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Temporal fluctuations in the potential energy of proteins: $1/f^{\alpha}$ noise and diffusion

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Abstract

Molecular dynamics (MD) simulation methods were used to investigate temporal fluctuations in the potential energy of plastocyanin (PC), an electron transport copper-containing protein. The related power spectra, studied within a range of sampling times, revealed the presence of $1/f^{\alpha}$ noise with $1 < \alpha < 2$ and Gaussian statistics, that is consistent with fractional Brownian motion (fBm) models describing sublinear diffusion. Analysis of the protein trajectory in the configurational space by the essential dynamics method, allowed us to confirm, in an independent way, the occurrence of such a sublinear diffusive process. The results are discussed also in connection with the self-similar properties, involving spatial and temporal disorder, of the investigated systems.

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Keywords: Plastocyanin; MD simulation; $1/f$ noise; Fractional Brownian motion

1. Introduction

Recently, we put into evidence the occurrence of $1/f^{\alpha}$ noise in the potential energy (E_{p}) fluctuations of plastocyanin (PC), an electron transfer copper-containing protein involved into the photosynthetic process, investigated by a molecular dynamics (MD) simulation approach [1,2]. Such a phenomenon could be traced back to the peculiar features of the protein dynamics, which involves also collective, non-linear motions and is connected to the sampling of the local minima (conformational substates) in the potential energy hypersurface [3–5]. Indeed, MD simulations evidenced in the past the presence of a large number of nearly isoenergetic minima in the energy landscape of a protein molecule [6]. These conformational substates appear organised in a hierarchical way and transitions among them, driven by collective, anharmonic motions of the polypeptide chain, seems to be coupled to the biological functionality [4].

In general, the presence of $1/f^{\alpha}$ noise, observed in a wide variety of different phenomena, can be hypothesised to be a sort of signature for complexity in the temporal domain [7–9]. A collection of many different random processes, each one having a single characteristic time with a power law distribution, may give rise to a $1/f^{\alpha}$ trend for the power spectrum [8,9]. Indeed, macromolecular functional collective motions involve the overcoming of different energy barriers which are

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distributed and lead to non-exponential relaxation behaviour [3,10].

Recently, $1/f$ noise has been explained by considering a random walk on a random, self-similar potential surface [11]. Statistical scale-invariant or self-similar random processes ($1/f^{\alpha}$ processes) have been thoroughly studied by Mandelbrot and Van Ness [12] in the framework of fractional Brownian motion (fBm). It can be shown [13] that the exponent α is connected to the self-similarity parameter H (or Hölder parameter) by the following equation:

$$\alpha = 2H + 1. \tag{1}$$

This is a general relationship, independent, under rather mild mathematical conditions [13], of the Gaussianity or non-Gaussianity of process statistics. Moreover, the mean square displacement (MSD) $\langle \Delta x^2 \rangle$ of the position process $x(t)$ is found to be proportional to t^{2H}, where H takes the value of 1/2 for simple Brownian motion; values of $H > 1/2$ ($< 1/2$) corresponding to superdiffusion (subdiffusion) [14,15].

On the other hand, Garcia and coworkers recently studied the trajectory of a protein in the configurational space within the framework of a particle diffusing in real space and getting trapped for a limited period of time in the energy minima. Both a small hydrophobic protein, crambin [16], and cytochrome *c* [17] were investigated and their collective motions, analysed by the essential dynamics (ED) method [5,18,19], show anomalous diffusion, in the sense that the mean square displacement is not proportional to time, as in traditional Brownian motion, but is substantially suppressed with $\langle \Delta x^2 \rangle \sim t^{2H}$, $H < 1/2$.

In the light of these observations and to better understand the physical significance of the $1/f^{\alpha}$ noise observed by some of us in the power spectrum of PC potential energy [1,2], we have carefully investigated the dependence of α in this system on the sampling time and we found that the values obtained are consistent with an fBm ($1 < \alpha < 2$) [13]. We therefore studied the dynamics in the configurational space of the protein by essential dynamics method. We found that the motions appear subdiffusive for times longer than 1 ps. The corresponding H values, independently extracted from the trajectory projected along the essential directions, appear to match relationship (1) reasonably well. These findings point out a possible physical link between a $1/f^{\alpha}$ behaviour of the potential energy and a sublinear diffusion process in the configurational space of the protein.

2. Methods

2.1. MD simulation methods

The simulated MD trajectories of hydrated PC (1PCL entry of the Brookhaven Protein Data Bank [20]) were computed by the GROMOS87 software package [21] with the force field modified according to Mark et al. [22]; hydration water having been modelled by the SPC/E potential [23]. Since the GROMOS force field does not include parameters for amino acids liganded to metal ions, a modified force field has been employed. In particular, a covalent bond between the copper and each ligand has been introduced to preserve the X-ray structure [24].

The protein (99 amino acid residues) was centred in a truncated octahedral obtained from a cube of edge of 6.20257 nm filled with 3514 water molecules and periodic boundary conditions were applied [21]. The energy of the resulting protein water system was minimised by using the steepest descent method. A cutoff radiu of 0.8 nm for non-bonded interactions and of 1.4 nm for the long-range charged interactions was employed.

Simulations were carried out in the canonical ensemble. The temperature (300 K) of the protein and of the solvent was separately coupled to an external temperature bath, with a relaxation time of 0.1 ps. The pressure was kept constant by a coupling to the bath at 1 bar with a relaxation time of 0.5 ps.

The dynamics was followed for 1100 ps. The simulation was performed by first assigning to each atom Maxwellian velocities; a decreasing positional restraining force, derived from a harmonic potential, with a force constant ranging from 9000 to 250 kJ/mol/nm^2, was introduced during the first 100 ps. Configurations of all trajectories and energy were saved every

6 fs. Additionally, another MD simulation was run and only the energy saved every 2 fs.

The kinetic and the potential energy, as well as the root-mean square deviation of the PC backbone and of the gyration radius, were monitored during the simulation time to assess the stability of the simulations and to check that the protein structures have properly equilibrated. On the basis of these results (data not shown), it comes out that, within the first 100 ps, the system has reached the thermal equilibrium. The last 1000 ps of the trajectory (i.e., from 100 to 1100 ps) were used for the ensuing analyses.

2.2. Potential energy fluctuations: $1/f^{\alpha}$ analysis and fractal analysis

The power spectrum $S(f)$ of the simulated potential energy (E_{p}) fluctuations, defined as the Fourier transform of the potential energy autocorrelation function,

$$S(f) = \int_0^{t_{\max}} \langle E_{\mathrm{p}}(0) E_{\mathrm{p}}(t) \rangle \, \mathrm{e}^{2\pi \mathrm{i} f t} \, \mathrm{d}t \tag{2}$$

was estimated by the maximum entropy method [25], in the implementation provided by the *mem_spec* routine included in the TISEAN package [26], by using 16 poles. The value of the α exponent was then extracted by a linear fit on the log–log plot, over a suited frequency interval where the plot is linear [27].

The spectra discussed were typically estimated over 100 ps wide time windows, having verified that our results do not depend on the window size nor on its position along the simulation time span.

For the sake of comparison with results presented in [28], the fractal dimension of curve graphs was determined according to the same computational procedure used therein, that is an implementation in the MATHEMATICA programming language of the method introduced by Dubuc et al. [29].

2.3. ED method

This method was used to separate in an MD trajectory large concerted structural rearrangements, which belongs to the so-called essential subspace, from the small, Gaussian fluctuations [5,18,19]. It is based on the diagonalisation of the covariance matrix C_{ij} built from the atomic fluctuations in an MD trajectory, from which overall translational and rotational motions have been removed:

$$C_{ij} = \langle (x_i - \langle x_i \rangle)(x_j - \langle x_j \rangle) \rangle. \tag{3}$$

Each eigenvalue represents the total mean square fluctuation of the system along the corresponding eigenvector and the method is equivalent to a multi-dimensional linear least squares fit of the trajectory, where the first eigenvector, i.e., that corresponding to the largest eigenvalue, represents the direction that fits best to the ensemble of configurations, the second to the second best, etc.

Here, the protein covariance matrix was constructed from the α-carbons (C_{α}) trajectories, including the copper atoms (300 degrees of freedom in total). Indeed it has been shown that the C_{α} atoms contain all the information for a reasonable description of the protein large concerted motions [18].

The analysis of the MD trajectory in configurational space was carried out using the WHAT–IF modelling package [30] and the essential dynamics routines supplied therein.

For each essential direction k, the MSD $\langle \Delta r_k^2(t) \rangle$, $0\,\mathrm{ps} < t < 500\,\mathrm{ps}$, was computed by projecting the MD trajectory on the corresponding kth eigenvector and then averaging the squared displacements along it $[r_k(t_0 + t) - r_k(t_0)]^2$ over all the time origins t_0 in the interval between 100 and 600 ps.

3. Results and discussion

3.1. Potential energy fluctuations

The temporal evolution of the total potential energy, E_{p} (including bond stretching and angle bending, dihedral angle bending and torsion, Lennard–Jones and Coulomb interactions) of the PC macromolecule is shown in Fig. 1 for the time interval 100–200 ps (the same behaviour could be observed in every 100 ps wide segment extracted from the total simulation length). The curve is characterised by fast fluctuations over a wide range of time scales; the distribution of the potential energy around its average value

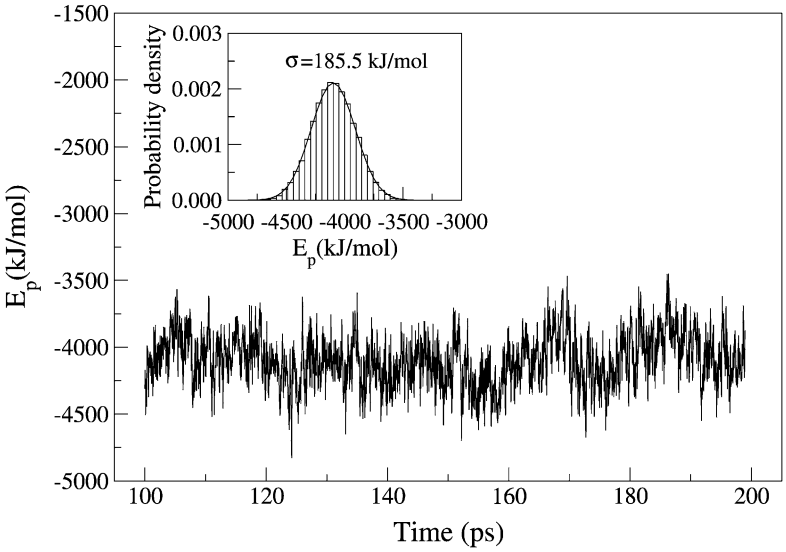

Fig. 1. Temporal evolution of the total potential energy for the time interval 100–200 ps. Inset: probability distribution of the total potential energy around its average value and the best fit by a Gaussian function. (data skewness = 0.0102, kurtosis = −0.0445, consistent with a Gaussian distribution).

has a standard deviation of 185.5 kJ/mol and can be very satisfactorily described by a Gaussian (inset in Fig. 1): according to the central limit theorem, this is consistent with a noise arising from a superposition of many independent sources.

In Fig. 2, we show the log–log plots of the power spectrum of the total potential energy for five different sampling times, from 48 to 2 fs.

In general, for lower frequencies, below 10^{11}–10^{12} Hz, the spectra are of a white-noise type: this means

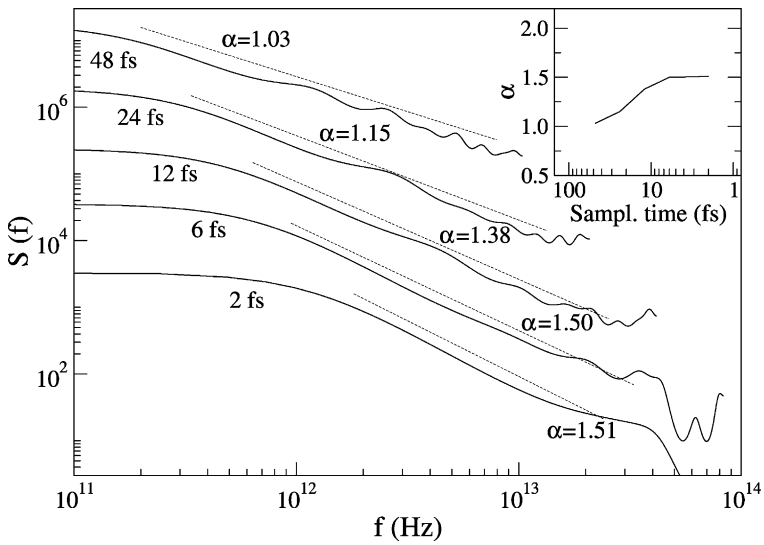

Fig. 2. Power spectra of total potential energy fluctuations, for the time interval 100–200 ps and five different values of the sampling time: 2, 6, 12, 24 and 48 fs. The plots are vertically shifted for clarity. The dashed lines show a $1/f^{\alpha}$ function with the indicated α exponent, determined by best fit over the linear spectral interval. Inset: trend of α values as function of sampling time.

that one must continue simulations at least 1–10 ps to obtain a stationary state. This behaviour was already observed, among others, by Takano et al. [31] in polypeptides. Then, after a linear tract, where an $1/f^{\alpha}$ trend over two decades can be clearly recognised, the highest frequencies show an oscillating behaviour, with a possible drop for the smallest sampling times (i.e., 6 and 2 fs), starting from about 5×10^{13} Hz. The amplitude of the oscillations themselves decreases sharply when the sampling time decreases. This behaviour is consistent with a small ratio between data numerosity and number of poles: indeed, when more data points are considered (i.e., 6 and 2 fs plots) the amplitude of the oscillations becomes much smaller. When using maximum entropy methods, a careful choice of the number of poles is needed [25] and in this respect we have chosen a value (16) better tuned for the finest steps.

Interestingly, the $1/f^{\alpha}$ trend is characterised by a slope which depends on the sampling time. Quantitatively, when the latter is decreased from 48 to 6 fs, the α exponent estimated in the linear spectral range (e.g., 10^{12} Hz $< f < 3 \times 10^{13}$ Hz for the 6 fs plot) varies from 1.03 to 1.50. On the other hand, the plot corresponding to a 2 fs sampling time clearly shows that further reducing the sampling time below 6 fs does not add any additional information, the estimated value of α being experimentally indistinguishable (inset in Fig. 2). This behaviour could be explained considering aliasing effects [32] which are particularly relevant when sampling wide band signals: using a sampling time moderately (i.e., about 10^1–10^3 times) larger than the threshold value dictated by the Nyquist criterion leads to artificially enhanced power spectra tails and therefore to lower estimated slopes. Indeed, according to that criterion, if B is the bandwidth, the sampling time must be kept smaller than $1/2B$. Needless to say, when dealing with real signals it is often difficult to measure a bandwidth value, which would be very useful to optimise the sampling time. Considering again Fig. 2, however, it is quite clear that the potential energy spectra estimated from the trajectory sampled every 6 fs and every 2 fs sharply drop at frequencies higher than about 5×10^{13} Hz: this value may be considered for all purposes the effective bandwidth B. Indeed, for a B equal to 5×10^{13} Hz the Nyquist criterion dictates a sampling time smaller than 10 fs.

At this stage of the research, the drop itself is not easy to explain, but, interestingly, an even sharper one, located at the very same frequencies, was noticed by Ohmine [33] in simulated potential energy fluctuations of bulk water, modelled by TIPS2 [34], who attributed it to the missing modelling of water intramolecular vibrations; the same explanation could be invoked for our case, since SPC/E too is an internally rigid water model. Also on the basis of results discussed in [35,36] interesting relationships could be speculated between hydrated protein behaviour and free water behaviour at those energies: a further investigation of this aspect is required.

The foregoing considerations on the most suited sampling time suggest that a particular care should be exercised when comparing actual values of the α exponent scattered in the literature, since different choices for the sampling time may lead to appreciably different results. For instance, the potential energy fluctuations discussed in Refs. [1,2], if analysed today using a finer sampling time would most probably show higher values, closer to 1.5 than to 1.0, in the whole range of temperatures therein investigated.

A value of $\alpha = 1.50$, joined with the additional evidence provided by the Gaussianity of the probability distribution, is a strong indication that potential energy fluctuations are well modelled as an fBm [12]. As already mentioned in Section 1, the spectral coefficient α may be also put geometrically into relationship to the corresponding Hölder coefficient H, via the formula (1). Actually, if we introduce the estimated value of α in Eq. (1) a value of 0.25 is obtained for H, consistent with a sublinear diffusive exploration of the potential energy landscape.

At this stage, and independently from the $1/f^{\alpha}$ analysis of potential energy fluctuations, it would be interesting to calculate the Hölder parameter from the MD trajectories projected in the essential space, and then to compare it with the H value above calculated from the α value via Eq. (1).

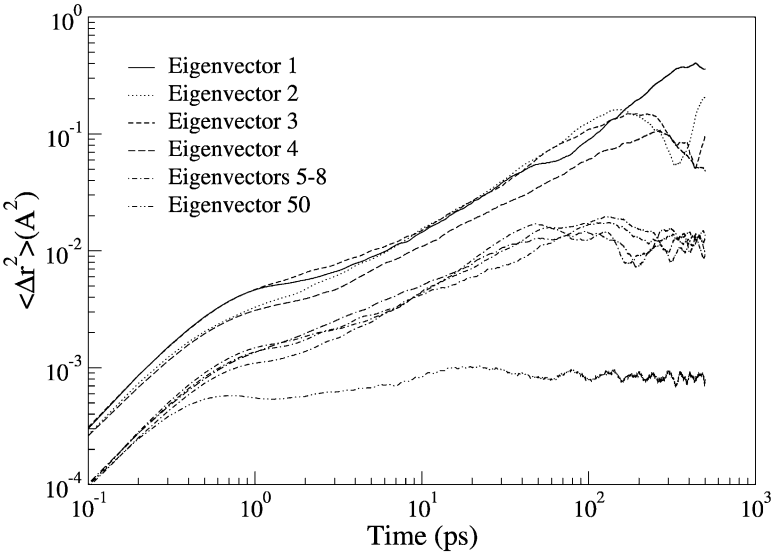

Fig. 3. Mean square displacement vs. time lag along each of the first eight eigenvectors ($1 \leq k \leq 8$) and the 50th one (5th–8th and 50th vertically shifted for clarity).

3.2. ED analysis

In Ref. [37], we showed that PC is characterised by a low-dimensional essential space, which is apt to explain most of the dynamical behaviour underlying its electron transfer functions. Quantitatively, from four to eight dimensions can be selected, depending on the specific criterion adopted [37,38]. In fact, the latter are somewhat sensitive to the threshold value set for the so-called correlation coefficient, which quantifies the anharmonicity and deviation from Gaussianity of the motion.

In this connection, Fig. 3 shows log–log plots of the mean square displacements $\langle \Delta r_k^2(t) \rangle$ vs. time lag t along each of the first eight ED eigenvectors, together with the 50th one, as representative of the dynamics along the higher order ED directions.

At very short times (< 1 ps) the behaviour along the different eigenvectors is indistinguishable and a ballistic region ($\langle \Delta r^2 \rangle \sim t^2$) may be evidenced. This kind of dynamical evolution is indeed reasonable and is shown, e.g., by diffusing water molecules belonging to the hydration layers of proteins [35,36].

For intermediate times the MSD along the first eigenvectors shows a power law trend, $\langle \Delta r^2 \rangle \sim t^{2H}$, with exponent $2H$ smaller than one. In Table 1, we report in detail the best fit values of the exponent evaluated over the linear tract of the log–log plots. The diffusive motion of the system covers less volume in the configurational space than a Brownian motion, indicating a suppression of diffusion: the macromolecule may undergo some sort of entanglement within the local minima of the rugged potential energy hypersurface. Garcia et al. [16] observed in

Table 1
Slope $2H$ extracted by a best linear fit of the log–log mean square displacement on the time span 5–100 ps for eigenvectors 1–4, 5–50 ps for eigenvectors 5–8

Eigenvector	$2H$
1	0.85
2	0.93
3	0.89
4	0.70
5	0.58
6	0.56
7	0.85
8	0.77

crambin and in cytochrome *c* [17] a similar behaviour as far as eigenvectors 1–3 and 1–2, respectively, were concerned, with a value of the Hölder exponent of 0.50. In our case, dealing with the whole set of eigenvectors distinctively belonging to the essential space, a moderate spread is present, around an average of about 0.76 for H.

Along the higher order harmonic directions, not belonging to the essential space, a plateau is rapidly reached—as shown in Fig. 3 by the plot corresponding to eigenvector 50—but this happens also for the first directions, with much longer characteristic times, however. The diffusive regime lasts about 400 ps for eigenvector 1, about 200 ps for eigenvectors 2–4, and about 80 ps for eigenvectors 5–8. Other proteins are known to be characterised by an especially long lasting diffusive dynamics along the first direction, which may even go ballistic sometimes [18,19,39]; in our case, however, we do not see unequivocal signs of this regime. In order to better investigate this issue, we have extended our analysis for the MSD up to 750 ps, by averaging over only 250 ps worth of different time origins t_0, at the cost of an increased noise (data not shown), with results further excluding the presence of a new ballistic regime. Returning to the plateau, it may be partially explained considering the finite size of the system that restricts $\langle \Delta r^2(t) \rangle$ to be finite [16], but further investigations are required in order to better understand our finding that different eigenvectors show different onset times.

In conclusion, the H values presented in Table 1 clearly show that, after an initial ballistic-type regime, the configurational space is explored subdiffusively along the essential directions for a long stretch of time, in complete analogy with the simultaneous exploration of the potential energy landscape. Even a good quantitative agreement could be found for the nature of those diffusion processes, with $H = 0.25$ for potential energy fluctuations and slightly larger values for diffusion along the essential degrees of freedom, which fall in the range between 0.25 and 0.45. Actually, the approach followed in the present study is supported and motivated by having shown sublinear diffusion of protein hydration water [35,36] and, as discussed in Refs. [1,2], the occurrence of $1/f^{\alpha}$ noise both in the macromolecule and the surrounding solvent, with the same value for the exponent, such a result suggesting a strong interplay in the temporal features of the protein and the hydration water.

3.3. Fractal analysis of potential energy fluctuations

It has been suggested [35,36,40] that the spatial disorder connected to the roughness of the protein surface could be in some way responsible for the anomalous diffusion of PC hydration water and a specific form of the propagator, holding for particles diffusing on a fractal surface, was adopted in the theoretical analyses.

Recently, fractality has been put into relationship to diffusion in the potential energy landscape by Lidar et al. [28], who studied the fractal dimension γ [13] of the $E_{\mathrm{p}}(t)$ curve graph and argued for a sort of universality of that parameter, depending only weakly on the type of molecular system. This, a priori unrelated, geometric approach in the study of the temporal fluctuations, interestingly turns out to be related to ours since, on the basis of general properties of fBm models, a power law $1/f^{\alpha}$ spectrum for large f implies a specific form of the short time autocorrelation function, that is, one proportional to $t^{\alpha-1}$. This functional form can be compared with that coming from a geometric study of the fractal structure, which may be proved to be $t^{4-2\gamma}$ [13]. Therefore, the following equation holds between the spectral exponent α and the fractal dimension γ of the graph of a typical realisation:

$$\gamma = \tfrac{1}{2}(5 - \alpha). \tag{4}$$

In this connection, it would be interesting to compare the γ value extracted from Eq. (4) by inserting in it the α value calculated for our system, with that independently computed with the ϵ-variation technique used by Lidar et al. [28]. Actually, these values turned out to be very close, 1.75 and 1.80, respectively. This good agreement is even more significant considering that, when dealing with limited size data sets, the latter estimate is indeed expected [29] to be slightly larger than the former.

It may be also remarked that the fractal dimension is a parameter very weakly sensitive to the sampling time used: increasing it from 6 to 48 fs leads to an experimentally indistinguishable $\gamma = 1.78$. This can be intuitively justified as follows. Using a large sampling time has the effect of excluding from the analysis the smallest scales: this implies that the estimated fractal dimension may not be appreciably affected provided the same kind of fractal structure is found in the scales still present. More technically, this happens when the ϵ-variation plot is straight over a sufficiently wide range of values of ϵ: the estimated slope (i.e., γ) does not change much if the data points corresponding to the smallest values of ϵ (i.e., the smallest scales) are discarded.

4. Conclusions

In this work, we have studied the temporal fluctuations in the potential energy of PC using the methods of MD simulation. Those are characterised by Gaussian statistics and, when analysed with a sufficiently small sampling time, reveal a power spectrum of the $1/f^{\alpha}$ type, with $1 < \alpha < 2$, thus providing an example of a physical process well modelled as a subdiffusive fBm. The occurrence of such a subdiffusive process is confirmed when the exploration of the configurational space is independently analysed by ED methods. Actually, an Hölder exponent smaller than 1/2 is obtained and it is shown that this H agrees reasonably well with the α value extracted from the power spectrum of the potential energy. It has been also demonstrated that the α exponent is linked to the fractal dimension γ which can be extracted from the potential energy graph. We may therefore suggest that the presence of $1/f^{\alpha}$ noise and of a subdiffusive process could be intimately connected and moreover related to the self-similar properties of the biological systems under study.

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