Fractons in Proteins: Can They Lead to Anomalously Decaying Time Autocorrelations?

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Motivated by recent studies on the fractal nature of folded proteins, we analyze the time-dependent autocorrelation function $\langle \vec{x}(t) \cdot \vec{x}(0) \rangle$ of the distance between two points on a thermally vibrating fractal. Using fractons, the vibrational excitations of a fractal, we show that for both strongly underdamped and overdamped vibrations this correlation function decays anomalously, displaying a crossover from a nearly stretched exponential decay at short times to a slow algebraic decay at long times. Relationship to single molecule experiments is discussed.

Recently, fluctuations of single folded proteins at equilibrium have been studied by Xie and co-workers [1]. Electron transfer between donor and acceptor in close proximity to each other has been used to monitor in time the distance between the two associated groups. The autocorrelation function for this distance has been found to decay very slowly in time following anomalous power laws. Furthermore, experiments by Lu and co-workers [2], involving long range energy transfer between relatively distant groups, report on long time scales under enzymatic reaction. It has been conjectured that equilibrium dynamics of enzymes play a major role in their function as catalysts [2,3].

Interestingly, by examining about 200 folded proteins, it has been recently found [4] that they can be described as mass fractals whose fractal dimension d_f is close to 2.5 (with a statistical standard deviation of about 0.2). This suggests that the vibrational excitations on a fractal—the so-called fractons [5–10]—can be used to describe static and dynamic properties of proteins. The use of fractons for proteins allows us to describe the thermally excited vibrational motion in proteins on a universal level, yet, still microscopic in essence. Consistent with this approach, the spectral dimension d_s, governing the density of vibrational states on a fractal, was deduced from electron spin relaxation measurements on proteins that were interpreted using the Raman relaxation mechanism [11]. For a number of modest-size proteins d_s was found from this experiment to be in range 1.3–1.7 [11]. Computational studies [12] extended the range of possible values of d_s from 1.3 in small proteins (~ 100 amino acids) to values close to 2 for very large proteins (over 2000–3000 amino acids). It thus appears that the (nearly) fractal properties of folded proteins are quite well established. Importantly, it has been argued that this property leads to large thermal fluctuations of the amino acid displacements u about their equilibrium position. These are predicted to diverge with the protein size *via* a generalized Landau-Peierls instability, $\langle u^2 \rangle \sim N^{2/d_s - 1}$ (for $d_s < 2$) where N is the number of amino acids [12]. In the case of enzymes, these large fluctuations may assist enzymatic activity. If $\langle u^2 \rangle^{1/2}$ reaches the equilibrium interamino acid distance, "melting" of the protein is expected; i.e., folding will not occur. Since evolution must have produced only proteins that have a strong tendency to fold, one expects a limit on their size for a given d_s, or a size dependent d_s approaching the value of 2 as N increases, as seen in computations [12].

In this Letter we concentrate on the equilibrium dynamic fluctuations of folded proteins using their fractal nature. For the sake of clarity, we review the main properties of the fracton model. Our system is a fractal cluster of beads, all identical, that are connected by harmonic springs. The fractal is embedded in the three-dimensional (3D) space and is characterized by a fractal dimension d_f, a manifold fractal dimension d_l, and a spectral dimension d_s. The beads in our model are defined rather ambiguously and model small groups on the protein involving, say, one alpha-carbon group [12] or an amino acid. The springs have a finite mean length, thereby giving a ground configurational state of finite size.

The fractal dimension d_f describes how the "mass" n (i.e., the number of beads that belong to the fractal) within a sphere of radius r scales with r, $n \sim r^{d_f}$, and $d_f \leq 3$. The manifold dimension d_l describes the fractality of the spring network in topological (or "chemical") space [9,10]. The chemical distance l is the shortest path between two points along the connecting springs. It relates to the real space distance through $l \sim r^{d_{\min}}$, $d_{\min} = d_f/d_l$. To clarify the meaning of d_l, consider a linear bead-spring chain folded self-similarly in the 3D space (e.g., a Gaussian or a self-avoiding chain) without forming new springs between neighboring beads. In this case $d_l = 1$ whatever the value of d_f. Similarly, a 2D bead-spring (membranelike) network, crumpled self-similarly in the 3D space with no new bonds (springs) created, corresponds to $d_l = 2$ (independent of d_f). The spectral dimension d_s describes dynamic quantities associated with the fractal, e.g., the probability density of a random walker to return to the origin at time t, $P_o(t) \sim t^{-d_s/2}$, and the density of vibrational states, $N(\omega) \sim \omega^{d_s - 1}$. These three broken dimensions obey the

inequalities $1 \leq d_s \leq d_l \leq d_f \leq 3$. We shall assume that for proteins $d_l \simeq d_f$, as neighboring groups are supposed to strongly interact and form new "springs" [12]. However, we keep d_l different from d_f for generality.

The internal "coordinate" (or the "name") of a bead in the manifold space is described here, even if just symbolically, by the "vector" $\vec{l}$ (taken to be dimensionless). The vector $\vec{R}(\vec{l})$ denotes the position of this bead in the 3D embedding space. The ground configurational state of the fractal is described by the set of coordinates $\vec{R}_{\rm eq}(\vec{l})$. Defining the deviation from the ground state by the displacements field $u(\vec{l}) = \vec{R}(\vec{l}) - \vec{R}_{\rm eq}(\vec{l})$, the Hamiltonian of the fractal in the scalar elasticity model is

$$H[\{\vec{u}(\vec{l})\}] = \frac{1}{2}m\omega_o^2 \sum_{\langle \vec{l}\vec{l}'\rangle}[\vec{u}(\vec{l}) - \vec{u}(\vec{l}')]^2, \qquad (1)$$

where $\langle \vec{l}\vec{l}'\rangle$ stands for nearest-neighbor pairs on the manifold, ω_o is the spring self-frequency, and m is the bead mass. The equilibrium spacing between beads (i.e., the spring unperturbed length) will be denoted by b.

We shall make use of the set of the eigenstates $\Psi_\omega(\vec{l})$ of the Hamiltonian Eq. (1). These are the fractons, namely, the vibrational excitations of the fractal [5,7,10]. Fractons are defined as the solution of the eigenvalue equation

$$\omega_o^2 \sum_{\vec{l}' \in \vec{l}}[\Psi_\omega(\vec{l}') - \Psi_\omega(\vec{l})] = -\omega^2 \Psi_\omega(\vec{l}), \qquad (2)$$

where $\vec{l}' \in \vec{l}$ denotes neighboring beads to $\vec{l}$ on the manifold. The left-hand side of Eq. (2) is the discrete Laplacian operator written on the fractal. The eigenstates $\Psi_\omega(\vec{l})$ form an orthonormal set [7]. Thus $\sum_{\vec{l}} \Psi_\omega^*(\vec{l})\Psi_{\omega'}(\vec{l}) = \delta_{\omega,\omega'}$ and $\sum_\omega \Psi_\omega^*(\vec{l})\Psi_\omega(\vec{l}') = \delta_{\vec{l},\vec{l}'}$. This allows us to define an eigenstate transform $\vec{u}_\omega = \sum_{\vec{l}}\vec{u}(\vec{l})\Psi_\omega^*(\vec{l})$ and an inverse transform $\vec{u}(\vec{l}) = \sum_\omega \vec{u}_\omega \Psi_\omega(\vec{l})$, so that $\vec{u}_\omega$ is the amplitude of the normal mode $\Psi_\omega(\vec{l})$. In the eigenstate "space," the Hamiltonian is thus diagonal

$$H[\{\vec{u}_\omega\}] = \frac{1}{2}m\sum_\omega \omega^2 \vec{u}_\omega^2. \qquad (3)$$

Equipartition theorem then dictates that at thermal equilibrium

$$\langle \vec{u}_\omega \cdot \vec{u}_{\omega'}\rangle_T = \frac{3k_BT}{m\omega^2}\delta_{\omega,\omega'}. \qquad (4)$$

The eigenstates $\Psi_\omega(\vec{l})$ are strongly localized in space, unlike the oscillatory behavior characteristic of uniform networks. A disorder averaged eigenstate may be defined according to $\bar{\Psi}_\omega(l) = \langle \Psi_\omega(0)\Psi_\omega(l)\rangle_{\rm dis}/\langle \Psi_\omega(0)^2\rangle_{\rm dis}$, where the averaging is performed over different realizations of the fractal, or over different origins $l = 0$ at a given realization (note that $\langle \Psi_\omega(0)^2\rangle_{\rm dis} = 1/N$). $\bar{\Psi}_\omega(l)$ obeys the

following scaling form [5]

$$\bar{\Psi}_\omega(l) = f((\omega/\omega_o)^{d_s/d_l}l), \qquad (5)$$

where $f(y)$ is the scaling function. For extremely large scaling arguments y, $f(y)$ is exponentially decaying [7,9,10]. More important for our analysis below is the behavior of the scaling function $f(y)$ near the origin $y = 0$. We assume that $f(y)$ is analytic at $y = 0$ and has a vanishing slope, thereby $f(y) \simeq 1 - {\rm const} \times y^2$ for $y \ll 1$. This is approximately confirmed by recent extensive simulations on fractal clusters [10] where it appears that, for small y, the "superlocalization" exponent in the manifold space is close to 2 (see Figs. 5 and 9 in Ref. [10]).

We now turn to discuss the dynamics of the fractal cluster vibrations. Following Eq. (1), the dynamics of the collection of beads is described by a set of Langevin equations (inertia being included) in which each bead is coupled to its fractal neighbors through the connecting springs. Friction and white noise forces are added to allow for thermal fluctuations in the system and they obey the fluctuation-dissipation theorem. Under the operation of the eigenstate transform defined above, we obtain Langevin equations for the normal mode amplitudes

$$m\frac{d^2\vec{u}_\omega}{dt^2} = -m\omega^2\vec{u}_\omega - m\gamma\frac{d\vec{u}_\omega}{dt} + \vec{\zeta}_\omega(t), \qquad (6)$$

where $m\gamma$ is the friction and $\vec{\zeta}_\omega(t)$ is thermal white noise. This is the Langevin equation for a harmonic oscillator and the resulting autocorrelation function is well known [13]. Here, however, we shall concentrate on two limiting cases. In the first case, we neglect the friction, which implies that modes are entirely undamped (or strongly underdamped), and we have pure vibrations. The strongly underdamped limit applies to short times such that $\gamma t \ll 1$, where $e^{-\gamma t/2} \simeq 1$, bearing in mind that this term will eventually become important at long times. In addition, considering the wide range of mode frequencies that appear in a large fractal cluster, $\omega_{\rm min} < \omega < \omega_o$, this limit requires that $\gamma \lesssim \omega_{\rm min} \sim R_g^{-d_f/d_s}$ where R_g is the gyration radius. Thus, it is assumed that energy transfer to the solvent is negligible, a situation that may occur in a large protein where the surface to volume ratio is small. Under this assumption, the autocorrelation function of the modes is purely oscillatory

$$\langle \vec{u}_\omega(t) \cdot \vec{u}_\omega(0)\rangle \simeq \langle \vec{u}_\omega^2\rangle_T \cos(\omega t). \qquad (7)$$

The second limit corresponds to strongly overdamped modes where $\gamma \gtrsim \omega_o$. This is the expected situation when each bead experiences a solvent Stokes drag. In this case

$$\langle \vec{u}_\omega(t) \cdot \vec{u}_\omega(0)\rangle \simeq \langle \vec{u}_\omega^2\rangle_T e^{-\omega^2 t/\gamma}. \qquad (8)$$

This case is similar to the "Rouse model" for linear

polymers [14] and fractal sol-gel clusters [15], except that it deals with *vibrations* on a fractal.

Consider now the autocorrelation function of the distance $\vec{X}(t)$ between two beads on the fractal, or the displacement difference $\vec{x}(t)$ autocorrelation. The latter is the correlation function that can be deduced from energy or electron transfer experiments [1,2]. Let $\vec{X}(t) = \vec{R}(\vec{l}, t) - \vec{R}(\vec{l}', t)$ and $\vec{x}(t) = \vec{u}(\vec{l}, t) - \vec{u}(\vec{l}', t)$. Then $\langle \vec{X}(t) \cdot \vec{X}(0) \rangle = \langle \vec{x}(t) \cdot \vec{x}(0) \rangle + \vec{X}_{eq}^2$ where $\vec{X}_{eq} = \vec{R}_{eq}(\vec{l}) - \vec{R}_{eq}(\vec{l}')$. The displacement difference autocorrelation is

$$\langle \vec{x}(t) \cdot \vec{x}(0) \rangle = \langle \vec{u}(\vec{l}, t) \cdot \vec{u}(\vec{l}, 0) \rangle + \langle \vec{u}(\vec{l}', t) \cdot \vec{u}(\vec{l}', 0) \rangle$$
$$- \langle \vec{u}(\vec{l}, t) \cdot \vec{u}(\vec{l}', 0) \rangle - \langle \vec{u}(\vec{l}', t) \cdot \vec{u}(\vec{l}, 0) \rangle. \quad (9)$$

Using translational invariance, after performing disorder averaging [see discussion following Eq. (4)],

$$\langle \vec{x}(t) \cdot \vec{x}(0) \rangle = 2[\langle \vec{u}(0, t) \cdot \vec{u}(0, 0) \rangle - \langle \vec{u}(\vec{l} - \vec{l}', t) \cdot \vec{u}(0, 0) \rangle]. \quad (10)$$

As this depends only on the difference $|\vec{l} - \vec{l}'|$ we now set $\vec{l}' = 0$ without loss of generality. Using the normal modes we have

$$\langle \vec{x}(t) \cdot \vec{x}(0) \rangle = \frac{2}{N} \sum_\omega [1 - \bar{\Psi}_\omega(l)] \langle \vec{u}_\omega(t) \cdot \vec{u}_\omega(0) \rangle. \quad (11)$$

Based on the Gaussian property of $\{\vec{u}_\omega\}$, we note that $\vec{x}(t)$ is a stochastic Gaussian variable. Therefore, higher order correlation functions of $\vec{x}(t)$ are related to $\langle \vec{x}(t) \cdot \vec{x}(0) \rangle$ through Wick's theorem.

Consider now the two limits discussed above. In the strongly underdamped limit, we have

$$\langle \vec{x}(t) \cdot \vec{x}(0) \rangle = \frac{2}{N} \sum_\omega \langle \vec{u}_\omega^2 \rangle_T [1 - \bar{\Psi}_\omega(l)] \cos(\omega t). \quad (12)$$

Equation (12) is similar to a Fourier sum, although the frequencies ω are not integer multiples of ω_{min} as in a regular Fourier sum. It shows that if there are very few, well separated, modes (i.e., for a small system), the autocorrelation function should show some oscillatory behavior. However, if the fractal cluster (i.e., protein) is sufficiently large, ω is nearly continuous and we transform the sum to an integral

$$\langle \vec{x}(t) \cdot \vec{x}(0) \rangle = \frac{2}{N} \int_{\omega_{min}}^{\omega_o} d\omega N(\omega) \langle \vec{u}_\omega^2 \rangle_T [1 - \bar{\Psi}_\omega(l)] \cos(\omega t), \quad (13)$$

where $N(\omega)$ is the density of states. Using Eqs. (4) and (5) and $N(\omega) = n_o \omega^{d_s - 1}$, with $n_o = N d_s / \omega_o^{d_s}$ chosen such that $\int_0^{\omega_o} d\omega N(\omega) = N$, leads to

$$\langle \vec{x}(t) \cdot \vec{x}(0) \rangle = 6 d_s \frac{k_B T}{m \omega_o^{d_s}} \int_{\omega_{min}}^{\omega_o} d\omega \, \omega^{d_s - 3} (1$$
$$- f((\omega / \omega_o)^{d_s / d_l} l)) \cos(\omega t). \quad (14)$$

Focusing on the time regime $\omega_o^{-1} \ll t \ll \omega_{min}^{-1}$ we may set the limits of integration to 0 and infinity. Changing the variable of integration to $z = \omega t$ we obtain the following scaling form

$$\langle \vec{x}(t) \cdot \vec{x}(0) \rangle = \frac{k_B T}{m \omega_o^2} (\omega_o t)^{2 - d_s} g(l / \ell(t)),$$
$$g(v) = 6 d_s \int_0^\infty dz \, z^{d_s - 3} [1 - f(z^{d_s / d_l} v)] \cos(z), \quad (15)$$

where $\ell(t) = (\omega_o t)^{d_s / d_l}$ is the length describing the propagation with distance in the manifold space of the bead-bead correlations. It also describes the response to a localized external perturbative force, or the spreading of a wave packet [5,16]. In real space, this propagation length is $\xi(t) \sim t^{d_s / d_f}$.

We now analyze Eq. (15) at short and long times. If $\ell(t) \ll l$, the argument of the eigenstate scaling function $f(y)$ is usually large (except for exceptionally small z) and, considering the strong localization, we may use $f(y) \ll 1$. This regime therefore corresponds to completely uncorrelated motion of the two beads. Thus, provided that $d_s < 2$, at short times we find stretched-exponential-like decay $\sim 1 - \text{const} \times t^{2 - d_s}$, or, more precisely,

$$\langle \vec{x}(t) \cdot \vec{x}(0) \rangle \approx \langle \vec{x}^2 \rangle - C \frac{k_B T}{m \omega_o^2} (\omega_o t)^{2 - d_s}, \quad (16)$$

where C is a numerical constant, $C = 6 d_s \times \cos(d_s \pi / 2) \Gamma[d_s - 2]$. The static variance is

$$\langle \vec{x}^2 \rangle \approx \text{const} \times \frac{k_B T}{m \omega_o^2} (r / b)^{d_f (2 - d_s) / d_s} \quad (17)$$

(provided that $2 \frac{d_s}{d_l} + d_s > 2$, assuming $f(y) \simeq 1 - \text{const} \times y^2$ for $y \ll 1$) showing the divergence with distance of the interparticle separation fluctuations, in accord with the Landau-Peierls effect. Note that the static variance may be described by an effective harmonic potential $\frac{1}{2} m \omega_{eff}^2 \vec{x}^2$ with [7] $\omega_{eff} \approx \omega_o (r / b)^{-d_f (1 - d_s / 2) / d_s}$, consistent with the measurements reported in Ref. [1]. Equation (16) shows that the initial decay of $\langle \vec{x}(t) \cdot \vec{x}(0) \rangle$ is due to *uncorrelated* subdiffusive motion of each bead resulting from the superposition of thermally excited fractons.

At long times such that $\ell(t) \gg l$, the correlation has already propagated much further than the distance l (or r, in real space), and the motion of the two particles is nearly perfectly correlated, thus leading to a vanishing autocorrelation of $\vec{x}(t)$. The precise decay form is very sensitive to the behavior of the scaling function $f(y)$ near the origin $y = 0$ [see discussion following Eq. (5)], and we find

$$\langle \vec{x}(t) \cdot \vec{x}(0) \rangle \approx \text{const} \times \frac{k_B T}{m \omega_o^2} l^2 (\omega_o t)^{-(2 d_s / d_l + d_s - 2)} \quad (18)$$

provided that $2 < 2 \frac{d_s}{d_l} + d_s < 3$ (which is required for the integral to converge). Thus, at long times we obtain a slow algebraic decay $\sim t^{-\alpha}$, where α can lie in the range

$0 < \alpha < 1$ (depending on d_s and d_l). This asymptotic behavior proceeds until times of order $\min[\gamma^{-1}, \omega_{\min}^{-1}]$.

Next consider the strongly overdamped limit. In this case

$$\langle \vec{x}(t) \cdot \vec{x}(0)\rangle = 6d_s \frac{k_B T}{m\omega_o^{d_s}}$$
$$\times \int_{\omega_{\min}}^{\omega_o} d\omega\, \omega^{d_s-3}(1 - f((\omega/\omega_o)^{d_s/d_l}l))$$
$$\times e^{-\omega^2 t/\gamma}. \tag{19}$$

This leads to the following propagation length $\ell(t) = (\omega_o^2/\gamma)^{d_s/2D}t^{d_s/2d_l}$. At the short time regime, $\ell(t) \ll l$, we obtain (for $d_s < 2$)

$$\langle \vec{x}(t) \cdot \vec{x}(0)\rangle \approx \langle \vec{x}^2\rangle - B\frac{k_B T}{m\omega_o^2}\left(\frac{\omega_o^2}{\gamma}t\right)^{1-d_s/2}, \tag{20}$$

where $B = 6d_s\Gamma[d_s/2]/(2 - d_s)$. For long times, $\ell(t) \gg l$, we get

$$\langle \vec{x}(t) \cdot \vec{x}(0)\rangle \approx \text{const} \times \frac{k_B T}{m\omega_o^2}l^2\left(\frac{\omega_o^2}{\gamma}t\right)^{-(d_s/d_l+d_s/2-1)} \tag{21}$$

assuming that $2\frac{d_l}{d_s} < 2 + d_l$.

To summarize the time dependencies, in the undamped limit we find

$$\langle \vec{x}(t) \cdot \vec{x}(0)\rangle \sim \begin{cases} 1 - \text{const} \times t^{2-d_s} & \text{for} \quad t \ll t_1^*; \\ t^{-(2d_s/d_l+d_s-2)} & \text{for} \quad t \gg t_1^*. \end{cases} \tag{22}$$

where $t_1^* \approx \omega_o^{-1}(r/b)^{d_f/d_s}$. In the strongly overdamped limit we have

$$\langle \vec{x}(t) \cdot \vec{x}(0)\rangle \sim \begin{cases} 1 - \text{const} \times t^{1-d_s/2} & \text{for} \quad t \ll t_2^*; \\ t^{-(d_s/d_l+d_s/2-1)} & \text{for} \quad t \gg t_2^*. \end{cases} \tag{23}$$

where $t_2^* \approx \frac{\gamma}{\omega_o^2}(r/b)^{2d_f/d_s}$.

We now turn to discuss the experimental implications of our results. Electron spin relaxation measurements [11] and computer simulations [12] show that d_s varies from one protein to another covering the range $1.3 \lesssim d_s \lesssim 1.9$. Since neighboring groups usually interact strongly, we can assume $d_l \simeq d_f$ and use the values obtained from computer analysis of over 200 proteins [4], $2.3 \lesssim d_f \lesssim 2.7$. We thus estimate the short time exponents to be in the ranges $0.1 \lesssim 2 - d_s \lesssim 0.7$ in the undamped model, and $0.05 \lesssim 1 - d_s/2 \lesssim 0.35$ in the overdamped case. The long time exponents are predicted to lie in the ranges $0.3 \lesssim 2\frac{d_s}{d_l} + d_s - 2 < 1$ in the undamped case, and $0.15 \lesssim \frac{d_s}{d_l} + d_s/2 - 1 \lesssim 0.7$ in the overdamped case. We note that in the overdamped case, for a 1D bead-spring (Rouse-like) chain ($d_l = d_s = 1$), both short and long time exponents have the value $1/2$. This behavior can be approximated by a

Mittag-Leffler function [17], and might be related to the experiments of Xie and co-workers [1].

In this Letter we have demonstrated that thermally excited fractons on a fractal, which model vibrational modes of proteins, lead naturally to a nonexponential decay of the autocorrelation function of the distance between two tagged groups. It is gratifying that, even for pure vibrations, we have obtained correlation functions that decay in time, and they do so as power laws. Moreover, in the case of pure vibrations, only fractals whose characteristic dimensions obey the inequalities $2 < 2\frac{d_s}{d_l} + d_s < 3$ and $d_s < 2$ will show these long time algebraic decays. These inequalities do *not* hold for uniform lattices in all dimensions, as expected. Our predictions are amenable for verification in single molecule experiments.

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