

FRACTAL CHARACTERISTICS OF PROTEINS SURFACES

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Abstract. A review of applications of fractal geometry concepts in studying the proteins surface is presented to indicate its roughness characterized by the surface fractal dimension. We refer to proteins belonging to different families; we study monomer and homo-multimer proteins and compare the fractal aspects of their surfaces.

Keywords: protein structure, surface fractal dimension, local surface fractal dimension.

1. Introduction

Fractals provide an avenue of research that may yield better methods of determining protein structure. The degree of complexity of the proteins irregular forms can be quantitatively described by the surface fractal dimension. The fractal dimensions associated to the protein surface and backbone can be an indicative of their folding strategy, their packing density and on their biological function. There are many papers published in the specific literature concerning fractal aspects of protein sequences [1-3], protein surfaces [4-15] and their tertiary structure, respectively [11-16]. The shape and physical properties of the protein surface are crucial for phenomena such as binding of small molecules, interactions with other proteins or nucleic acids or molecular recognition. Usually the surface of a protein is very irregular presenting a lot of cavities and channels having different sizes. It is known that binding and active sites of proteins are often associated with structural pockets and cavities. The fractal dimension of the proteins surface lies between 2 and 3 and it depends on the way we define the surface of the protein [4-15, 17, 18]. The fractal dimension of the pockets surfaces also lies between 2 and 3, but it may differ from the global surface fractal dimension [5, 12].

The aim of this paper is to make a review on the fractal aspects of protein surfaces and to connect this aspect to proteins structural characteristics expressed in their biological functions.

2. Surface fractal dimensions of different protein families

The surface of a protein has a large variety of shapes and sizes, and for these reason the roughness of the protein surface can be described using fractal geometry [4-15]. There are a few possibilities to define and represent the protein surface: the van der Waals surface (vdWSA), the contact surface (CS) [17], the molecular surface (MS) and the accessible solvent area (AS) [18]. The protein surface can be visualized using several modeling tools starting from the structural file taken from Protein Data Bank [19]. The surface of the diene lactone hydrolase (PDB code 1DIN) and its accessible solvent area, generated using Swiss-Pdb Viewer [20], are presented in figures 1(a) and 1(b) respectively.

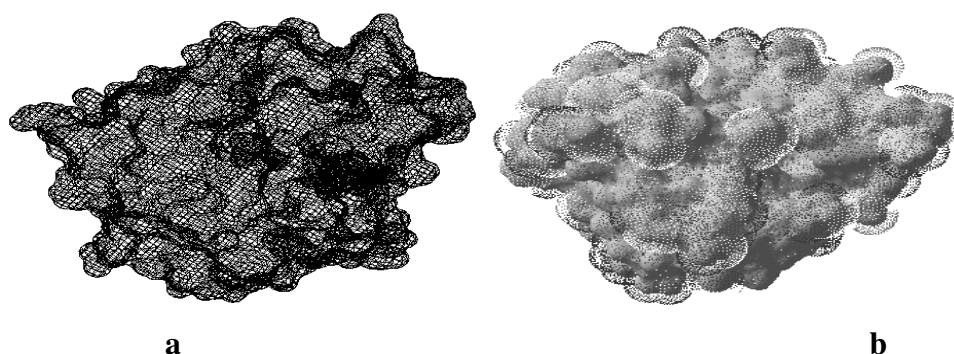


Figure 1 - (a) The surface of diene lactone hydrolase (entry code 1DIN), and (b) the accessible surface area

First study concerning the fractal features of protein surfaces has been done by Lewis and Rees [5]. Their study on lysozyme, ribonuclease A and superoxid-dismutase has illustrated that these proteins present regions with different surface fractal dimensions, the regions with higher roughness being responsible for protein interactions and the finest ones corresponding to the active sites. A similar result has been obtained by our group concerning hemoglobins [12]. We have analyzed 19 proteins belonging to hemoglobin protein family: 3 for plants, 4 for invertebrates and 12 for vertebrates. We have compared the surface fractal dimension computed for the entire molecular surface (as a global property) with the surface fractal dimension computed for the biggest pocket surface (as a local property). For all monomer hemoglobins we notice a higher local surface fractal dimension in comparison to

the global surface fractal dimension reflecting the functionality of the pockets as binding and active sites, this result being in good correlation with literature data [5]. We can mention for plant hemoglobin (code 1ASH) the global surface fractal dimension $D_s = 2.296$ and the local surface fractal dimension $D_s = 2.658$; for vertebrate hemoglobin (code 2MBW) the global surface fractal dimension is $D_s = 2.229$ and the local surface fractal dimension is $D_s = 2.935$.

The specific literature reveals fractal characteristics for a few isolated proteins belonging to the hydrolase family [5] and also concerning some subfamilies of hydrolases: proteases [6] and O-glycosidases [7]. Stawisky and his coworkers have been investigating distinct classes of proteins, proteases and non-proteases [6]. They have revealed that even if these two classes of proteins have similar surface fractal dimensions, $D_s = 2.17$, proteases have smaller surface area due to a more compact folding in order to prevent auto-degradation. Another study made by the same group on O-glycosidases and non-O-glycosidases has shown a higher roughness, correlated with their catalytic activity, for the first class ($D_s = 2.67$) than the second one ($D_s = 2.53$) [7].

For one of our studies we have randomly chosen an unbiased set of 30 hydrolases belonging to different organisms [16]. To determine the accessible surface (AS) of a protein, we applied the ball-rolling model [17]. The accessible surface has been calculated using the GETAREA on-line free software [21] where the probe radii used are of 1, 1.2, 1.4, 1.6, 1.8 and 2 Å and the surface fractal dimension has been determined from the plot $\log(AS)$ versus $\log(R)$ according to the scaling law $AS \sim R^{2-D_s}$ as it is presented in figure 2.

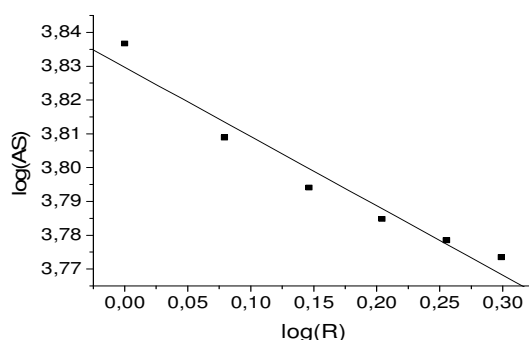


Figure 2 - Determination of the surface fractal dimension for diene lactone hydrolase (entry code 1DIN)

The different values for the surface fractal dimensions of investigated proteins reflect different degrees of packing density and of surface smoothness which seem to be in correlation with their structural classes and their concrete biological functions. Some of these values are close to $D_s = 2.17$ which corresponds to proteases [6] and only a few of them tend to $D_s = 2.64$ which corresponds to O-glycosidases [7].

Our group has also analyzed some EFCaBPs having extended or compact tertiary structures. Extended EFCaBPs show a smoother surface ($D_s=2.15$) than compact EFCaBPs ($D_s=2.28$) as a result of different packing mechanisms. For this protein family we demonstrate the fact that roughness of the protein surface does not depend on the protein content in secondary structure elements.

Within another study we have calculated the surface fractal dimension for two sets of 50 proteins each, one for monomer and the other for homo-multimer proteins. The mean surface fractal dimension is $D_s = 2.294 \pm 0.018$ for monomers and $D_s = 2.21 \pm 0.012$ for multimers, the two means being significantly different [15]. These results are in good agreement with other published data reflecting that aggregation behavior of proteins is correlated with specific surface properties [9].

3. Conclusions

The surface fractal dimension is the result of the mechanism of protein folding reflecting different degrees of packing density and of surface smoothness and it is strongly related to the complex local and global shapes needed to fit specific interactions governing the protein aggregation, ligand binding or other dynamic interactions. This property seem to be in correlation with the structural classes and concrete biological functions of proteins. The results presented indicate that the surface fractal dimension is a generic property of all proteins belonging to a structural subfamily and is independent on the protein content in secondary structure elements. The results presented here underlie that the concepts of fractal geometry may be successfully applied to characterize protein surfaces.

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