Anomalous Features of Diffusion in Corrugated Potentials with Spatial Correlations: Faster than Normal, and Other Surprises

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Normal diffusion in corrugated potentials with spatially uncorrelated Gaussian energy disorder famously explains the origin of non-Arrhenius $\exp[-\sigma^2/(k_BT^2)]$ temperature dependence in disordered systems. Here we show that unbiased diffusion remains asymptotically normal also in the presence of spatial correlations decaying to zero. However, because of a temporal lack of self-averaging, transient subdiffusion emerges on the mesoscale, and it can readily reach macroscale even for moderately strong disorder fluctuations of $\sigma \sim 4 - 5k_BT$. Because of its nonergodic origin, such subdiffusion exhibits a large scatter in single-trajectory averages. However, at odds with intuition, it occurs essentially faster than one expects from the normal diffusion in the absence of correlations. We apply these results to diffusion of regulatory proteins on DNA molecules and predict that such diffusion should be anomalous, but much faster than earlier expected on a typical length of genes for a realistic energy disorder of several room k_BT, or merely 0.05–0.075 eV.

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Diffusion and transport processes in disordered amorphous materials, including various polymer glasses and biopolymers such as DNAs and proteins have been in the research spotlight already for over fifty years [1–3]. A paradigm in this field is provided by hopping transport modeled by continuous time random walks (CTRW) with energy disorder on the sites of localization and their continuous space analogy—diffusion of overdamped particles in random potentials (static or quenched disorder). Exponential energy disorder on sites can easily yield anomalous diffusion when the dispersion of energy fluctuations σ exceeds thermal energy k_BT. It gave rise to the famous CTRW model of anomalous transport by Montroll, Scher, Weiss, Shlessinger, and others [3,4] featured by heavy-tailed residence time distributions on sites $\psi(\tau) \sim \tau^{-1-\alpha}$ possessing no mean value, with $\alpha \sim k_BT/\sigma$ within a mean-field approximation. This model became very popular in recent years in the context of weak ergodicity breaking [5,6] and aging [6], where the ensemble and trajectory averages do not coincide and can behave very differently. Such a behavior was indeed found experimentally [7].

However, exponential disorder needs to be modified [8] to describe a typical non-Arrhenius, Vogel-Fulcher dependence of transport coefficients such as (sub)diffusion coefficient $D(T) \propto \exp[-\sigma/k_B(T - T_0)]$, for $T > T_0$, on temperature T. Moreover, the temperature dependences of diffusion and mobility in glasslike materials are often described as $D(T) \propto \exp[-\sigma^2/(k_BT)^2]$ [2,9–12]. This dependence is not easy to distinguish experimentally from the Vogel-Fulcher law [13]. Concurrently, the model of Gaussian disorder, rather than exponential energy disorder, has been justified for a number of materials [12]. Gaussian disorder emerges naturally by virtue of the central limit theorem, e.g., in molecularly doped polymers with dipolar disorder [14]. Furthermore, genetic material was already foreseen as an aperiodic disordered crystal by Schrödinger in his famous book [15]. Indeed, interaction of transcription factors and signaling proteins with DNA macromolecules —a problem central to gene expression in molecular biology—is also well described by the Gaussian energy disorder [16,17]. If Gaussian disorder is spatially uncorrelated, no anomalous diffusion and transport regime is possible. This is because any Gaussian energy disorder yields in the mean-field approximation local residence time distributions with all the moments being finite. Accordingly, the classical result by de Gennes, Zwanzig, and Bässler yields the renormalization (suppression) of normal transport coefficients by the factor $\exp[-\sigma^2/(k_BT)^2]$. This famously explains the origin of this non-Arrhenius temperature dependence [2,9–11]. However, in dipolar organic glasses the long-range correlations in site energy fluctuations emerge [14]. Short-range correlations also naturally emerge for diffusion of proteins on DNAs. Indeed, let us consider the contact area of DNA and a bound protein. It involves typically from 5 to 30 base pairs (bp) in length [18]. The interaction energy is a pairwise sum of the energy of interaction of a base in contact and protein. It is approximately Gaussian distributed [16]. When the protein slides by one base along DNA, it remains in contact

with all the same bases except one new and one past. This fact most obviously introduces spatial correlations in the random binding energy profile on a typical length of DNA-protein contact, even if pairwise correlations are totally absent. Obviously, any correlations in the bp sequence or inclusion of long-range electrostatic interactions [19] can only enhance spatial range of such correlations. This provokes the question, How do the binding energy correlations affect diffusion along DNA? Will it still be normal, or maybe anomalous diffusion regime emerges? Notice that this problem is very different from the problem of Sinai-type or random force diffusion, which leads to the *growing* with distance correlations in the energy fluctuations [1] described, e.g., by fractional Brownian motion [20]. In this respect, decaying in space energy correlations renders the corresponding force correlations profoundly negative with the total integral of the quenched force autocorrelation function be always zero.

Below we show that decay of energy correlations guarantees self-averaged ergodic character of unbiased diffusion on very large distances. Diffusion is asymptotically normal, and the renormalized diffusion coefficient is described by the same well-known result of Ref. [10]. However, some older [21] and very recent [22,23] simulations do reveal anomalous diffusion and transport. Is something wrong with these simulations? No. We confirm them in some basic features. Anomalous diffusion emerges indeed. Moreover, the ensemble and trajectory averages become transiently very different. However, contrary to the earlier arguments [22], this subdiffusion is not based on a residence time distribution with divergent moments. Averaged exit times from any finite spatial domain and their variance are not only finite, but they become much smaller than in the absence of correlations. Transient subdiffusion indeed makes mesoscopic transport processes faster overall, not slower, as generally believed [24]. Subdiffusion can last very long because on the corresponding mesoscale no self-averaging is attainable. However, on very large distances, it smoothly changes into the normal diffusion. This provokes the question, How large is very large? What determines the corresponding mesoscale? When the classical result is indeed physically relevant, and when it becomes of lesser utility, or can even mislead? These are the major questions we answer with this work.

Model.—We consider a standard model of overdamped diffusion in a spatially disordered potential $V(x)$ [2,9,10]. It is described by the Langevin equation

$$\eta\dot{x} = -\frac{\partial U(x)}{\partial x} + \sqrt{2k_BT\eta}\zeta(t), \tag{1}$$

at temperature T. Here, η is frictional coefficient and $\zeta(t)$ is unbiased white Gaussian noise, $\langle\zeta(t)\zeta(t')\rangle = \delta(t-t')$. The potential energy, $U(x) = U_{\rm reg}(x) + V(x)$, consists generally of two parts, a regular $U_{\rm reg}(x)$, e.g., $U_{\rm reg}(x) = -f_0x$ for a constant force f_0, and a random part $V(x)$. It obeys unbiased Gaussian distribution, $\langle V(x)\rangle = 0$, with variance σ^2 and normalized correlation function $g(z)$,

$$\langle V(x)V(x')\rangle = \sigma^2 g(|x-x'|), \tag{2}$$

$g(0) = 1 \geq g(z)$, being a wide sense stationary random process in space. In application to diffusion on DNA, regular potential also includes a mean binding energy $V_0 \sim 10$–$20k_BT_{\rm room}$, and $\sigma \ll |V_0|$. V_0 is crucial for the protein binding and dissociation, but it does not influence sliding along DNA. The simplest model is provided by exponentially decaying short-range correlations, $g(z) = \exp(-|z|/\lambda)$, with correlation length λ, which is about the linear size of the protein-DNA contact. In numerical simulations, this model was effectively regularized to make the mean-square fluctuation of random force $f(x) = -(\partial V(x)/\partial x)$ finite [25].

Theory and results.—Normal transport coefficients renormalized by disorder can be found by a standard trick with periodization of random potential [1], imposing an artificial spatial period L, and considering the limit $L \to \infty$ at the end of calculation. Following Refs. [10,28], one obtains (at finite L)

$$D_{\rm ren} = \frac{D_0}{\overline{C_L^+}\,\overline{C_L^-}} \tag{3}$$

for the renormalized diffusion coefficient in the unbiased case ($f_0 \to 0$) [25]. Here,

$$\overline{C_L^\pm} = \frac{1}{L}\int_0^L e^{\pm\beta V(x)}dx \tag{4}$$

is a spatially averaged random function $w_\pm(x) := e^{\pm\beta V(x)}$. Furthermore, $D_0 = k_BT/\eta$ is the free diffusion coefficient and $\beta = 1/(k_BT)$ is the inverse temperature. The earlier result [10,28] readily follows upon identifying the spatial average in Eq. (4) with the ensemble average $\langle C_L^\pm\rangle = \langle e^{\pm\beta V(x)}\rangle$ over random realizations of $V(x)$. Since for any zero-mean Gaussian variable ξ, $\langle\exp(\xi)\rangle = \exp(\langle\xi^2\rangle/2)$, for arbitrary Gaussian disorder, we obtain

$$D_{\rm ren} = D_0 e^{-\sigma^2/(k_BT)^2}. \tag{5}$$

Remarkably, this is precisely the same result obtained earlier for noncorrelated potentials [10]. Correlations have no influence on it. This is a very important conclusion, and numerics completely confirm it in Fig. 1, for the particular model considered.

This brings us to our crucial point. Namely, we wish to reexamine the ergodic assumption leading to Eq. (5). When does it work in the strict limit $L \to \infty$? Even more important, for which *finite* L does it become well justified? This will give us a characteristic mesoscopic scale of

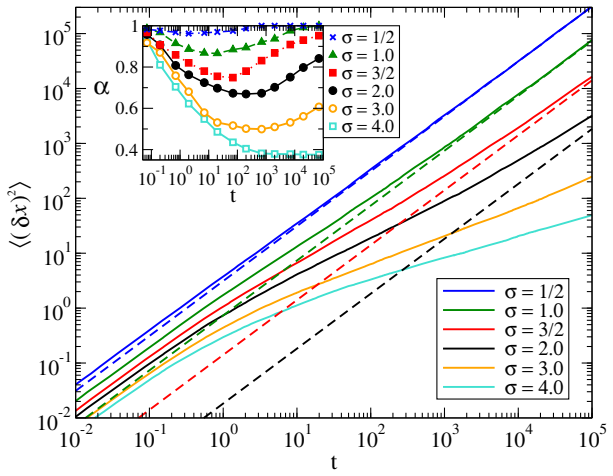

FIG. 1 (color online). Ensemble-averaged diffusion for different values of disorder strength σ in units of k_BT for exponentially decaying correlations. In doing numerics, we fixed $\sigma = \sigma_0$ and varied temperature. Distance is measured in units of correlation length λ and time in units of $\tau_0 = \lambda^2\eta/\sigma_0$. For $\sigma_0 = 2k_BT_{\rm room} = 0.05$ eV, $D_0 = k_BT_{\rm room}/\eta = 3\ \mu{\rm m}^2/{\rm s}$, and $\lambda = 5.25$ nm (15 bp), $\tau_0 \approx 4.6\ \mu$s. Initially, diffusion is normal, $\langle\delta x^2(t)\rangle = 2D_0t$. The dashed lines present asymptotically normal behavior $\langle\delta x^2(t)\rangle = 2D_{\rm ren}t$, for $\sigma/(k_BT) = 1/2, 1, 3/2, 2$. Transient subdiffusion is much faster than this limit. Averaging over 10^4 particles is done in 10 different realizations of random potential replicated with period $L = 10^4$ (10^3 particles per a potential realization). Particles are initially uniformly distributed over the length L.

transiently anomalous diffusion. For L smaller than a typical ergodicity length $L_{\rm erg}$, we expect anomalous diffusion, which becomes asymptotically normal for $L \gg L_{\rm erg}$. To establish the corresponding criterion, one has to consider statistical variations of $\overline{C_L^{\pm}}$. Remarkably, a similar problem also emerges for the model of exponential energy disorder studied in Ref. [5], where fluctuations do not vanish even in the strict limit $L \to \infty$. Following a standard procedure [29], we consider the (relative) ensemble variance, $[\langle(\overline{C_L^{\pm}})^2\rangle - \langle\overline{C_L^{\pm}}\rangle^2]/\langle\overline{C_L^{\pm}}\rangle^2$, of the trajectory average $\overline{C_L^{\pm}}$, which is called the ergodicity breaking parameter (EBP) [6,30]. It must vanish for any ergodic process in the limit $L \to \infty$. Then, one can use $\langle C_L^{\pm}\rangle$ instead of $\overline{C_L^{\pm}}$. A sufficient condition for this is that the ensemble-averaged autocorrelation function $K_{\pm}(x) = \langle\delta w_{\pm}(x_0)\delta w_{\pm}(x_0+x)\rangle$ of the random process $\delta w_{\pm}(x) := e^{\pm\beta V(x)} - \langle e^{\pm\beta V(x)}\rangle$ vanishes in the limit $x \to \infty$ [29]. After some straightforward algebra, we obtain

$$K_{\pm}(x) = e^{\beta^2\sigma^2}\{\exp[\beta^2\sigma^2 g(x)] - 1\}. \tag{6}$$

From this important result, it follows immediately that diffusion is indeed asymptotically ergodic and normal for any random Gaussian potential with vanishing correlations, $\lim_{x\to\infty} g(x) = 0$. Then, the result in Eq. (5) is valid.

We focus on short-ranged correlations, which seemingly justified the use of the approximation of uncorrelated disorder in the bulk of previous research work [2,9,10]. Even here, with growing σ, diffusion becomes transiently anomalous, $\langle\delta x^2(t)\rangle \propto t^{\alpha(t)}$, with a time-dependent $0 < \alpha(t) \le 1$. It starts from $\alpha = 1$ at $t = 0$ and tends to $\alpha = 1$ asymptotically; see inset in Fig. 1. The time duration and spatial extension of subdiffusion depend very strongly on σ. For example, for $\sigma = 4$ in Fig. 1, there is no signature of growing $\alpha(t)$ on the whole time scale of simulation. Indeed, $\alpha \approx 0.4$ for $10^3 < t < 10^5$. The emergence of this subdiffusion is due to a transient breaking of ergodicity. Importantly, it is also non-Gaussian in the subdiffusive regime; see Fig. S2 in the Supplemental Material [25]. There exists an ergodicity length $L_{\rm erg}(\sigma)$, such that self-averaging occurs only for $L \gg L_{\rm erg}(\sigma)$. However, no self-averaging occurs on the mesoscale defined by the requirement that the above EBP equals one, which leads to the condition

$$\int_0^1 (1-y)e^{\beta^2\sigma^2 g(Ly)}dy = 1. \tag{7}$$

The solution of this equation for unknown L gives $L_{\rm erg}$. Another estimation yields $L_{\rm erg}(\sigma) \sim \lambda e^{\sigma^2/(k_BT)^2}$ [17], which indeed displays a major trend with σ. For example, for $\sigma = 2$, Eq. (7) yields $L_{\rm erg}(2) \approx 35\lambda$ (while $e^4 \approx 54.6$). This is indeed consistent with the trend one observes in Fig. 1 for $\sigma = 2$, where $\langle\delta x^2(t_{\rm max})\rangle \sim 3000\lambda^2$. In this respect, a recent experiment shows that $1d$ diffusion along DNA is suppressed by a factor of 100 with respect to one in the bulk [31]. This suggests $\sigma \sim 2k_BT_{\rm room} \sim 0.05$ eV, with experimental values $D_0 = 3\ \mu{\rm m}^2/{\rm s}$ and $D_{\rm ren} = 0.046\ \mu{\rm m}^2/{\rm s}$ [31]. Applying this result to diffusion of a protein on DNA with $\lambda = 15$ bp suggests that protein diffusion should still be anomalous on a typical gene length about 1000 bp. Remarkably, another experiment reveals even a larger suppression factor of about 10^4 [32], which would correspond to $\sigma \sim 3k_BT_{\rm room}$. Then, from Eq. (7), $L_{\rm erg}(3) \approx 2070\lambda$ (while $e^9 \approx 8103$), a drastic increase. This would mean that a typical subdiffusion length would cover about 30–120 genes in the bacterial genome, which can have important consequences for gene regulation. In a more general context, already for $\sigma = 4k_BT$, $L_{\rm erg}(4) \sim 1.2 \times 10^6\lambda$, i.e., for $\lambda \sim 10$ Å, $L_{\rm erg}(4) \sim 1.2$ mm, subdiffusion clearly reaches a macroscale. Other models of decaying correlations cannot change this conclusion much. Then, the classical result in Eq. (5) can mislead, even being formally valid.

Given the nonergodic origin of such subdiffusion, it becomes important to study single-trajectory averages, $\overline{\delta x^2(t)}^{T_w} := [1/(T_w - t)]\int_0^{T_w - t}[\delta x(t|t')]^2dt'$, of the mean-squared displacement, $\delta x(t|t') = x(t+t') - x(t')$, over a time window T_w, assuming $t \ll T_w$ [7,32]. The results for $\sigma = 2$ display a typical scatter in Fig. 2. It can be characterized by a broadly distributed subdiffusion

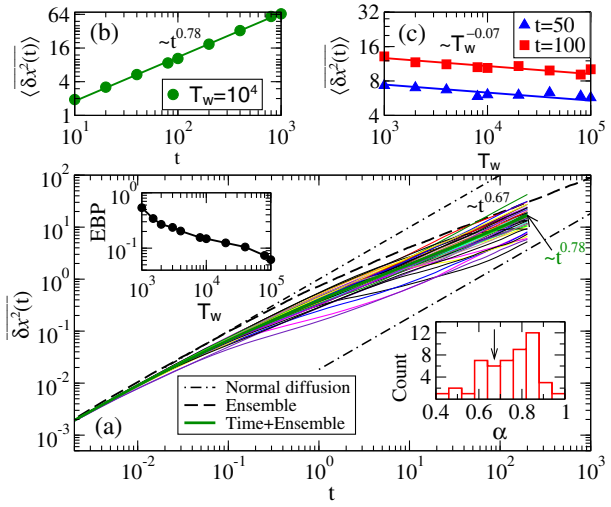

FIG. 2 (color online). (a) Single-trajectory averages are scattered between the free and disorder-renormalized diffusion limits (depicted with dash-dotted lines). Time window $T_w = 2 \times 10^4$ for averaging is chosen 100 times larger than the maximal time t. Each trajectory is characterized by individual subdiffusion index α distributed as shown in the lower inset. Arrow indicates the value of $\alpha = 0.67$ which corresponds to the ensemble average depicted with dashed line. The ensemble average of time averages with $\alpha = 0.78$ is depicted as full green line. It is also depicted in (b) as function of time t for $T_w = 10^4$, and also in (c) as a function of T_w for two fixed values of t. The latter decays as $\langle \overline{\delta x^2(t)} \rangle \sim T_w^{-0.07}$. Moreover, the corresponding ergodicity breaking parameter in the upper inset of (a) gradually decays as a function of T_w. This indicates that no ergodicity breaking takes place asymptotically, $T_w \to \infty$.

exponent α. Similar features are indeed seen in many experiments [7]. The corresponding ensemble average $\langle \overline{\delta x^2(t)}^{T_w} \rangle$ is different from the standard ensemble average $\langle \delta x^2(t) \rangle$, even having a different anomalous exponent; see Figs. 2(a) and 2(b). Recent experimental findings [32] indirectly corroborate our results. Indeed, in Ref. [32] a huge scatter of the diffusional constants for LacI protein on a bacterial DNA has been reported, which the authors attributed to a wildly (over 3 orders of magnitude) distributed normal diffusion coefficient. When we increase σ to $\sigma = 3k_BT$, the scatter indeed further increases; see in Fig. S3 of the Supplemental Material [25].

Strikingly enough, all the single-trajectory averages reveal subdiffusion, which proceeds much faster than expected from Eq. (5); see Fig. 2(a). It must be emphasized that even though our results are somewhat reminiscent of those obtained for CTRW subdiffusion with divergent mean residence times, or with exponential energy disorder [6], in fact, they are very different. First, single trajectory averages also yield subdiffusion (without any boundary effects). Second, the drift of these averages with growing time window T_w is much less pronounced; see Fig. 2(c). Moreover, the related EBP shows a clear tendency to zero with increasing T_w, cf. inset in Fig. 2(a).

It is especially important that the corresponding residence time distribution to stay in any finite-size spatial domain is neither featured by diverging mean residence time nor by diverging variance. In this respect, our results also essentially differ from the results in Ref. [22]. They are somewhat closer in this particular aspect to viscoelastic subdiffusion. However, the latter is mostly ergodic by its origin [33], and therefore is also different. We investigate the distribution of escape times out of spatial domain $[-\lambda, \lambda]$ for the particles initially localized in the middle of it. For disorder-renormalized normal diffusion, the residence time distribution can be derived as $\psi(t) = \pi \sum_{n=0}^{\infty} (-1)^n (2n+1) e^{-\pi^2 (2n+1)^2 t/4}$, with time in units of $\lambda^2/D_{\rm ren}$. It is dominated by a single-exponential $\psi(t) \propto \pi \exp(-\pi^2 t/4)$ at large times. For small disorder, this result is nicely confirmed numerically in Fig. 3(a) which also provides one of the successful tests of the accuracy of our numerics. However, already for $\sigma = k_BT$, deviations are observed in Fig. 3(b). The mean time not only exists, but it is much smaller that one expects from normal diffusion, even though the distribution becomes broader than exponential. For a sufficiently large disorder, its essential part is nicely described by the log-normal distribution $\psi(t) = 1/(\sqrt{2\pi}\sigma_\tau t) \exp[-\ln^2(t/\tau_0)/(2\sigma_\tau^2)]$, with two parameters τ_0 and σ_τ, which are related to the finite mean and variance of this distribution depicted in Fig. 3(d). Such a distribution can be confused for a power-law distribution, $\psi(t) \propto 1/t$, at short times. However, it is profoundly different. The numerical mean and variance are much smaller than those expected from disorder-renormalized normal diffusion.

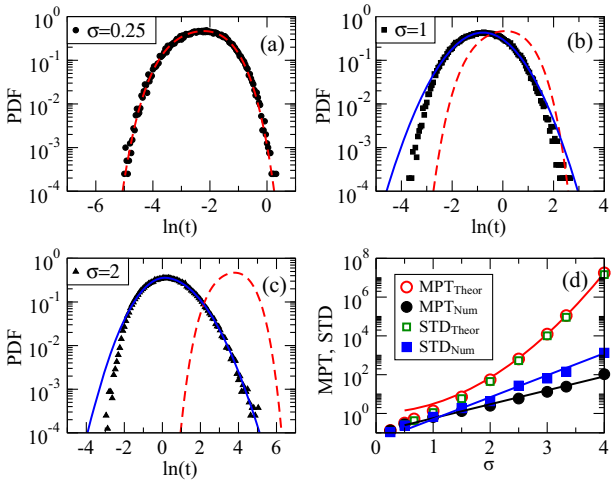

FIG. 3 (color online). (a)–(c) Probability density function (PDF) of waiting times derived from numerics (symbols), its fit with a log-normal distribution (full lines), and the result expected from normal diffusion with $D_{\rm ren}$ (dashed lines) for three different values of σ/k_BT. (d) Mean first passage time (MPT) and its standard deviation (STD) derived from numerics (symbols) and their exponential fits (full lines), as well as MPT and STD expected from normal diffusion characterized by $D_{\rm ren}$, which obey a const $\times \exp[-\sigma^2/(k_BT)^2]$ dependence.

Moreover, they exhibit a linear dependence on $\sigma/(k_BT)$ in the exponential, i.e., $\propto \exp[\sigma/(k_BT)]$, rather than quadratic, i.e., $\propto \exp[\sigma^2/(k_BT)^2]$. Figure 3(d) illustrates this very important finding. A subdiffusional search due to spatial correlations is thus expected to proceed much faster than one naively expects from the well-known renormalization by disorder.

To conclude, we summarize the important findings of this work. First, the famous result in Eq. (5) remains valid asymptotically for any model of decaying correlations. Diffusion is suppressed by the factor responsible for the well-known non-Arrhenius temperature dependence [13]. However, a similar factor also characterizes the spatial range of transient subdiffusion in units of the disorder correlation length λ. Second, subdiffusion readily reaches a macroscale even for a moderately strong disorder of $\sigma \sim 4$–$5k_BT$. Third, already for $\sigma \sim 2k_BT_{\text{room}} \sim 0.05$ eV, diffusion of regulatory proteins on DNAs becomes essentially anomalous on a typical length of genes, with a large scatter in single-trajectory averages. Fourth, and the most surprising, such subdiffusion proceeds much faster than one expects when Eq. (5) is applied to transport processes on the mesoscale. We believe that these important findings provide a new vista on the role of correlations in Gaussian disorder and subdiffusion, and will inspire related experimental work.

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