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ABOUT APPLYING FRACTAL GEOMETRY CONCEPTS IN BIOLOGY AND MEDICINE

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ABSTRACT. *Our purpose is to describe some recent progress in applying fractal concepts to systems of relevance to biology and medicine. We review several biological systems characterized by fractal geometry and we also discuss the application of fractal scaling analysis in medical quantitative diagnosis. We illustrate the applicability of these concepts by determining the fractal dimension of the chicken troponin C protein backbone,* $D_f = 1.68 \pm 0.04$, *and* $D_s = 2.097 \pm 0.002$ *that of its molecular surface.*

KEY WORDS: *fractals, fractal dimension, troponin, diagnosis*

INTRODUCTION

The term of fractal has been introduced in 1975 by the French mathematician, Benoit Mandelbrot, who was the first to recognize that the geometry of many of natural objects revealed a similar pattern regardless of the scale it was examined on [1]. The more you magnify the image, the more the structure appears the same. In classical geometry the points, lines, surface areas and cubic structures all represent dimensions expressed in integers, 0, 1, 2, and 3 dimensions, respectively. Fractal geometry is employed to model images that are more "interdimensional."

Within this report paper we reveal a few most common applications of the fractal geometry concepts in biology and medicine and we illustrate how these concepts are applied for determining the fractal dimensions of the chicken troponin C protein backbone and surface.

METHODOLOGY

A fractal object is a geometric shape which can be subdivided (or multiplied) in parts and each part is a reduced-size (multiplied-size) copy of the whole [1]. Quantitative characterization of fractal objects could be obtained using the concept of fractal dimension (FD). There are many modalities to define the fractal dimension and they are not always equivalent. Usually, to determine the fractal dimension we use a standard unity for measurements. In case of measurements of length for a segment, then we use a standard length unit, ε, and the total length of the segment, L, is given by

$$L=N\varepsilon \qquad (1)$$

where N is the number of the units ε needed to cover the entire segment [2]. If we need to cover a surface, than we use a square with a standard length ε and the entire surface is given by

$$L^2=N\varepsilon^2 \qquad (2)$$

and the same is happening for a volume

$$L^3=N\varepsilon^3 \qquad (3)$$

In all these equations, N is the number of standard units needed to cover the object under investigation. From all these equations we obtain

$$N=(L/\varepsilon)^D \qquad (4)$$

where D is the topological dimension of the investigated media. In case of fractal objects, equation (4) is written as

$$N=(L/\varepsilon)^{D_f} \qquad (5)$$

where D_f is the fractal dimension given by

$$D_f=\frac{\ln N}{\ln\left(\frac{L}{\varepsilon}\right)} \qquad (6)$$

This algorithm has been successfully applied to determine the fractal dimension of protein backbone, respective that of protein surface [3, 4-7]. In case of protein backbone, there is a scaling behavior similar to equation (6) between the length of the backbone (calculated as the sum of distances between the carbon alpha atoms) and the interval of amino acids used to calculate it [3]. It is also true for the scaling behavior of the molecular surface area with the radius of a probe sphere rolled on the protein's surface [3].

Fractal objects rise from non-linear growing processes and the value of the fractal dimension of a natural or artificial object is a measure of its complexity. Many natural objects are fractals: clouds, mountains, blood vessels network, many animal and plant tissues and so on [8].

In case of medical investigations, the interpretation of fractal images analysis is one of the quantitative non-invasive diagnosis methods and it uses integrated histogram fractal dimension computed from nuclear medicine images. There is always a threshold for FD values which allow to distinct between physiological respective pathological phenomena.

RESULTS AND DISCUSSIONS

Many biological systems present fractal aspects of their structure and dynamics, from molecular level to the entire organism. At molecular level, it has been demonstrated that proteins backbones and surfaces are fractal [2-7]. At cell level, there are also many evidences of fractal organization of different cell types which is also true for tissues [9] and at the organism level, there are studies providing the role of non-linear phenomena in sustaining live [10]. Within this paper we shortly review some fractal aspects of cells and tissues belonging to the animal body and we also underline the possibility to use fractal analysis of images as a quantitative, non-invasive technique for medical diagnoses. We also illustrate the applicability of the fractal geometry concepts for studying structural aspects of proteins in correlation with their biological functions. The most studied cells from the point of view of fractal analysis are the cells belonging to nervous system. For neurons and glyal cells, Pastor and his coworkers [11] have been revealed their fractal aspects and that a higher morphological complexity implied a higher fractal dimension. For neurons belonging to rat embryonic brain at 18 weeks, the determined fractal dimension was 1.33 and for these cells grown in laboratory conditions, their fractal dimension has also grown upon the equation

$$D_f(t) = A + B\exp(-t/\tau) \qquad (7)$$

with A, B and τ constants [11]. The same equation is valid for glyal cells, but with other values for constants. The dendritic structure of the neuron is also a manifestation of its fractal structure wich favorize synaptic transfer.

Another cell that was studied from the fractal point of view is the S1 cell of renal tubes [12]. Measurements of the cellular intervals in electronic micrographic images of the transversal section of renal tubes have allowed the computation of the fractal dimension of cells diameters, 1.78. The fractal patterns corresponding to measured dimension could be assembled into a three dimensional structural model that resembles very well to that of renal tubes.

Cellular components have been also revealed as being fractal. Cellular and intracellular membranes are very complex and dynamic structures and there are numerous studies indicating their fractal structure and behavior. For example, for humans, their nose membranes are least complex than those of dogs and dogs have a better smell than humans. Also, brain membranes are much complex than those of other animals and humans are more intelligent. A few examples of fractal dimensions for some cellular media are given in the table 1 [13, 14].

TABLE 1. Examples of fractal dimensions for some cellular media [13, 14]

Media	Fractal dimension
Alveolar membrane	2.17
Mitochondria membrane	2.09÷2.52
Mitochondria membrane contour	1.54
Plasma membrane contour	1.07÷1.43
Nucleus membrane contour	1.027
Plant nucleus (tomato and green pepper)	1.5÷1.8
Neuron cytoplasm	1.47÷1.7
Reticulum endoplasm	1.72

Measurements of fractal dimension for different cell types have been also used as a method for cancer and diabetic diagnoses. For example, perimeter measurements for the transversal section of lymphocytes allowed the differentiation between healthy subjects and cancer disease. For healthy subjects, fractal dimension of lymphocyte diameter is always under 1.28, but it is superior for subjects having leukemia [15]. The same type of analysis could also be used to detect diabetic disease [16], the fractal dimension of monocyte perimeter being always higher for diabetic subjects.

Another technique widely used in medical diagnosis is that of analysis of images obtained in medical examinations. For example, in lung cancer examination, the physical meanings and consequent implications of fractal analysis are useful in quantifying the heterogeneous distribution of carbon particle radioaerosol in the lungs [17]. Another example is detecting breast cancer from fractal analysis of tumors in mammograms [18]. Breast masses present shape and texture characteristics that vary between benign masses and malignant tumors in mammograms. The fractal dimension of the contour of a mass may be computed either directly from the two dimensional contour or from one-dimensional signatures derived from the contour. A one-dimensional signature was derived from each contour by using the Euclidean distance of each contour point to the centroid of the contour. The fractal dimension of the signatures indicated the possibility of discriminating malignant tumors from benign masses with an accuracy of 95%.

This method has been also successfully applied in accurate diagnosis of arthritis [19]. Arthritis due to calcium pyrophosphate deposition disease (CPPD), rheumatoid arthritis, and spondyloarthropathy, induce complex changes in the cartilage and the articular surface. The fractal dimension provides a measure of the complexity of a signal. Acceleration signals were obtained from the finger joint of arthritis patients with rheumatoid arthritis, spondyloarthropathy, and CPPD of the finger joint. Obtained results showed that there were significant differences between the fractal dimension of acceleration signals from patients having CPPD and rheumatoid arthritis, respective spondyloarthropathy. So, fractal dimension of acceleration signals, in concert with other clinical symptoms, can be used to classify different types of arthritis.

Troponin C is a calcium binding protein which is involved in signal transduction. After calcium binding, this protein undergoes a conformational change that allows it to interact with a target peptide, this interaction contributing to signal transduction processes. There are many experimental studies concerning troponin C structure and interactions with target peptides and they reveal an extended conformation of the native protein which turns into a compact structure when it binds the peptide [20]. These structural data are used in order to determine the fractal dimension of the protein backbone, respective that of its surface, the code in protein data bank for the structural file being 4TNC. The fractal diagram for troponin C backbone is presented in figure 1. Within this fractal diagram we notice two linear regions, one corresponding to the interval of 1 to 73 amino acids and the other to the interval 74-167. First linear region gives a slope of -0.451 which means a fractal dimension of D_f=1.68 ± 0.04 and it corresponds to folding of the N-terminal domain. Second linear region shows a high slope which means a small fractal dimension corresponding to the interactions between the N-terminal and C-terminal domains.

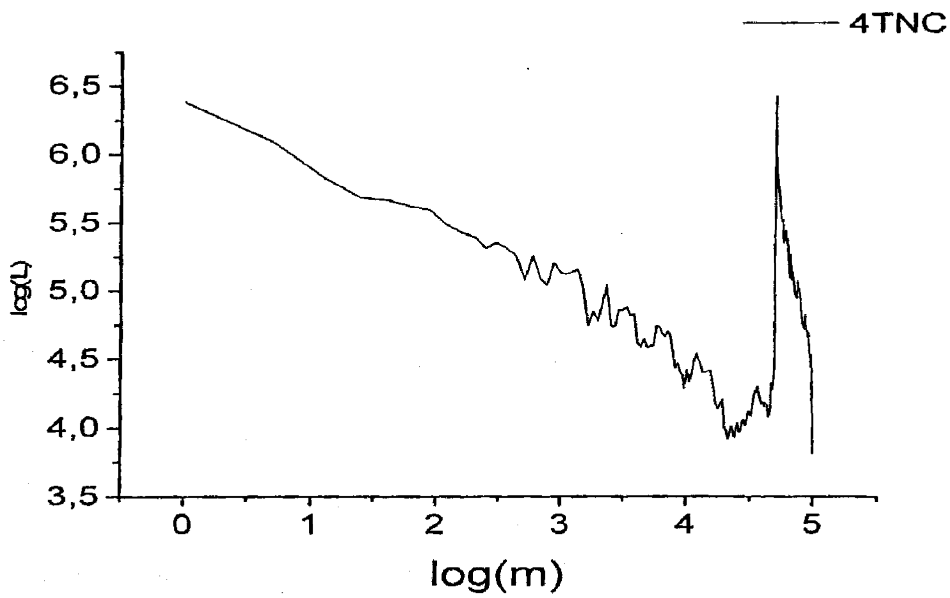

FIG. 1. The fractal diagram for chicken troponin C backbone

These results are in good agreement with other data presented in the literature [3-7] and revealing two linear regions in the fractal diagram of proteins backbones, one related to local folding and the other related to global folding.

For molecular surface area of chicken troponin C, its scaling behavior with the radius of the molecule used as a probe sphere rolled on the surface is presented in figure 2. Using this diagram in double logarithmical scale we obtain from the slope the fractal dimension of the protein surface, D_s=2.097 ± 0.002, this value indicating a very smooth surface for this protein and being in good agreement with other values obtained for the fractal dimensions of molecular surfaces of other extended calcium binding proteins [21].

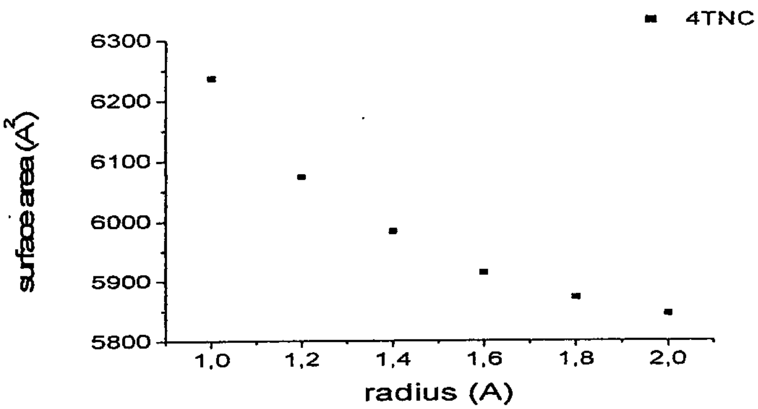

FIG. 2. Scaling of the molecular surface area with the radius of the probe sphere for chicken troponin C.

CONCLUSIONS

This short review underlines the applications of the concepts of fractal geometry in a wide range of biological phenomena and medical investigations. Fractal geometry is very useful to describe the very complex structures and behavior of biological systems at any of their levels and fractal analysis of images obtained through different methods provides to be a quantitative, non-invasive tool for medical diagnoses.

REFERENCES:

1. **Mandelbrot B.** - *Obiecte fractale (traducere)*, Ed. Nemira, Bucureşti, 1998
2. **Bunde A., Havlin S.** - *Fractals and desordered systems*, Springer Verlag, New York, 1992
3. **Dewey T.G.** - *Fractals in molecular biophysics*, Oxford University Press,1997
4. **Isvoran A., Licz A., Unipan L., Morariu V.V.** - *Determination of the fractal dimension of the lysozyme backbone for three different organisms*, Chaos Solitons&Fractals, 12, 757-760, 2000
5. **Isvoran A.** - *Search for evidence of the chaotic behavior of haemoglobin upon oxigen binding,* International Journal of Chaos Theory and Applications, 7, 27-32, 2002
6. **Isvoran A.** - *Describing some properties of adenylat kinase using fractal concepts,* Chaos Solitons&Fractals, 19, 141-145, 2004
7. **Isvoran A., Pitulice L. , Craescu C.T., Chiriac A.** - *Fractal aspects of calcium binding proteins,* Chaos Solitons&Fractals, 2007 a, in press
8. **Dick O.,** *Fractali,* Ed. Teora, Bucureşti, 1996

9. **Aon M. A., Cortassa S.** - *On the fractal nature of cytoplasm*, FEBS Letters, 334, 1-4, 1994
10. **Volkenstein M.** - *Biophysics*, Ed. Mir, Moscova, 1984
11. **Pastor J., Bru A., Fernaud I., Bru I., Berenguer C., Fernaud M.J., Melle S.** - *Fractal dimension and tempoeral evolution of neurons*, Anales de Fisica, X, 1-2, 1998
12. **Welling D., Urani J., Welling L., Wagner E.** - *Fractal analysis and imaging of the proximal nephron cell*, Am J Physiol Cell Physiol., , 270, C953-C963, 1996
13. **Losa G.** - *Do complex cell structure share a fractal-like organization*, Proceedings de le 6-eme Congres Europeenes des Scineces du Sistemes, 2005
14. **Morariu V.V., , Crăciun C., Neamțu S., Iarinca L., Mihali C.** - *Fractal and long-range correlation analysis of plant nucleus utrastructure*, Rom. J. Biophys, 16, 243-252, 2006
15. **Bauer W., Mackenzie C.D.** - Cancer Detection via Determination of Fractal Cell Dimension, Quantitative Biology, 21, 3-5, 1995
16. **Bianciardi G, Tanganelli I, Totagiancaspro D, Brogi M, Carducci A, De Santi MM.** - *Fractal analysis of monocytes in diabet*, Clin Hemorheol Microcirc, 35, 269-272, 2006
17. **Chung H-W., Huang Y. H.** - *Fractal Analysis of Nuclear Medicine Images for the Diagnosis of Pulmonary Emphysema*, Chaos Solitons&Fractals, 6, 171-201, 1995
18. **Nguyen M., Rangayyan R.M.** - *Fractal Analysis of Contours of Mammographic Masses*, Biomedical Engineering, Editors K.-P. Adlassnig, M. Bracale, 458-806, 2005
19. **Shah E.N., Reddy N.P., Rothschild B.M.** - *Fractal analysis of acceleration signals from patients with CPPD, rheumatoid arthritis, and spondyloarthroparthy of the finger joint*, Computer Methods and Programs in Biomedicine, 77, 233-239, 2005
20. **Satyshur, K.A., Rao, S.T., Pyzalska, D., Drendel, W., Greaser, M., Sundaralingam, M.** - *Refined structure of chicken skeletal muscle troponin C in the two-calcium state at 2-A resolution*. J. Biol. Chem., 263, 1628-1647, 1988
21. **Pitulice L., Craescu C.T., Isvoran A., Chiriac A.** - *Scaling properties of radius of gyration and surface area for E-F hand calcium binding proteins*, The IX-the National Conference of Biophysics, Bucharest, 11-14 May, 2007

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