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Proteins as fractals: Role of the hydrodynamic interaction

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Exploiting the fractal nature of folded proteins, we study the effect of the hydrodynamic interaction between amino acids using a Zimm-type model. We compute the time-dependent mean square displacement of an amino acid and the time-dependent autocorrelation function of the distance between two amino acids, and we show that these dynamic quantities evolve anomalously, similar to the Rouse-type behavior, yet with modified dynamic exponents. Good agreement is found with recent neutron spin-echo studies of myoglobin and hemoglobin.

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Recently there has been much theoretical focus on the fractal nature of natively folded proteins [1–9]. It has been shown that each protein can be associated with characteristic broken dimensions in analogy with mathematically constructed fractals. This viewpoint allows description of protein dynamics on a universal level. A universal anomalous dynamics has emerged in which the specificity is associated with the unique dynamic exponents that characterize each protein [3,5,8]. On the experimental side, evidence came from electron spin relaxation measurements [10] and neutron scattering [11]. Single-molecule experiments have reported anomalous behaviors involving power laws in time [12]. More recently neutron spin-echo studies at large wavenumbers demonstrated a stretched exponential relaxation that was interpreted as anomalous subdiffusion of the amino acids [13]. Anomalous dynamics has also been observed in molecular dynamics simulations [14,15].

Mathematically constructed fractals are either deterministic fractals, e.g., the Sierpinski gasket and carpets, or disordered, e.g., the infinite percolation cluster at the percolation threshold [16]. They can be characterized by a few broken dimensions: (i) the mass fractal dimension d_f, which governs the scaling $M(r) \sim r^{d_f}$ of the mass $M(r)$ enclosed in concentric spheres of radius r; (ii) the spectral dimension d_s, which governs the scaling $g(\omega) \sim \omega^{d_s-1}$ of the vibrational density of states (DOS) $g(\omega)$ with frequency ω [17,18]; and (iii) the topological dimension d_l, which governs the scaling $M(l) \sim l^{d_l}$ of the mass $M(l)$ enclosed in concentric "spheres" of radius l in the topological (or "manifold"/"chemical") space. One may also define, instead of d_l, the chemical length (or minimal path) dimension $d_{\min} = d_f/d_l$ that relates the real space distance r between two points on the fractal to the minimal path distance l between these points along the fractal network links, $l \sim r^{d_{\min}}$.

The dimensions d_f and d_s have been computed for a large number of proteins using the native fold structures obtained from the protein data bank [7]. d_f is straightforwardly computed using these structures. The computation of d_s requires a network elasticity model, and the Gaussian network model (GNM) has been mostly used [19]. The topological dimension d_l has also been computed and found close to the fractal dimension d_f [20]. The spectral dimension of the vast majority of proteins has been found to be smaller than two [4,6,7]. Importantly, it has been argued that this property leads to large thermal fluctuations of the amino acid displacements u_i about their equilibrium, native fold, position. These are predicted to diverge with the protein size via a generalized Landau-Peierls instability, $\langle u_i^2 \rangle \sim N^{\frac{2}{d_s}-1}$ (for $d_s < 2$), where N is the number of amino acids [4,6]. By invoking marginal stability, which allows proteins to attain maximum fluctuations (or "flexibility") but keep their native fold structure, a universal equation of state has been deduced that relates d_s, d_f, and N of all natively folded proteins [6]. The equation has been checked for about 5,000 proteins, and remarkable agreement has been found, regardless of their source and function [7].

Protein vibrations have been described so far within the vanishing damping and the high damping limits [3,5]. In the latter, it was assumed that the hydrodynamic drag is local, similar to the Rouse model of polymers. Random walk (RW) on the protein fold has been also studied, and using its mapping to the Rouse-type vibrational model allowed to deduce valuable information on vibrations [8]. However, the role of the hydrodynamic coupling between amino acids, similar to the Zimm model of polymers [21–24], has not been studied so far in this context. Yet, like in polymers, forces acting on an amino acid lead to its motion and induce a velocity field in the solvent, which in turn generates motion of another amino acid. The interaction decays very slowly, as $\sim 1/r$, so its effect can be strong. We study this effect here using the general analytical framework formulated in Ref. [5].

We repeat briefly the model definitions and assumptions, following the notations of Ref. [5]. Protein vibrations are discussed using the GNM [17,19]. The model assigns identical springs between α-carbon pairs that are distant less than a cutoff distance R_c, whose typical values range between 6 and 8 A. Each α-carbon, henceforth named a "bead," is assigned an averaged amino acid mass. In what follows, we assume that the network forms a disordered fractal. The index of a bead, or its coordinate in topological space, is denoted symbolically by the "vector" $\vec{l}$. The vector $\vec{R}(\vec{l})$ denotes its position in real space. The ground configurational state of the protein is described by the set of coordinates $\vec{R}_{\rm eq}(\vec{l})$, and deviations from the ground state are denoted by the displacements $\vec{u}(\vec{l}) = \vec{R}(\vec{l}) - \vec{R}_{\rm eq}(\vec{l})$. The GNM Hamiltonian 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 pairs connected by springs, ω_o is the spring natural frequency, and m is the bead mass ($m\omega_o^2$ is the

spring constant). The eigenstates (normal modes) $\Psi_\alpha(\vec{l})$ of the Hamitonian (1) are solutions of the eigenvalue equation

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

where $\vec{l}' \in \vec{l}$ denotes beads connected by springs to the bead $\vec{l}$. $\{\Psi_\alpha(\vec{l})\}$ form an orthonormal set [18], allowing us to define a normal mode transform $\vec{u}_\alpha = \sum_{\vec{l}} \vec{u}(\vec{l})\Psi_\alpha(\vec{l})$, where $\vec{u}_\alpha$ is the amplitude of the normal mode $\Psi_\alpha(\vec{l})$. In the normal mode "space", the Hamiltonian is diagonal, $H[\{\vec{u}_\alpha\}] = \frac{1}{2}m\sum_\alpha \omega_\alpha^2 \vec{u}_\alpha^2$. The equipartition theorem then dictates that at thermal equilibrium $\langle \vec{u}_\alpha \cdot \vec{u}_\beta \rangle_T = \frac{3k_BT}{m\omega_\alpha^2}\delta_{\alpha,\beta}$.

On a fractal, the normal modes $\Psi_\alpha(\vec{l})$ are strongly localized in space. A disorder averaged eigenstate may be defined according to $\bar{\Psi}_\alpha(l) = N\langle \Psi_\alpha(0)\Psi_\alpha(l)\rangle_{\rm dis}$. It has been shown that $\bar{\Psi}_\alpha(l)$ obeys the following scaling form: $\bar{\Psi}_\alpha(l) = f[(\omega_\alpha/\omega_o)^{d_s/d_l} l]$, where $f(y)$ is the scaling function [16–18]. For $y \gg 1$, $f(y)$ is exponentially decaying, and, for $y \ll 1$, $f(y) \simeq 1 - \text{const.} \times y^2$ [18,25,26].

We now turn to discuss the dynamics of the fractal network, generalizing the treatment of Ref. [5] to include the hydrodynamic interaction. The dynamics is described by a set of Langevin equations in the strong damping limit that follow from Eq. (1), in which friction is modeled by the Oseen mobility tensor. The Oseen tensor describes how the velocity $\vec{v}_i$ of a bead i is influenced by the force $\vec{f}_j$ acting on another bead j a distance $\vec{r}_{ij}$ apart, via $\vec{v}_i = \mathbf{L}(\vec{r}_{ij}) \cdot \vec{f}_j$, and in the Stokes approximation it is [21] $\mathbf{L}(\vec{r}) = (\hat{r}\otimes\hat{r} + \mathbf{1})/(8\pi\eta r)$. We assume, for simplicity, that each bead is hydrodynamically coupled to all other beads in the network and that all amino acid pairs experience the same hydrodynamic interaction. White-noise forces are added as usual to allow for thermal fluctuations in the system, and they obey the fluctuation-dissipation theorem. With these simplifying assumptions, the Langevin equations of motion become

$$\frac{d\vec{u}(\vec{l})}{dt} = m\omega_o^2 \sum_{\vec{l}'} \mathbf{L}(\vec{R}_{\vec{l}\vec{l}'}) \cdot \sum_{\vec{l}''\in\vec{l}'} [\vec{u}(\vec{l}'') - \vec{u}(\vec{l}')] + \vec{\zeta}(\vec{l},t), \tag{3}$$

where $\vec{R}_{\vec{l}\vec{l}'} = \vec{R}(\vec{l}) - \vec{R}(\vec{l}')$ is the vector separation between beads $\vec{l}$ and $\vec{l}'$.

The dynamics described by Eq. (3) is essentially nonlinear. The nonlinearity emerges from the dependence on distance of the Oseen tensor, which also implies dependence on displacements. We thus linearize these equations, introducing a few simplifications. First, vibrations are assumed small such that $\vec{R}_{\vec{l}\vec{l}'} \simeq \vec{R}_{\vec{l}\vec{l}',eq}$. Second, we angularly preaverage the Oseen tensor; namely, we replace it by a scalar equal to the angularly averaged tensor, $\langle \mathbf{L}(\vec{r})\rangle = \Lambda(r)\mathbf{1}$ [21]. The latter depends only on the distance $r = |\vec{r}|$, $\Lambda(r) = 1/(6\pi\eta r)$. Note that, unlike for polymers [21,22], we do not require here interbead distance preaveraging, as the network merely vibrates around its ground-state structure. Under these approximations, the Langevin equations (3) become

$$\frac{d\vec{u}(\vec{l})}{dt} = m\omega_o^2 \sum_{\vec{l}'} \Lambda(R_{\vec{l}\vec{l}'}) \sum_{\vec{l}''\in\vec{l}'} [\vec{u}(\vec{l}'') - \vec{u}(\vec{l}')] + \vec{\zeta}(\vec{l},t). \tag{4}$$

The vibrational normal modes do not diagonalize Eq. (4) due to the hydrodynamic interaction, yet we shall still use them to develop this equation. We first plug in the normal mode inverse transform $\vec{u}(\vec{l}) = \sum_\beta \vec{u}_\beta \Psi_\beta(\vec{l})$ on both sides of Eq. (4) and make use of the modes defining Eq. (2). Next we multiply both sides by $\Psi_\alpha(\vec{l})$ and sum over $\vec{l}$, making use of the orthonormality of the modes, to arrive at the following Langevin equations for the normal mode amplitudes u_α:

$$\frac{d\vec{u}_\alpha}{dt} = -m\sum_\beta \omega_\beta^2 \Lambda_{\alpha\beta}\vec{u}_\beta + \vec{\zeta}_\alpha(t), \tag{5}$$

where

$$\Lambda_{\alpha\beta} = \sum_{\vec{l},\vec{l}'} \Lambda(R_{\vec{l}\vec{l}'})\Psi_\alpha(\vec{l})\Psi_\beta(\vec{l}'). \tag{6}$$

Next we perform disorder averaging over Eq. (5), which amounts to disorder averaging over $\Psi_\alpha(\vec{l})\Psi_\beta(\vec{l}')$ in Eq. (6). Considering frequencies that are not too low, $\omega_\alpha, \omega_\beta \gg \omega_{\rm min}$, the normal modes are strongly localized in space and centered in different regions of the protein/fractal, thus making the sum in Eq. (6) small for $\alpha \neq \beta$. Hence, for such frequencies, off-diagonal terms are negligible, and $\langle\Lambda_{\alpha\beta}\rangle_{\rm dis}$ becomes effectively diagonal. Using the disorder averaged eigenstate $\bar{\Psi}_\alpha(\vec{l})$ we have

$$\langle\Lambda_{\alpha\beta}\rangle_{\rm dis} = \frac{\delta_{\alpha\beta}}{N}\sum_{\vec{l},\vec{l}'} \Lambda(R_{\vec{l}\vec{l}'})\bar{\Psi}_\alpha(\vec{l}-\vec{l}'). \tag{7}$$

Summing over $\vec{l}'$, noting that the sum terms depend only the difference $\vec{l}-\vec{l}'$ and not on $\vec{l}'$ and $\vec{l}$ alone, and neglecting boundary effects (i.e., taking the large system limit and both $\vec{l}$ and $\vec{l}'$ far from the boundaries), we obtain $\langle\Lambda_{\alpha\beta}\rangle_{\rm dis} = \delta_{\alpha\beta}\Lambda_\alpha$, where

$$\Lambda_\alpha = \sum_{\vec{l}} \Lambda(R_{\vec{l}})\bar{\Psi}_\alpha(\vec{l}) \tag{8}$$

is the normal mode transform of $\Lambda(R_{\vec{l}})$. The Langevin equations thus become diagonal in the disorder averaged eigenstate space

$$\frac{d\vec{u}_\alpha}{dt} = -m\omega_\alpha^2\Lambda_\alpha\vec{u}_\alpha + \vec{\zeta}_\alpha(t). \tag{9}$$

As a result of this effective diagonalization, the time autocorrelation function of mode amplitude is simply $\langle\vec{u}_\alpha(t)\cdot\vec{u}_\alpha(0)\rangle = \langle\vec{u}_\alpha^2\rangle e^{-\Gamma_\alpha t}$, where $\Gamma_\alpha = m\omega_\alpha^2\Lambda_\alpha$ is the mode relaxation rate. This will serve us in calculating desired observables.

In order to evaluate Λ_α using Eq. (8), we use the scaling form of the eigenstates, $\bar{\Psi}_\alpha(l) = f[(\omega_\alpha/\omega_o)^{d_s/d_l} l]$, and the scaling behavior $R_l \sim l^{1/d_{\rm min}} \sim l^{d_l/d_f}$, connecting the chemical length l to the real space length R_l. Approximating the sum in Eq. (8) by an integral leads to $\Lambda_\alpha = (A/6\pi\eta b)(\omega_\alpha/\omega_o)^{\frac{d_s}{d_f}-d_s}$, where A is a numerical constant, $A = \int_0^\infty \frac{d^{d_l}x}{x^{d_l/d_f}} f(x)$, and b is the mean bond length. The mode relaxation rate becomes

$$\Gamma_\alpha \simeq \bar{A}\omega_\alpha^{\frac{d_s}{d_f}+2-d_s} \tag{10}$$

with $\bar{A} = A\,m/(6\pi\eta b\omega_o^{\frac{d_s}{d_f}-d_s})$.

We now discuss the implications of the above dynamics on two dynamical observables. Consider first the vibrational

mean square displacement (MSD) of a bead, averaged over all network beads. The MSD can be expanded in terms of the modes to obtain

$$\langle \Delta\vec{u}(t)^2\rangle \equiv \langle(\vec{u}(t)-\vec{u}(0))^2\rangle = \frac{2}{N}\sum_{\alpha}\langle\vec{u}_{\alpha}^2\rangle(1-\mathrm{e}^{-\Gamma_{\alpha}t}). \quad (11)$$

We approximate the sum by an integral over the frequency ω using the DOS $g(\omega)=n_o\omega^{d_s-1}$, with $n_o=Nd_s/\omega_o^{d_s}$ chosen such that $\int_0^{\omega_o}d\omega g(\omega)=N$. Focusing on the time regime $\Gamma(\omega_o)^{-1}\ll t\ll\Gamma(\omega_{\min})^{-1}$ and assuming $d_s<2$, leads to an *anomalous subdiffusion*

$$\langle \Delta\vec{u}(t)^2\rangle = Bt^{\nu}, \quad (12)$$

where the anomalous diffusion exponent ν is

$$\nu=\frac{2-d_s}{2-d_s+d_s/d_f}=\frac{d_w-d_f}{d_w-d_f+1}. \quad (13)$$

Here $d_w=2d_f/d_s$ is the RW anomalous diffusion exponent ($\langle r^2\rangle\sim t^{2/d_w}$). The prefactor B is $B=6d_s\frac{\Gamma(\frac{1}{d_w-d_f+1})}{2-d_s}\frac{k_BT}{m\omega_o^{d_s}}\bar{A}^{\nu}$, where $\Gamma(x)$ is the Gamma function.

Next we consider the autocorrelation function of the fluctuations in distance between two beads on the fractal $\vec{x}(t)$, which can be deduced from single-molecule experiments [12]. Using $\vec{x}(t)=\vec{u}(\vec{l},t)-\vec{u}(\vec{l}',t)$, performing disorder average, and making use of the normal modes, we obtain the following scaling form for the time regime $\Gamma(\omega_o)^{-1}\ll t\ll\Gamma(\omega_{\min})^{-1}$:

$$\langle\vec{x}(t)\cdot\vec{x}(0)\rangle=\frac{k_BT}{m\omega_o^{d_s}}(\bar{A}t)^{\nu}g\left[l/\ell(t)\right], \quad (14)$$

where $g(v)$ is a scaling function and $\ell(t)=\omega_o^{d_s/d_l}(\bar{A}t)^{\frac{d_f}{d_l(d_w-d_f+1)}}$ is the length describing the propagation with distance, in topological space, of the bead-bead correlations or force and energy perturbations. In real space, this propagation length scales with time as $\xi(t)\sim t^{\zeta}$, where $\zeta=1/(d_w-d_f+1)$.

We now analyze $\langle\vec{x}(t)\cdot\vec{x}(0)\rangle$ at short and long times. If $\ell(t)\ll l$, the two beads' motion is uncorrelated. Provided that $d_s<2$, at short times we find $\langle\vec{x}(t)\cdot\vec{x}(0)\rangle\approx\langle\vec{x}^2\rangle-Bt^{\nu}$. The static variance diverges with distance as $\langle\vec{x}^2\rangle\sim r^{d_w-d_f}$, as recently verified numerically for about 500 proteins [8]. At long times such that $\ell(t)\gg l$ the motion of the two particles is nearly perfectly correlated, thus leading to a vanishing autocorrelation of $\vec{x}(t)$. Using $f(y)\simeq 1-\text{const.}\times y^2$ for $y\ll 1$, we find, provided that $2<2\frac{d_s}{d_l}+d_s$,

$$\langle\vec{x}(t)\cdot\vec{x}(0)\rangle\approx\text{const.}\frac{k_BT}{m\omega_o^{d_s}}\,l^2\,(\bar{A}t)^{-\mu}, \quad (15)$$

where

$$\mu=\frac{2\frac{d_s}{d_l}+d_s-2}{2-d_s+d_s/d_f}=\frac{2\frac{d_f}{d_l}+d_f-d_w}{d_w-d_f+1}. \quad (16)$$

To summarize the time dependencies, we find

$$\langle\vec{x}(t)\cdot\vec{x}(0)\rangle\sim\begin{cases}1-\text{const.}\,t^{\nu} & \text{for}\quad t\ll t^*,\\ t^{-\mu} & \text{for}\quad t\gg t^*,\end{cases} \quad (17)$$

where $t^*\sim r^{d_w-d_f+1}$. As for most proteins d_f and d_s are in the range $2<d_f<3$ and $1.3<d_s<2$, we obtain a variety of values of ν and μ that can be found specifically for each protein [7,27].

Similar behaviors have been found using the Rouse-type model, yet the values of the dynamical exponents ν, μ, and ζ are different [3,5,24]. The Rouse-type model leads to $\nu=1-d_s/2$, independent of d_f, whereas here we find d_f dependence [Eq. (13)], manifesting how the hydrodynamic coupling "senses" the object geometry. The propagation length exponent ζ, which is simply $\zeta=1/d_w=d_s/(2d_f)$ in the Rouse-type model, manifesting the mapping to the RW problem, is now modified to $\zeta=1/(d_w-d_f+1)$ [28]. Note that for purely 1D objects ($d_f=d_l=d_s=1$) one recovers the well-known Rouse exponent $\nu=1/2$ (ignoring logarithmic corrections). This exemplifies the known weak (in fact, marginal) hydrodynamic coupling that is present in 1D.

It is interesting to compare our results to the dynamics of linear polymer chains and branched polymers forming fractal-like, sol-gel, clusters [21–24]. In these systems, and unlike in our study, the clusters and chains can fluctuate between all their possible configurations. The Zimm model in these systems leads to an anomalous diffusion exponent $\nu=2/3$, regardless of the fractal dimension d_f, demonstrating the strong effect of the hydrodynamic interaction [21,22,24]. However, for our vibrating fractal, which models a folded protein, ν is dependent on d_f and d_s (or, alternatively, d_f and d_w) and can significantly deviate from 2/3 (it equals 2/3 for a Gaussian linear chain where $d_l=d_s=1$, $d_f=2$). The hydrodynamic interaction "renormalizes" the dynamic exponents but, unlike in polymer systems, does not smear entirely their fractal character.

Importantly, the dynamic structure factor $S(q,t)$ of proteins is expected to decay mainly due to the evolution in time of the MSD, $S(q,t)\simeq S(q)\exp[-\frac{1}{6}q^2\langle\Delta\vec{u}(t)^2\rangle]$, from which the MSD may be extracted [13,21,22]. At large wavenumbers q corresponding to $qR_g\gg 1$, where R_g is the gyration radius, the result is a stretched exponential relaxation. Recent neutron spin-echo studies on horse heart myoglobin (Mb) and bovine hemoglobin (Hb) indeed find a stretched exponential relaxation in the large q and low concentration regimes with $\nu\simeq 0.4\pm 0.03$ for both proteins. Taking the values [29] $d_s=1.56$, $d_f=2.38$ for Mb, and $d_s=1.74$, $d_f=2.52$ for Hb, we obtain, from Eq. (13), $\nu=0.40$ for Mb, in good agreement with experiment, and $\nu=0.27$ for Hb, in less good agreement. The Rouse exponents, $\nu=1-d_s/2$, are 0.22 (Mb) and 0.13 (Hb), which do not quite agree with experiment. However, in view of the computational and experimental errors this comparison is not conclusive. It should be noted that the experimental exponent is quite far from the polymer Zimm exponent $\nu=2/3$, even if one puts aside the inapplicability of this model to folded proteins. On the more fundamental level, the observed stretched exponential decay is strong support for the fractal nature of proteins manifested in their dynamic behavior.

The theory can be tested also for other systems exhibiting fractal structures. Colloidal gels consist of diffusion-limited fractal aggregates made of polystyrene particles [30]. In this system bond-bending elasticity dominates the vibrations rather than scalar elasticity, so some modifications to the present calculation are required. Bond bending is known to modify the spectral dimension that controls the DOS to a different value, which we shall denote d_E, such that $g(\omega)\sim\omega^{d_E-1}$. With this modification, all steps of our derivation may be

repeated leading to the same expressions for the MSD $\langle \Delta \vec{u}(t)^2 \rangle$ and distance autocorrelation $\langle \vec{x}(t) \cdot \vec{x}(0) \rangle$, just that d_E is now replacing d_s. The value of d_E for diffusion-limited aggregates may be inferred from the work of Webman and Grest [31], and the following expression is obtained: $d_E = 2d_f/(2 + d_B + d_f)$, where d_B is the bond dimension [30,32] (denoted as the backbone dimension D' in Ref. [31]). Using this expression we find a modified anomalous diffusion exponent $\nu_E = (2 + d_B)/(3 + d_B)$. It is gratifying that Krall and Weitz arrived at the same expression using a more heuristic approach [30]. Moreover, since $d_B \simeq 1.1$ for diffusion-limited clusters [32], one obtains $\nu_E \simeq 0.76$, consistent with the measured value 0.66–0.70 [30].

We have found that, in thermally vibrating fractals, the hydrodynamic interaction modifies various dynamic exponents but does not alter their universal, anomalous, form. Making use of the similarity between proteins and fractals, we suggest an explanation for the anomalous diffusion inferred from recent neutron spin-echo measurements on proteins [13], which may motivate further experiments in this direction.

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