metzler and J. Klafter, Phys. Rep. **339**, 1 (2000).
[3] R. Metzler and J. Klafter, J. Phys. A **37**, R161 (2004).
[4] I. M. Sokolov and J. Klafter, Chaos **15**, 026103 (2005).
[5] *Anomalous Transport: Foundations and Applications,* edited by R. Klages, G. Radons, and I. M. Sokolov (Wiley-VCH, Weinheim, 2008).
[6] R. Metzler, J.-H. Jeon, A. G. Cherstvy, and E. Barkai, Phys. Chem. Chem. Phys. **16**, 24128 (2014).
[7] A. Caspi, R. Granek, and M. Elbaum, Phys. Rev. Lett. **85**, 5655 (2000).
[8] K. M. Douglass, S. Sukhov, and A. Dogariu, Nat. Photonics **6**, 834 (2012).
[9] A. N. Malmi-Kakkada, X. Li, H. S. Samanta, S. Sinha, and D. Thirumalai, Phys. Rev. X **8**, 021025 (2018).
[10] F. Amblard, A. C. Maggs, B. Yurke, A. N. Pargellis, and S. Leibler, Phys. Rev. Lett. **77**, 4470 (1996).
[11] I. Y. Wong, M. L. Gardel, D. R. Reichman, E. R. Weeks, M. T. Valentine, A. R. Bausch, and D. A. Weitz, Phys. Rev. Lett. **92**, 178101 (2004).
[12] L. Le Goff, O. Hallatschek, E. Frey, and F. Amblard, Phys. Rev. Lett. **89**, 258101 (2002).
[13] T. Hwa, E. Marinari, K. Sneppen, and L.-H. Tang, Proc. Natl. Acad. Sci. U.S.A. **100**, 4411 (2003).
[14] I. M. Tolić-Nørrelykke, E.-L. Munteanu, G. Thon, L. Oddershede, and K. Berg-Sørensen Phys. Rev. Lett. **93**, 078102 (2004).
[15] T. J. Lampo, S. Stylianidou, M. P. Backlund, P. A. Wiggins, and A. J. Spakowitz, Biophys. J. **112**, 532 (2017).
[16] I. M. Sokolov, Soft Matter **8**, 9043 (2012).
[17] F. Höfling and T. Franosch, Rep. Prog. Phys. **76**, 046602 (2013).
[18] S. K. Ghosh, A. G. Cherstvy, D. S. Grebenkov, and R. Metzler, New J. Phys. **18**, 013027 (2016).
[19] T. E. Harris, J. Appl. Probab. **2**, 323 (1965).
[20] M. Kollmann, Phys. Rev. Lett. **90**, 180602 (2003).
[21] B. Lin, M. Meron, B. Cui, S. A. Rice, and H. Diamant, Phys. Rev. Lett. **94**, 216001 (2005).
[22] A. Taloni and F. Marchesoni, Phys. Rev. Lett. **96**, 020601 (2006).
[23] L. Lizana and T. Ambjörnsson, Phys. Rev. Lett. **100**, 200601 (2008).
[24] L. Lizana and T. Ambjörnsson, Phys. Rev. E **80**, 051103 (2009).
[25] L. Lizana, T. Ambjörnsson, A. Taloni, E. Barkai, and M. A. Lomholt, Phys. Rev. E **81**, 051118 (2010).
[26] J.-B. Delfau, C. Coste, and M. Saint Jean, Phys. Rev. E **84**, 011101 (2011).
[27] N. Leibovich and E. Barkai, Phys. Rev. E **88**, 032107 (2013).
[28] P. L. Krapivsky, K. Mallick, and T. Sadhu, Phys. Rev. Lett. **113**, 078101 (2014).
[29] A. Ryabov, *Stochastic Dynamics and Energetics of Biomolecular Systems* (Springer, Cham, 2016).
[30] K. Hahn, J. Kärger, and V. Kukla, Phys. Rev. Lett. **76**, 2762 (1996).
[31] Q.-H. Wei, C. Bechinger, and P. Leiderer, Science **287**, 625 (2000).
[32] C. Lutz, M. Kollmann, and C. Bechinger, Phys. Rev. Lett. **93**, 026001 (2004).
[33] M. A. Lomholt and T. Ambjörnsson, Phys. Rev. E **89**, 032101 (2014).
[34] D. Lacoste and M. A. Lomholt, Phys. Rev. E **91**, 022114 (2015).
[35] P. Illien, O. Bénichou, C. Mejía-Monasterio, G. Oshanin, and R. Voituriez, Phys. Rev. Lett. **111**, 038102 (2013).
[36] O. Bénichou, A. Bodrova, D. Chakraborty, P. Illien, A. Law, C. Mejía-Monasterio, G. Oshanin, and R. Voituriez, Phys. Rev. Lett. **111**, 260601 (2013).

[37] O. Bénichou, P. Illien, G. Oshanin, A. Sarracino, and R. Voituriez, J. Phys. Condens. Matter **30**, 443001 (2018).
[38] E. Teomy and R. Metzler, J. Phys. A **52**, 385001 (2019).
[39] A. M. Berezhkovskii, L. Dagdug, and S. M. Bezrukov, J. Chem. Phys. **142**, 134101 (2015).
[40] J.-P. Bouchaud and A. Georges, Phys. Rep. **195**, 127 (1990).
[41] A. M. Berezhkovskii, L. Dagdug, and S. M. Bezrukov, J. Chem. Phys. **141**, 054907 (2014).
[42] O. Bénichou, P. Illien, G. Oshanin, A. Sarracino, and R. Voituriez, Phys. Rev. Lett. **115**, 220601 (2015).
[43] T. Sandev, A. Iomin, H. Kantz, R. Metzler, and A. Chechkin, Math. Model. Nat. Phenom. **11**, 18 (2016).
[44] A. Lapolla and A. Godec, Front. Phys. **7**, 182 (2019).
[45] A. J. Spakowitz, Front. Phys. **7**, 119 (2019).
[46] Y. He, S. Burov, R. Metzler, and E. Barkai, Phys. Rev. Lett. **101**, 058101 (2008).
[47] J.-H. Jeon and R. Metzler, Phys. Rev. E **81**, 021103 (2010).
[48] A. G. Cherstvy, A. V. Chechkin, and R. Metzler, New J. Phys. **15**, 083039 (2013).
[49] The TAMSD is defined by $\bar{\delta}^2(t) = \lim_{\tau\to\infty}(\tau - t)^{-1}\times \int_\tau^t (x_{s+t} - x_s)^2 \mathrm{d}s = \langle x_t^2\rangle$. The centralized TAMSD is obtained by subtracting the square of the mean displacement along an ergodically long trajectory that reads $\bar{\delta}(t) = \lim_{\tau\to\infty}(\tau - t)^{-1}\int_\tau^t (x_{s+t} - x_s)\mathrm{d}s = \langle x_t\rangle = vt$.
[50] A. C. Barato and U. Seifert, Phys. Rev. Lett. **114**, 158101 (2015).
[51] T. R. Gingrich, J. M. Horowitz, N. Perunov, and J. L. England, Phys. Rev. Lett. **116**, 120601 (2016).
[52] The TUR was originally proposed in the form $\epsilon^2 \dot{W}_{\rm ss} t \geq 2k_{\rm B}T$, where $\epsilon^2 = \sigma_x^2/(vt)^2$ is the relative uncertainty and $\dot{W}_{\rm ss}t$ the total dissipation [50,51].
[53] P. Pietzonka, A. C. Barato, and U. Seifert, Phys. Rev. E **93**, 052145 (2016).
[54] J. M. Horowitz and T. R. Gingrich, Phys. Rev. E **96**, 020103(R) (2017).
[55] S. Ito, Phys. Rev. Lett. **121**, 030605 (2018).
[56] A. Dechant and S.-i. Sasa, Proc. Natl. Acad. Sci. U.S.A. **117**, 6430 (2020).
[57] S. Ito and A. Dechant, Phys. Rev. X **10**, 021056 (2020).
[58] K. Liu, Z. Gong, and M. Ueda, Phys. Rev. Lett. **125**, 140602 (2020).
[59] P. Pietzonka, A. C. Barato, and U. Seifert, J. Stat. Mech. (2016) 124004.
[60] N. Shiraishi, K. Saito, and H. Tasaki, Phys. Rev. Lett. **117**, 190601 (2016).
[61] P. Pietzonka and U. Seifert, Phys. Rev. Lett. **120**, 190602 (2018).
[62] V. Holubec and A. Ryabov, Phys. Rev. Lett. **121**, 120601 (2018).
[63] A. C. Barato and R. Chetrite, J. Stat. Mech. (2018) 053207.
[64] T. Koyuk, U. Seifert, and P. Pietzonka, J. Phys. A **52**, 02LT02 (2019).
[65] A. C. Barato, R. Chetrite, A. Faggionato, and D. Gabrielli, New J. Phys. **20**, 103023 (2018).
[66] T. Koyuk and U. Seifert, Phys. Rev. Lett. **125**, 260604 (2020).
[67] K. Proesmans and C. Van den Broeck, Europhys. Lett. **119**, 20001 (2017).
[68] Y. Hasegawa, Phys. Rev. Lett. **126**, 010602 (2021).
[69] A. C. Barato, R. Chetrite, A. Faggionato, and D. Gabrielli, J. Stat. Mech. (2019) 084017.
[70] G. Falasco, M. Esposito, and J.-C. Delvenne, New J. Phys. **22**, 053046 (2020).
[71] J. M. Horowitz and T. R. Gingrich, Nat. Phys. **16**, 15 (2020).
[72] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevLett.127.080601, which includes Refs. [73–76], for explicit and detailed calculations.
[73] T. Speck, J. Mehl, and U. Seifert, Phys. Rev. Lett. **100**, 178302 (2008).
[74] E. Barkai and R. Silbey, Phys. Rev. E **81**, 041129 (2010).
[75] D. Hartich and A. Godec, arXiv:2011.04628.
[76] A. Lapolla and A. Godec, New J. Phys. **20**, 113021 (2018).
[77] P. H. Nelson and S. M. Auerbach, J. Chem. Phys. **110**, 9235 (1999).
[78] D. W. Jepsen, J. Math. Phys. (N.Y.) **6**, 405 (1965).
[79] J. Evans, Physica (Amsterdam) **95A**, 225 (1979).
[80] B. Cooley and P. K. Newton, SIAM Rev. **47**, 273 (2005).
[81] D. Lucena, D. V. Tkachenko, K. Nelissen, V. R. Misko, W. P. Ferreira, G. A. Farias, and F. M. Peeters, Phys. Rev. E **85**, 031147 (2012).
[82] P. E. Rouse, J. Chem. Phys. **21**, 1272 (1953).
[83] S. Fugmann and I. M. Sokolov, Phys. Rev. E **81**, 031804 (2010).
[84] J. Wuttke, arXiv:1103.4238.
[85] C. W. Gardiner, *Handbook of Stochastic Methods*, 3rd ed. (Springer, Berlin, 2004).
[86] A. Rebenshtok and E. Barkai, Phys. Rev. E **88**, 052126 (2013).
[87] A. Lapolla, D. Hartich, and A. Godec, Phys. Rev. Research **2**, 043084 (2020).
[88] A. Barato and R. Chetrite, J. Stat. Phys. **160**, 1154 (2015).
[89] V. Holubec, K. Kroy, and S. Steffenoni, Phys. Rev. E **99**, 032117 (2019).
[90] G. I. Taylor, Proc. R. Soc. A **219**, 186 (1953).
[91] C. Van den Broeck, D. Maes, and M. Bouten, Phys. Rev. A **36**, 5025 (1987).
[92] M. Kahlen, A. Engel, and C. Van den Broeck, Phys. Rev. E **95**, 012144 (2017).
[93] E. Aurell and S. Bo, Phys. Rev. E **96**, 032140 (2017).
[94] K. Macieszczak, K. Brandner, and J. P. Garrahan, Phys. Rev. Lett. **121**, 130601 (2018).
[95] E. Lutz, Phys. Rev. E **64**, 051106 (2001).
[96] A. Godec and R. Metzler, Phys. Rev. E **88**, 012116 (2013).
[97] O. Niggemann and U. Seifert, J. Stat. Phys. **178**, 1142 (2020).
[98] O. Niggemann and U. Seifert, J. Stat. Phys. **182**, 25 (2021).
[99] A. Godec, M. Bauer, and R. Metzler, New J. Phys. **16**, 092002 (2014).

[100] K. Proesmans and J. M. Horowitz, J. Stat. Mech. (2019) 054005.
[101] H.-M. Chun, L. P. Fischer, and U. Seifert, Phys. Rev. E **99**, 042128 (2019).
[102] R. Metzler and I. M. Sokolov, Europhys. Lett. **58**, 482 (2002).
[103] S. Burov and E. Barkai, Phys. Rev. Lett. **100**, 070601 (2008).
[104] S. Burov and E. Barkai, Phys. Rev. E **78**, 031112 (2008).
[105] I. Goychuk, Phys. Rev. Lett. **123**, 180603 (2019).
[106] I. Goychuk and T. Pöschel, Phys. Rev. E **102**, 012139 (2020).
[107] A. Dechant and S. ichi Sasa, J. Stat. Mech. (2018) 063209.