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Backbone fractal dimension and fractal hybrid orbital of protein structure

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ABSTRACT

Fractal geometry analysis provides a useful and desirable tool to characterize the configuration and structure of proteins. In this paper we examined the fractal properties of 750 folded proteins from four different structural classes, namely (1) the α-class (dominated by α-helices), (2) the β-class (dominated by β-pleated sheets), (3) the (α/β)-class (α-helices and β-sheets alternately mixed) and (4) the ($\alpha+\beta$)-class (α-helices and β-sheets largely segregated) by using two fractal dimension methods, i.e. "the local fractal dimension" and "the backbone fractal dimension" (a new and useful quantitative parameter). The results showed that the protein molecules exhibit a fractal behavior in the range of $1 \leqslant N \leqslant 15$ (N is the number of the interval between two adjacent amino acid residues), and the value of backbone fractal dimension is distinctly greater than that of local fractal dimension for the same protein. The average value of two fractal dimensions decreased in order of $\alpha > \alpha/\beta > \alpha+\beta > \beta$. Moreover, the mathematical formula for the hybrid orbital model of protein based on the concept of backbone fractal dimension is in good coincidence with that of the similarity dimension. So it is a very accurate and simple method to analyze the hybrid orbital model of protein by using the backbone fractal dimension.

1. Introduction

Like other biological macromolecules such as polysaccharides and nucleic acids, proteins are essential parts of organisms and participate in virtually every process within cells. Almost all vital activities and phenomena of life can be presented by proteins, so that the researches on protein structure and function are extremely important [1,2].

Fractal theory is a very active mathematic branch of modern nonlinear science, which has been used widely to describe irregular and non-differentiable geometric shapes existing in both natural world and man-made substance. Since the term fractal was coined by Mandelbrot in 1977, the theory and application of fractal has been permeated through every field of natural science [3]. A fractal is usually "a rough or fragmented geometric shape that can be split into parts, each of which is (at least approximately) a reduced-size copy of the whole," which is also called self-similarity. To a fractal object, we can adopt a non-integer parameter, i.e. fractal dimension, to quantificationally describe the complexity and irregularity of structure in some way [4].

Usually, it is popularly believed that the spatial structures of proteins are complicated and changeable, and there are a lot of surface corrugation and roughness in the protein, even with tiny holes through the body, so it is unrealistic to expect that constructs that are otherwise adequate to describe the complexity of simple structures (spheres, cubes, other regular structures of idealistic shape and characteristics) will be facilitate attempts to describe proteins, that is, protein molecule cannot

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be simply described in terms of the Euclidean geometry. Actually, proteins have been described as 'complex mesoscopic systems' and characterized by various aspects of symmetry of self-similarity prevalent in the protein interior [5], which indicated that proteins have fractal characters. More importantly, the fractal geometry theory, which is a new mathematical tool for dealing with an irregular pattern, is desirable for the analysis of protein conformational nature [6]. So we can use fractal method to characterize complexly spatial and dynamical structures of proteins.

The researches of protein structure based on the concept of fractal analysis have been found in a number of literatures during the past decades. For example, the fractal dimension of 200 folded proteins taken from the Protein Data Bank (PDB) are evaluated by computer simulation [7] based on the notion of mass fractal dimension. It is found that the average fractal dimension of this set is equal to 2.5 and the fractal dimension ranges from 2.3 for smaller proteins with about 100 amino acids to 2.6 for sufficiently large proteins with more than about 1000 amino acids. Moreover, Matthew et al. investigated the influence of buried and hydration water molecules on the mass fractal dimension and found that including the water molecules in the calculation of mass fractal dimension could slightly increase the corresponding value [8]. In recent years, the mass fractal dimension of biomacromolecules such as protein and ribosome were also investigated and the results indicated that mass fractal dimension could give a measure of the macromolecular compactness [9,10].

In addition, the spatial structure and the fractal dimension of protein in buffer solutions can be examined by small-angle neutron scattering [11,12]. It is worth noting that loosening of the protein structure under denaturing conditions is followed by the reduction of the fractal dimension, as was demonstrated, particularly, for bovine serum albumin (the fractal dimension decreased from 2.30 to 1.76 [11]) and lysozyme (the fractal dimension decreased from 2.80 to 2.50 [12]).

Furthermore, the statistical self-similarity of protein was revealed in many research aspects such as fractal analysis of tertiary structure for protein with different structural classes [13,14], cluster fractal dimension of aggregating proteins [15], the relationship between fractal characteristic of protein backbone and hydrogen bridges [16], the multifractal properties of potential energy hypersurface of proteins [17], mass-size relation of proteins [18], the accessible surface area as function of the number of amino acids and as the function of gyration radius [19,20], residue network in protein native structure [21], the fractal analysis of serine proteinase [22] and so on. In this sense, the fractal dimension analysis may elucidate the intrinsic structural characteristics and dynamical behavior of protein molecules.

In this article we propose a novel parameter i.e. "backbone fractal dimension" to characterize the spatial feature of protein and use two fractal dimension methods, "the local fractal dimension" and "the backbone fractal dimension", to calculate the corresponding value for each protein in a set of 750 proteins selected from the Protein Data Bank (PDB) [23]. In addition, we also apply the backbone fractal dimension to the investigation of hybrid orbital model of protein because the structure and shape of protein polypeptide chains are goverened by the hybridized state of atomic orbital. The fractal theory can provide much useful insight into the structure and conformation of protein molecules.

2. Method

2.1. Local fractal dimension

Usually, the mean-square end-to-end and the mean gyration radius of a polymer chain are usefully mathematical measures in characterizing a statistical ensemble of polymer chain. But they are not well enough to describe the configurational shape and structure of a single regular polymer chain. By reason of these deficiencies, Havlin and Ben-Avraham have proposed "the local fractal dimension" based on the theory of self-avoiding walk model (SAW) and the fractal dimension concept, which has an advantage in characterizing the protein molecular chain [24–27]. In the following way the definition of the local fractal dimension has been presented. Firstly, the mean square length of end points of a segment with N monomers in a protein chain with N_0 elements ($\langle R_N^2\rangle_{N_0}$) is given as:

$$\langle R_N^2\rangle_{N_0} = \frac{1}{N_0 - N + 1}\sum_{i=1}^{N_0-N+1}\left\langle R_{i,i+N}^2\right\rangle_{N_0} \tag{1}$$

where $\langle R_{i,i+N}^2\rangle_{N_0}$ is the square distance of two elements separated by N steps in the ith and the $(i+N)$th sites of a chain.

Secondly, the methodology and definition of local fractal dimension $D_{N_0}(N)$ is defined as:

$$D_{N_0}(N) = \log\left(\frac{N+1}{N}\right)\Big/\log\left(\frac{\langle R_{N+1}^2\rangle_{N_0}}{\langle R_N^2\rangle_{N_0}}\right)^{1/2} \tag{2}$$

where it should be noted that the subscript N_0 stresses the fact that the polymer chain in the above mentioned is a finite polymer molecule.

Finally and importantly, it is worth noting that if "$D_{N_0}(N) = D_L$" tends to be a constant and is independent of N, then the local fractal dimension can be written as follows:

$$\left[\left(\left\langle R_N^2\right\rangle_{N_0}\right)^{1/2}\right]^{D_L} = AN \tag{3}$$

where A is a constant of proportionality. So in practice we can use Eq. (3) to calculate the local fractal dimension of protein molecule chain from the slope of "log$N$–log $\left(\left\langle R_N^2\right\rangle_{N_0}\right)^{1/2}$" diagram. Indeed the local fractal dimension is a measure of winding property for the polymer chain in a certain scale N [24–27].

2.2. Backbone fractal dimension

Besides the above local fractal dimension D_L, we can use another fractal dimension, "the backbone fractal dimension D_B", to describe the structure and dynamics of a protein in the framework of fractal theory. It is generally accepted that the two fractal dimensions (D_L and D_B) and the Euclidean dimension are identical for the ideal rigorously self-similar polymer chain, but they are different for the real protein molecular chain. So it is necessary to use D_L or D_B to characterize a protein chain. In the following paragraph we will delineate the calculation method of the backbone fractal dimension.

For simplicity, a protein molecular chain is usually considered as a space curve in three-dimensional Euclidean space, namely a folded massless and linear chain without side groups. By the same token, it can be also treated as a planar curve in two-dimensional Euclidean space [28]. Based on the fractal theory and previous studies [28], the backbone fractal dimension of a planar curve, may be expressed in a general form as:

$$(length)^{\frac{1}{D_B}} = K(area)^{\frac{1}{2}} \tag{4}$$

where '*length*' represents the total length of planar curve; '*area*' means the maximum potential area of space which the planar curve occupies; D_B is known as the backbone fractal dimension, and K is a constant. It is worth to note that the results can be extended to three-dimensional Euclidean space based on the concept of fractal geometry. Moreover, a protein molecule can be regarded as a globular object for the most part, so we can obtain the fractal dimension of protein chain in three dimensional Euclidean space from the relationship as following:

$$L^{\frac{1}{D_B}} \propto K\left(\pi D^2\right)^{\frac{1}{2}} \propto K\sqrt{\pi}D \tag{5}$$

where L is the chain length of a protein molecule; D is the diameter of a protein molecule (in this paper the diameter is approximately equal to the mean end-to-end length between two atoms). And then, we obtain:

$$L^{\frac{1}{D_B}} \propto CD \tag{6}$$

where $C = K\sqrt{\pi}$, is also a constant. Thus the backbone fractal dimension can be deduced from the slope of log$L$–log$D$ plot.

In addition, based on the principle of local fractal dimension illustrated by Havlin and Ben-Avraham [24,27] we can calculate L and D of the protein molecule according to the following relations:

$$(L_N)_M = \frac{1}{M-N}\sum_{i=1}^{M-N}(L_{i,i+N})_M \quad (N = 1, 2, \ldots, N_0) \tag{7}$$

$$(D_N)_M = \frac{1}{M-N}\sum_{i=1}^{M-N}(D_{i,i+N})_M \quad (N = 1, 2, \ldots, N_0) \tag{8}$$

where M in these equations corresponds to the total number of amino acid residues of a protein molecule; N_0 is the amount of the intervals between two adjacent amino acid residues, that is, $M = N_0 + 1$; $(L_N)_M$ is the mean length of peptide segment containing N residues in a peptide chain consisting of M residues; $(D_N)_M$ is the mean end-to-end distance of a peptide chain with $(L_N)_M$ mean length; $(L_{i,i+N})_M$ is the length of C^{α}-atom chain between the ith and the $(i+N)$th amino acids in a peptide chain with M residues; and $(D_{i,i+N})_M$ is the C^{α}-atom distance between the ith and the $(i+N)$th amino acids with $(L_{i,i+N})_M$ peptide chain length. Therefore, the backbone fractal dimension is determined from the slope of a log–log plot of $(L_N)_M$ versus $(D_N)_M$.

2.3. Fractal hybrid orbital model

In general, organic compound is constituted of the carbon hybrid orbitals. As a matter of fact, the protein is also a kind of organic compound, thus its structure and shape can be determined by the hybridized states of atomic orbitals in a biopolymer chain [29]. Usually the polypeptide chains exhibit a sawtooth-like shape, that closely resemble the Koch curve [3]. So the conformation and structure of proteins are associated with the bond angle of atomic orbitals as shown in Fig. 1.

Moreover, the protein chain can be regard as a series of such space molecular model or generators being connected to each other [30]. According to the previous research [30], it is found that the C^{α}-atom distance between two adjacent amino acid residues is approximately 0.38 nm. Thus we can safely supposed that the length of AO is equal to that of BO, namely $AO = BO$. Furthermore, assuming $\angle AOB = \theta$ ($0^\circ < \theta^\circ < 180^\circ$), then the distance between AB is only dependent on the degree of angle. So we can calculate the backbone fractal dimension of such molecule model according to its definition:

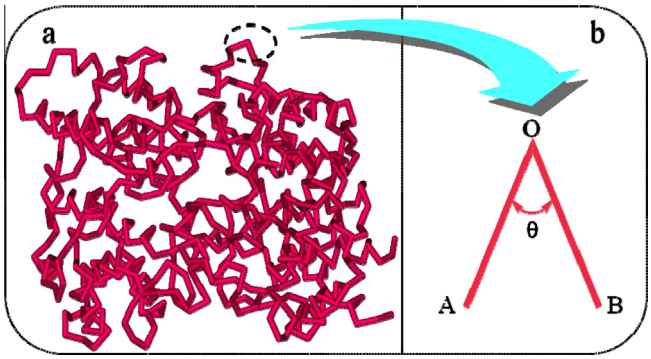

Fig. 1. A simple schematic representation of amino acid chain (a) and the bond angle in a dipeptide chain (b). In this protein model the amino acid is denoted by the C^{α}-atom of amino acid residue. The red thick line represent the length between two adjacent amino acid residues. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

$$D_B = \frac{\log(\|AO\| + \|BO\|)}{\log(\|AB\|)} = \frac{\log 2}{\log\sqrt{2(1-\cos\theta)}} \tag{9}$$

Here it should be pointed out that the mathematical formula of the fractal dimension deduced in this paper is very same as the calculation introduced by Torrens based on the similarity dimension [31,32]. Based on the theories of quantum chemistry, namely the orthogonality of hybrid molecular orbital, the bond angle θ_{ij} between ψ_i and ψ_j orbitals for a given polymer chain is expressed as following [29]:

$$\cos\theta_{ij} = -\sqrt{\frac{s_i s_j}{(1-s_i)(1-s_j)}} \tag{10}$$

where s_i and s_j represent the ratio of containing s orbital inside the sp^n hybrid orbitals ψ_i and ψ_j, respectively.

Therefore:

$$D_B = \frac{2\log 2}{\log\left[2\left(1+\sqrt{\frac{s_i s_j}{(1-s_i)(1-s_j)}}\right)\right]} \tag{11}$$

For the equivalent hybrid orbital, $s_i = s_j = s$, then

$$\cos\theta = -\frac{s}{1-s} \tag{12}$$

and

$$D_B = \frac{2\log 2}{\log\left[2\left(1+\frac{s}{1-s}\right)\right]} \tag{13}$$

Obviously, Equation (13) can be conveniently applied to the explanation of very close relationship between the fractal dimension and the hybrid orbital state of a protein molecule to some extent. The D_B values are 1.000, 1.262 and 1.413, respectively, for the $sp(n=1)$, $sp^2(n=2)$ and $sp^3(n=3)$ ideal hybrid chains, whereas $D_B = 2.000$ for the $p(n=\infty)$ orbital bonding chain [32].

In this paper we are mainly interested in investigating the self-similarity of 750 different protein molecules. These proteins are selected from the Protein Data Bank [23] with X-ray diffraction as the structure elucidation method. We have filtered out proteins exceeding 30% sequence identity and proteins that have ligands, RNA, or DNA. We have also dismissed incomplete data sets that contained only the data of α-carbons. Moreover we have also removed the proteins whose sequence length are less than 250 amino acids, because those are too short to be considered as fractals. The class was determined according to the SCOP database [33].

2.4. Statistical analysis

The least-squares method is used to fit functions through a regression analysis. Statistical analyses are performed with SPSS (version 15.0, SPSS Inc., Chicago, IL, USA). Analyses of variance (ANOVA) and Tukey's HSD test with a significance level of 0.05 are applied.

3. Results and discussion

3.1. Fractal dimension for protein molecules

As shown in Fig. 2, the power law property of protein is presented as the double logarithmical plot for two kind of fractal dimensions: the local fractal dimension (Fig. 2A) and the backbone fractal dimension (Fig. 2B). The illustrated calculation is performed by using a membrane protein squalene–hopene cyclase [PDB ID: 2SQC, 631 amino acids (a.a.)] as an example. From the fractal diagram, we can find that there exists a range where the curve has a good linearity in general. With regard to the calculation range for the fractal dimension, it is a question that needs careful consideration in practice. Actually, in this work we compute the fractal dimensions of proteins based on the following aspect. To avoid possible finite-size effects when computing the fractal dimensions, we must consider the computation interval of the length scale. Namely, owing to the finite-size effect, there are both upper and lower size limits, beyond which a protein is no longer fractal or the value of fractal dimensions change markedly [24]. Moreover, it is interesting to note that an inflexion point around $N = 15$ (N is the number of the interval between two adjacent amino acid residues) is observed in Fig. 2, and the linearity is poor for high N values and the curve is tortuous. Similar characters are also found for the other proteins studied in this paper. Overall, this range strikes a balance between having enough points to meaningfully compute the fractal dimensions and keeping the fractal dimension essentially constant, namely, over a range where the fractal dimension does not change much with small changes in the number of points used in the calculation. Therefore, the fractal dimensions are calculated only in the range of $1 \leqslant N \leqslant 15$, and the slope of the curve is the fractal dimension [34,35]. This means that a protein can be regarded as a fractal object only

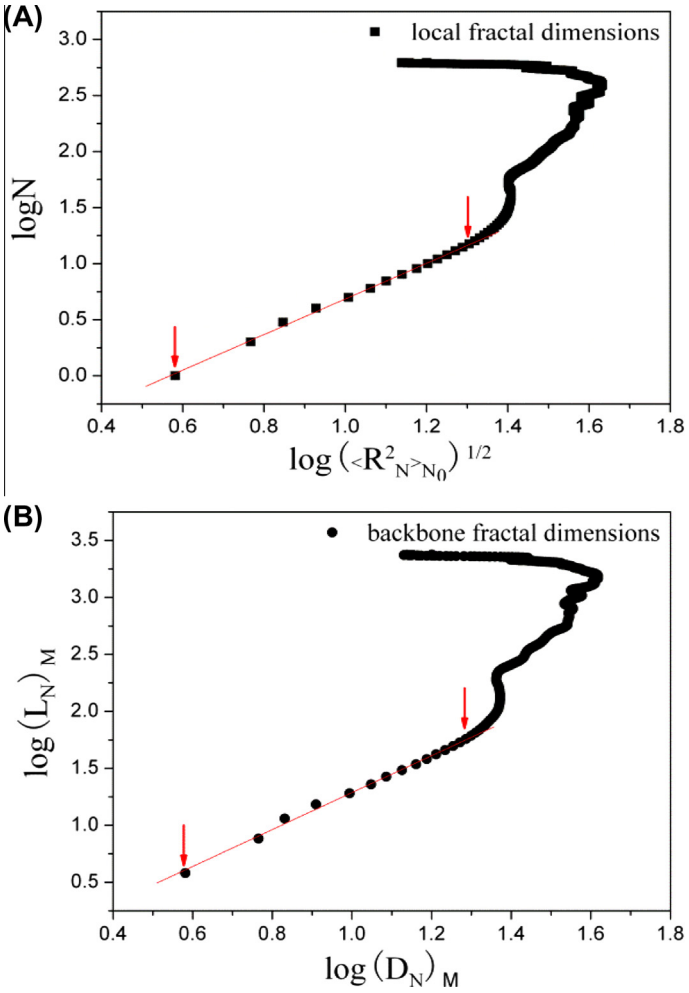

Fig. 2. The log–log plot of N versus $(\langle R_N^2 \rangle_{N_0})^{1/2}$ for determining the local fractal dimension (a) and the log–log plot of $(L_N)_M$ versus $(D_N)_M$ for determining the backbone fractal dimension (b) of protein. N is the number of the interval between two adjacent amino acid residues. The red solid lines indicate best fits in the range of $1 \leqslant N \leqslant 15$ (indicated by the arrow) for the fractal dimension calculation by using least-square linear fitting method. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in a definite range of N value and a protein seems to have the fractal behavior within some certain ranges. Similar characters are also found for the other proteins studied in this paper. It is evident that the values of fractal dimensions depend on the range of N to a great extent.

As shown in Fig. 3, the local fractal dimension and the backbone fractal dimension are computed for each protein with different size, namely the number of amino acid of each protein, $(N+1)$. It can be seen that the values of two kinds of fractal dimensions are distributed mainly in the range from 1.30 to 1.80, and for the most proteins the fractal dimension values are ranged from 1.50 to 1.60. This phenomenon is very accordance with the previous studies. For example, Tejera et al. investigated the local fractal dimension of a set of 870 proteins, and found that the value represented as global median (the 25–75th quartile intervals) was 1.54 (1.50–1.58) via the computational study [35].

According to the investigation of self-avoiding walk (SAW) model [24], if the conformation of a protein chain obeys the rules of SAW, then the fractal dimension of protein molecule can be calculated as $D_f = (d + 2)/3$, where d is referred to the Euclidean dimension. Thus when $d = 2$, then $D_f \approx 1.333$, and when $d = 3$, then $D_f \approx 1.667$. Moreover, Li et al. deemed that protein molecules have two kinds of chain conformation, namely a planar type in two-dimensional space and a curve-balling type in three-dimensional space [28]. It is important to note that the fractal behaviors of proteins in three-dimensional Euclidean space basically conform to the rules of SAW. On the other hand, protein molecules have not only the above two chain conformations but also another kind of chain conformation between them, namely a mixture type, which might have a large proportion in the natural proteins.

It can be also found from Fig. 3 that the values of local fractal dimension are basically less than those of backbone fractal dimension. This may be caused by the degree of complexity between the local and global structure of protein. That means the local fractal dimension is computed according to the local scale of length (just considering the end-to-end distance); while the calculation of backbone fractal dimension is based on the global chain structure (considering not only the end-to-end distance, but also the length of peptide chain). In other words, for a real peptide chain, it can be regarded as a straight line in terms of local fractal dimension (just like β-sheet in shape), whereas from backbone fractal dimension point of view it can be regarded as a zigzag line (resembling α-helix or turn in shape). Moreover, in a globular protein, the fractal dimension values for α-helix, reverse turn, parallel β-sheet, anti-parallel β-sheet, and twisted β-sheet are 1.44, 1.59, 1.09, 1.06, and 1.07, respectively [36]. Hence the influence of α-helix and turn on the fractal dimension is positive and relatively strong. So D_B is usually bigger than D_L. Meanwhile, there is a strong dependence between two fractal dimensions with the correlation coefficient $R = 0.95309$.

The mean local fractal dimension and the mean backbone fractal dimension of four structural classes and all proteins are listed in Table 1. It is found that there are significant differences among four different structural classes for local fractal dimension or backbone fractal dimension, except for the backbone fractal dimension of α-class and (α/β)-class

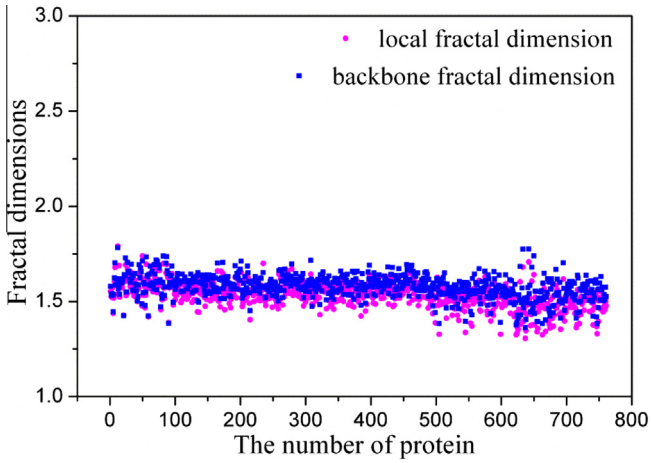

Fig. 3. The scatter diagram of fractal dimensions of proteins.

Table 1
The average value of local fractal dimension and backbone fractal dimension for four structural classes and 750 proteins. The standard deviation of the corresponding number of the estimation is in the parentheses.

	α	β	$\alpha + \beta$	α/β	750 protein
D_L	1.59(0.04)	1.47(0.05)	1.51(0.03)	1.55(0.03)	1.53(0.03)
D_B	1.61(0.04)*	1.53(0.06)	1.56(0.03)	1.59(0.03)*	1.57(0.04)

Mean values with symbol (*) are statistically similar ($p > 0.05$). (ANOVA and Tukey's HSD test).

($p > 0.05$).It can be seen that the order of mean values of two fractal dimensions for four structural classes is $\alpha > \alpha/\beta > \alpha + \beta > \beta$, which is good agreement with the data reported by Li et al. [34]. This is because the fractal dimension describes the irregularity of the object, and four structural classes of protein are recognized based on the predominant types and arrangements of secondary structure elements, namely α-helix and β-sheet. The α class is comprised entirely of α-helices and the β class contains only β-sheets. The α/β protein consists of α-helices and β-strands that are alternately mixed, and the $\alpha + \beta$ protein consists of the conformation in which α-helices and β-strands are largely separated [37,38]. Thus the local structure of β class is extended more than that of α class, and those of α/β and $\alpha + \beta$ classes are between that of α and β class [34], i.e. the α and β class show the largest and the smallest fractal dimension values, respectively. This suggests the values of local fractal dimension and backbone fractal dimension for four structural classes are probably determined by their secondary structures. This suggests that the fractal dimension is an important and meaningful parameter to describe the spatial structure and to predict the structural features of proteins.

3.2. Fractal hybrid orbital model

The relationships of "D_B (the backbone fractal dimension) – s ratio" and "D_B-n index" are plotted in Fig. 4. It can be seen that s ratio and n index of different classes of proteins are distributed in the same areas of diagram and it is very hard to distinguish one class proteins from the others. Moreover, it is found that there exist no obvious correlations between "the molecular mass or the molecular chain length" and "the fractal dimension, s ratio or n index" (see Supplementary Material Fig. S1).

The mean values of s ratio and n index for four structural classes and for 750 proteins are presented in Table 2. We can find that there are very marked differences between distinct classes of proteins. The calculated mean ratio of containing s orbital in the sp^n hybrid orbitals for α class proteins is the smallest, which shows $sp^{5.364}$ like type hybrid orbitals, far away

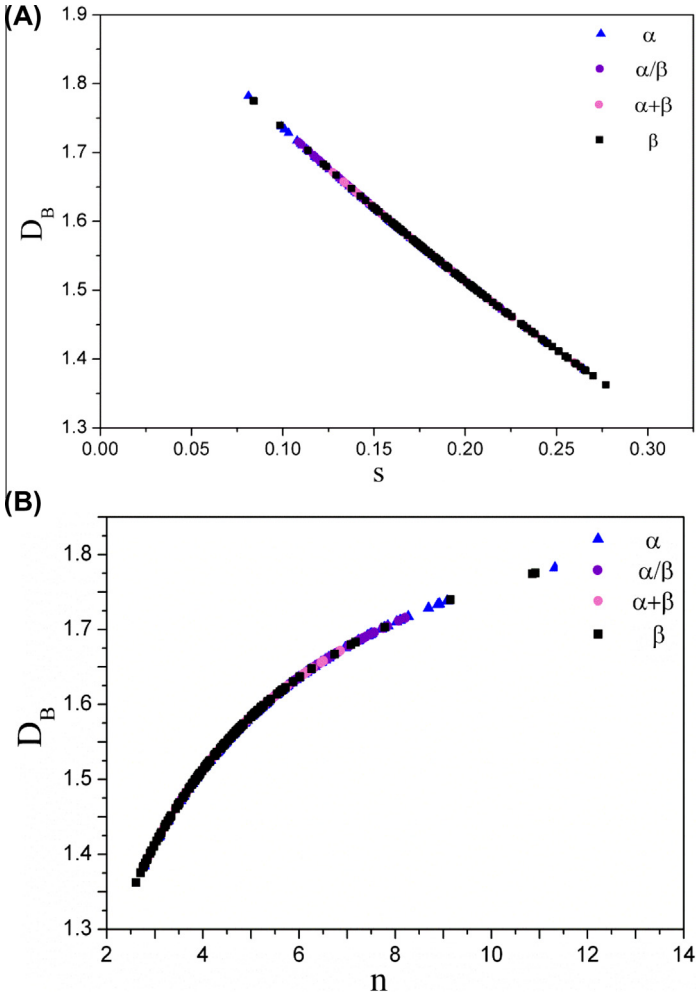

Fig. 4. Protein backbone fractal dimensions as a function of s ratio (a) and as a function of n index (b).

Table 2
The average value of *s* ratio and *n* index in the sp^n hybrid orbitals for four structural classes and 750 proteins.

	α	β	$\alpha+\beta$	α/β	750 proteins
s ratio[a]	0.157	0.191	0.179	0.162	0.170
n index[b]	5.364	4.237	4.573	5.164	4.889

[a] Ratio of containing *s* orbital in the sp^n hybrid orbitals.
[b] *n* index in the sp^n hybrid orbitals.

beyond tetrahedral sp^3 hybrid orbitals. But the proteins of β class possess a contrary characterization, which exhibits $sp^{4.237}$ like type hybrid orbitals, near to sp^3 hybrid orbitals. A average value *s* of 0.170 for all proteins predicts $sp^{4.889}$ hybrid orbitals, between sp^3 and *p* hybrid orbitals.

4. Conclusions

The local fractal dimensions (D_L) and the backbone fractal dimensions (D_B) of 750 proteins selected from four different structural classes were calculated by using computer simulations in this work. From the results we can conclude that: (1) the protein molecules exhibit a fractal behavior in the range of $1 \leqslant N \leqslant 15$; (2) the value of D_B is distinctly greater than that of D_L for the same protein; (3) there is a good relationship between D_B and D_L ($R = 0.95309$); (4) the order of mean values of D_B and D_L for four structural classes is: $\alpha > \alpha/\beta > \alpha+\beta > \beta$, which is in good agreement with other researches illustrated earlier.

According to the theory of backbone fractal dimension, the methodology and definition of fractal hybrid orbital were derived, the results are similar to the pioneering work reported by other researchers. Due to its simplicity and generality, the backbone fractal dimension is very suitable for the research of hybrid orbital model of protein. Meanwhile we also find that the differences of *s* ratios (or *n* indexes) among four structural classes of proteins are not quite obvious.

To sum up, the present results corroborate that a protein can be regarded as a fractal object with self-similarity and self-affinity, and the fractal analysis can be used to characterize some intrinsic properties of proteins.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cnsns.2013.05.005.

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