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Early Recognition of Lung's Air Sacs Wall Collapsing

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Abstract—The paper discusses the possibility of applying a non-linear analysis approach on air density distribution within lung airways tree at any level of branching¹. Computed Tomography (CT) 2 source images of the lung are subjected to two phases of treatment in order to produce a fractal coefficient of the air density distribution. In the first phase, raw pixel values from source images, corresponding to all possible air densities, are processed by a software tool, developed in order to, construct a product image. This is done through Cascading Elimination of Unwanted Elements (CEUE): a preprocessing analysis step of the source image. It identifies values of air density within the airways tree, while eliminating all non-air-density values. Then, during the second phase, in an iterative manner, a process of Resolution Diminution Iterations (RDI) takes place. Every resolution reduction produces a new resultant histogram. A resultant histogram is composed of a number of peaks, each of which corresponding to a cluster of air densities. A curve is plotted for each resolution reduction versus the number of peaks counted at this particular resolution. It permits the calculation of the fractal dimension from the regression slope of log-log power law plot.

Keyword- Medical image processing, nonlinear systems and fractal analysis.

I. INTRODUCTION

The World Health Organization estimates 600 million people worldwide have Chronic Obstructive Pulmonary Disease (COPD) [1]. Lung cancer, stomach cancer and Human Immunodeficiency Virus (HIV) will be the 5th, 8th and 9th most common causes of death respectively [1]. An economic analysis of data from a large-scale international survey (in Canada, France, Italy, The Netherlands, Spain, the U.K and the U.S.A.), results demonstrated lost productivity due to COPD has a particularly high impact on the economy in France, The Netherlands and the U.K. accounting for 67%, 50% and 41% of overall costs, respectively [1]. COPD is a major and increasing health problem, which is predicted to become the third commonest

cause of death and the fifth commonest cause of disability in the world by 2020 [2]. Between 1966 and 1995, the age-adjusted death rates for coronary heart disease and stroke declined by 45% and 58%, respectively, whereas the death rate for COPD increased by 71%! [2]. Because of the enormous burden of disease and escalating healthcare costs, there is now renewed interest in the underlying cellular and molecular mechanisms and a search for new therapies, resulting in re-evaluation of the disease [2]. Between 45 and 65% of patients with COPD are not formally diagnosed because many accept breathlessness and limited exercise tolerance as features of aging and regard their smoker's cough as normal. In Spain, 9% of adults aged between 40 and 70 yr are affected by COPD [3], although only 22% are diagnosed and receive some kind of treatment for their disease [4]. In the "Confronting COPD in North America and Europe" survey [5], attempts were made to overcome such problems by collecting data on symptoms suggestive of COPD as well as recording doctor-diagnosed COPD. On the basis of these criteria, the prevalence of COPD in smokers was shown to be consistent across many countries (ranging from 5.4% in the Netherlands and 4.5% in the United States and Canada to 3.2% in France) [6]. The interpretation of experimental results from functional medical imaging is complicated by inter-subject and inter-species differences in airway geometry [7]. The application of computational models in understanding the significance of these differences requires methods for generation of subject-specific geometric models of the bronchial airway tree [7]. So in such manner like that the trees have been extended to model the entire conducting airway system, by using a volume-filling algorithm to generate airway centerlines locations within detailed volume descriptions of the lungs or lobes.

The term fractal is used to designate objects that are self-similar and have details at different scales. Fractal dimension is a measure to quantify how densely fractal occupies the space in which it lies. This characteristic has been used in texture classification [8]. Many natural objects do display some degree of 'statistical' self-similarity, at least over a limited range of spatial or temporal scales. For

¹ This study has been implemented on Marie-Lannelongue hospital at CNRS UMR 8162, University of Paris-Sud 11 (ORSAY) - France.

² Computerized Axial Tomography (CAT) is a technique that is implemented through an X-ray machine to produce computerized cross-sectional images of the body organs.

example, lung's branches show statistical self-similarity over 14 dichotomies, and trees branching over 8 dichotomies [9].

The overall goal of this work is: attempting to get such a tool, based on a non-linear analysis approach, in order to make precise evaluation of the air sac wall collapse and to facilitate research and application of lung image analysis.

II. FRACTAL GEOMETRY APPLICATIONS IN BIOLOGY

Fractal geometry has proven to be a useful tool to quantify the structure of a wide range of idealized and naturally occurring objects, from pure mathematics, through physics and chemistry, to biology and medicine.

In the past few years fractal analysis techniques of nonlinear systems have gained increasing attention in signal and image processing, especially in medical sciences; pathology, neuropsychiatry, cardiology.... Etc. As example, Heart Rate Variability (HRV) is a physiological phenomenon defined as variation in the normal-to-normal RR intervals during normal sinus rhythm. It reflects the effects of the autonomic nervous system and other physiological control mechanisms on cardiac function. HRV is not a clearly periodic or regular phenomenon, and the HRV signal is sooner nonlinear than linear [10, 11].

A number of new methods like fractal analysis have been recently developed to quantify complex heart rate dynamics [12-13]. They may reveal abnormalities in time-series data and the break down of fractal properties that are not apparent when conventional statistics are used [11], [14-16]. Also nonlinear mechanisms included, fractal approach are involved in studying the genesis of heart rate dynamics [17, 18], analysis of the dynamic behavior of cardiac signals, therefore by this mechanism has opened up a new approach towards the assessment of normal and pathological cardiovascular behavior.

The present work intends to describe fractal techniques and its applications by concentrating on applications of fractal geometry.

III. DIMENSIONAL MANAGEMENT TECHNIQUE

It is used to think that a good measurement is characterized by its mean and variance and that a good theory is characterized by its ability to predict the values measured in an experiment. The property of nonlinear systems called fractals has now taught that this isn't necessarily true. Data from fractal systems extend over many scales and so cannot be characterized by a single characteristic average number. This means that a valid mathematical model will not be able to predict the values of the time series.

In (1949) Erwin Chargaff, who discovered that the amounts of A (adenine) and T (thymine) are paired with the amounts of G (guanine) and C (cytosine) in Deoxyribonucleic Acid (DNA), wrote that it is not the goal of science to tear at the tapestry of the world and pull out the threads and determine the color of each thread. It is the goal of science to see the picture on the tapestry. Here, we would like to step back a bit

from the tapestry of nonlinear systems and try to make clear two important things: 1) how to use statistics to analyze the experimental data and 2) how to judge the validity of given mathematical models. These bases are often stated in technical terms, but here it is needed to make their dramatic implications for everyday science as clear as possible.

Lewis and Rees (1985) [19], determined the fractal dimension of protein surfaces ($2 \leq D \leq 3$) using microprobes. A mean surface dimension of $D = 2.4$ was determined using microprobe radii ranging from 1-3.5 angstroms. More highly irregular surfaces ($D > 2.4$) were found to be sites of inter-protein interaction. Wagner et al. (1985) [20], estimated the fractal dimension of helium and iron-sulfur proteins using crystallographic coordinates of the carbon backbone. They found that the structural fractal dimension correlated positively with the temperature dependence of protein relaxation rates.

Takahashi (1989) [21], hypothesized that the basic architecture of a chromosome is tree-like, consisting of a concatenation of 'mini-chromosomes'. A fractal dimension of $D = 2.34$ was determined from an analysis of first and second order branching patterns in a human metaphase chromosome.

Xu et al. (1994) [22], hypothesized that the twisting of DNA binding proteins have fractal properties.

Smith et al. (1989) [23], used fractal dimension as a measure of contour complexity in two-dimensional images of neural cells. They recommend D as a quantitative morphological measure of cellular complexity.

A fractal is an object in space that has an ever larger number of ever smaller pieces. It is self-similar, meaning that the smaller pieces are reduced copies of the larger pieces. For some fractals, the smaller pieces are exact copies of the larger pieces. For most fractals in nature, the smaller pieces are kind-of-like the larger pieces. A tree is such a fractal. It has an ever larger number of ever smaller branches. A fractal can also be a process in time. There can be an ever larger number of fluctuations of ever smaller amplitude. A fractal can also be a set of numbers from experimental data. There can be an ever larger number of ever smaller numbers.

This system has the surprising property that it is possible to completely predict the values of the system over brief times, but unable to predict their values over long times [24].

IV. GEOMETRIC SCALING APPROACH

Analysis of the geometry of the scan-based and model-based airways has verified their consistency with measures from previous anatomical studies, and has provided new anatomical data for the bronchial tree. The fractal dimension is most commonly estimated from the regression slope of log-log power law plot. However, the definition of 'independent' and 'dependent' variables is not straightforward in such applications [25]. This is a serious but largely unrecognized problem, for using least square regression in this way results in a biased slope estimate increase in dimension: a rough curve has a dimension between 1 and 2, and a rough surface has a dimension somewhere between 2 and 3.

One of the applications of the bronchial tree model is to make simulations of inert gas mixing [26] and airway thermodynamics. Others have similarly attempted to generate bronchial tree models [27]. Using an identical parameter set, the volume-filling algorithm has produced airway trees with branching asymmetry appropriate for the human lung, demonstrating the dependence of the method on the shape of the lung or lobe volume. The human bronchial tree has an asymmetric branching pattern, but it is more symmetric than other mammalian lungs [28].

How long is the coastline of Great Britain? At first sight this question may seem trivial. Given a map one can sit down with a ruler and soon come up with a value for the length. The problem is that repeating the operation with a larger scale map yields a greater estimate of the length. If we actually went to the coast and measured it directly, then still greater estimates would result. It turns out that as the scale of measurement decreases the estimated length increases without limit [24]. Thus, if the scale of the (hypothetical) measurements were to be infinitely small, then the estimated length would become infinitely large! Lewis Fry Richardson noted this dependence of measured length on the measuring scale used. In discussing measurement, scale can be characterized in terms of a measuring stick of a particular length: the finer the scale, the shorter the stick. Thus at any particular scale, we can think of a curve as being represented by a sequence of sticks.

V. Numerical Image Analysis Problem

Low Attenuation Areas (LAA) considered as a characteristic of emphysema. One technique identifies areas of low attenuation based on a single density index threshold or a range of density indices. Here, any areas having densities, lower than 910 Hounsfield Units (HU)³, or in the lowest fifth percentile, or falling within a given range of densities of the histogram are considered to be emphysematous. The lowest fifth percentile of the histogram of emphysematous subjects has been shown to correlate well with the surface area of walls of distal air spaces per unit lung volume [29, 30]. The second method computes the mean lung density as a defining characteristic of emphysema. These studies have reported good correlation with some pulmonary function tests [29].

Many models could aid in the ability to interrogate model-based hypotheses regarding the principles that govern the regional distribution of ventilation and perfusion, with the ability to evaluate the model predictions by comparison with in vivo measures based on imaging of the individual from whom the model was constructed. Anatomic customized models of different individuals or different species can be used to probe the sensitivity of predictions to differences in geometry, whether subtle (normal temporal change in airway caliber of an individual) or major (between species).

³ The density assigned to a pixel in a CT (computed tomography) scan on an arbitrary scale on which air has a density -1000; water, 0; and compact bone +1000.

The dimension of a fractal curve is a number that characterizes the way in which the measured length between given points increases as scale decreases [31, 32]. First challenge that faced the application of the analysis technique was how to get a digital plan of the fine structure of all the levels and generations of lung airways. This plan that maps the whole air pixel intensities is essential for further steps of image processing. It will be obtained as a final result of Cascading Elimination of Unwanted Elements (CEUE) process.

VI. APPLIED TECHNIQUE AND MANIPULATION STEPS

The chosen characterized morphological parameter "fractal dimension" quantifies the relative number of small values compared to the large values, and it is related to the slope of log-log power law plot. With the availability of a realistic structural description and a more precise mapping of the lung architecture, simulations that concern the gas flow and particle deposition can now be performed with higher accuracy [33]. The availability of a realistic computer representation of the lung that can be scaled is an important step forward in lung research, toxicology and clinical applications including functional predictions [34]. While the predictions of ventilation are established in clinical routine, methods based on conventional CT-data are not since data only up to the seventh order is resolved [33]. Although fractals are irregular, not all irregular structures or erratic time series are fractal. A key feature of the class of fractals seen in biology is a distinctive type of long-range order, [12]. This property generates correlations that extend over many scales of space or time.

Using the act of modifying whole image's resolution in textural features extraction is the base of proposed image treatments in this work, which is different from the studies entries illustrated in some sections above.

In order to prepare the source image, figure 1, for an iterative Resolution Diminution Iterations (RDI) process, that there is a proven obvious need to eliminate many areas that will badly affect the detected Region of Interest (ROI) histogram, figure 2.

In the first step of CEUE, an automatic mask is established, shown in figure 3 for processing the source image. Treated image histogram at this step of eliminate unwanted data is shown in figure 4.

After that many sequences must be applied to archive the elimination process. End product image shown in figure 5 represents the optimal image at the end of CEUE treatments, and figure 6 displays its Histogram plot. This is done as a first phase of treatment to eliminate unwanted data which followed by RDI treatments. The image analysis features, of MATLAB program, facilitated this study. These included: providing the automated mask, encoding all pixels in the image, defining their values and conducting all RDI steps in an exceedingly short time.

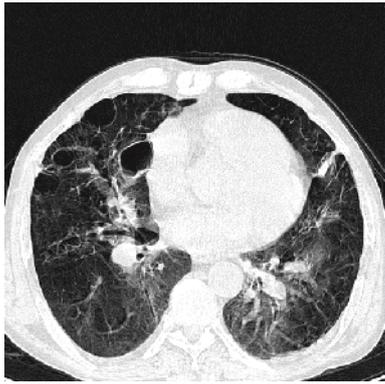


Fig. 1. The source images before CEUE treatments

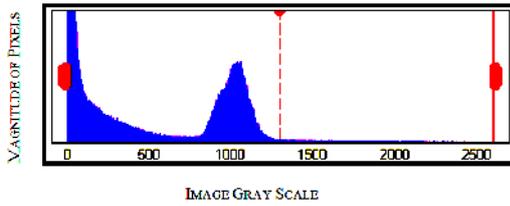


Fig. 2. Histogram plot for source image

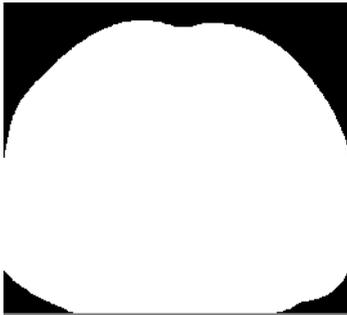


Fig. 3. Automatically established mask.

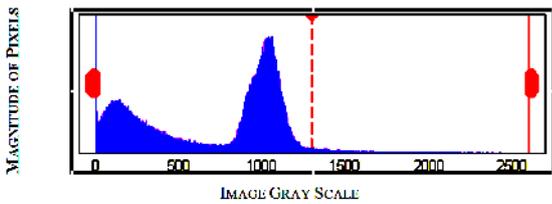


Fig. 4. Histogram plot for source image



Fig. 5. Whole extracted intensities of air pixels by CEUE treatments.

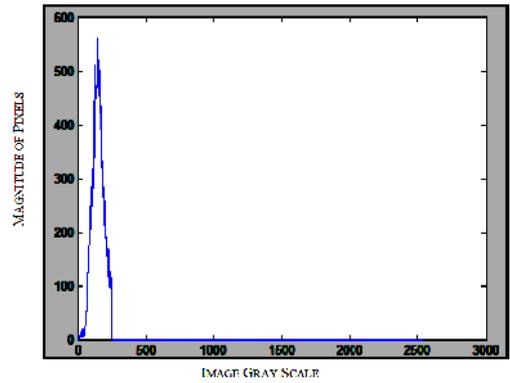


Fig. 6. Histogram plot for produced image at the end of CEUE treatments.

VII. SURVEILLANCE IMPLICATIONS POINTS

The proposed fractal tool is based on the nonlinear approach. Its efficiency in characterizing the self-similar properties of the lung airways properties needs to be verified to validate the tool's punctuality. This is discerned by two verification points.

The first, verification is realized by the demonstration of the success the CEUE treatments by the proposed tool, through a visual comparison between three histograms for these images respectively; source image, treated image at first step in CEUE process, and product image, as seen in figure 2, figure 4, and figure 6. The second is the directly proportional relationship between the counted numbers of peaks at each step of RDI process, figure 7, representing clusters of air intensity values, in the histogram versus the image texture resolution, as demonstrated in figure 8.

Figure 8 displays the reduction of peaks number, representing clusters of air intensity values histogram, as a result of modification the resolution in an iterative manner of the produced image from CEUE phase.

It takes place by increasing its scanning scale width. In his phase every resolution reduction by increasing the reading scale width produces a new resultant histogram.

A resultant histogram is composed of a number of peaks, each of which corresponding to a cluster of air densities. This illustrated correlation is an essential characteristic of the adopted theoretical approach.

VIII. FRACTAL MULTI-SCALE COMPLEXITY SOLUTION

For complex processes, fractal long-range correlations are the mechanism underlying a memory effect; the value of some variable like heart rate at a particular time is related not only to immediately preceding values, but also to fluctuations in the remote past. Certain diseases are marked by a breakdown of this long-range organization property producing an uncorrelated randomness.

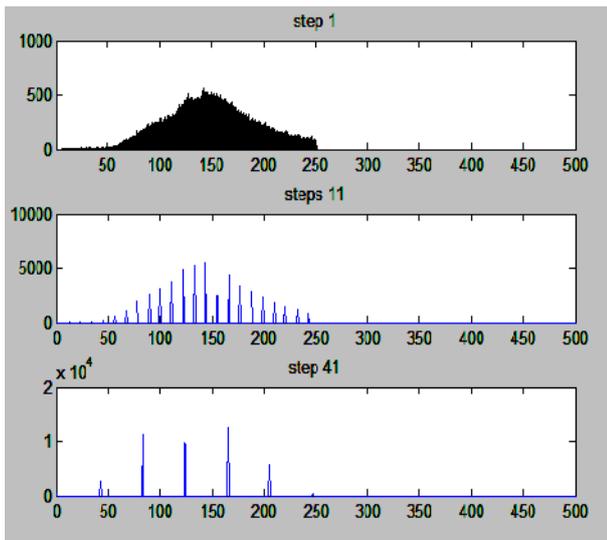


Fig. 7. Some ROI histograms of the produced image from CEUE phase while the modification of its resolution process take place in RDI phase.

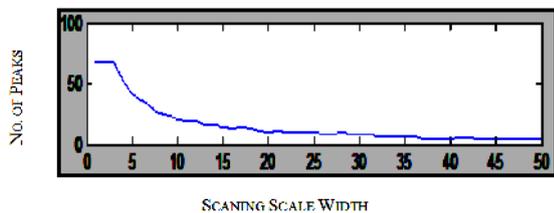


Fig. 8. Displays the reduction of peaks number, representing clusters of air intensity values histogram, as a result of modification the resolution of the produced image from CEUE phase by increasing its scanning scale width.

A number of different statistical evaluations were performed to describe the properties of the new established geometric reference model [33]. The model has a tree-like structure where the trachea is the 'stem' and the bronchi and bronchioles branch out from the trachea. This means the model is considered to be a bifurcating system: each parent branch, b parent, gives rise to two daughter branches b_1 and b_2 which are generally asymmetrical with respect to branch dimension and volume of lung supplied by each daughter branch. Individual properties of branches are named Analogical, e.g. A_1 and A_2 are the cross-sectional area of daughter branches; having considered 1453 branches, 727 of these are endpoints, below referred to as leaves of the tree. Every branch supports downstream a certain part of the total lung volume.

A key to the statistical description is the way in which the bronchial tree elements are numerically ordered. Traditional ordering assigns the trachea to the first order, the immediate daughter branches are second order and so on, a schema that is referred to as Weibel ordering. If asymmetric branching patterns prevail, branches having different diameter may have the same order, which produces inconsistencies in subsequent statistical evaluations.

Complex fluctuations with the statistical properties of

fractals have not only been described for heart-rate variability but also for fluctuations in respiration, systemic blood pressure, [35] human gait, [36] and white blood cell counts, [37] as well as certain ion-channel kinetics. Furthermore, if scale-invariance is a central organizing principle of physiological structure and function, we can make a general, but potentially useful, prediction about what might happen when these systems are severely perturbed. If a functional system is self organized in such a way that it does not have a characteristic scale of length or time, a reasonable anticipation would be a breakdown of scale-free structure or dynamics with disease.

How does a system behave after such a pathological transformation? The antithesis of a scale-free (fractal) system—i.e., one with multiple scales—is one that is dominated by one frequency or scale. A system that has only one dominant scale becomes especially easy to recognize and characterize because such a system is by definition periodic i.e., it repeats its behavior in a highly predictable (regular) pattern.

The paradoxical appearance of highly periodic dynamics in many disease states (disorder) is one of the most compelling examples of the notion of complexity loss in disease. Complexity here refers specifically to a multi-scale, fractal-type of variability in structure or function.

IX. CONCLUSIONS AND DISCUSSIONS

The designed software does not need any complementary programs like curve fitting or non-linear integration programs. It has a relatively small size, it is compatible with Windows operating system, and can be run adequately by a trained person. The software can also be converted to C or C++ languages, extending its usability to other platforms; it can be uploaded to any type of CT's mainframe systems as well as the internal PACS system of a hospital.

The software can manipulate images in (JPEG) ⁴ and (DICOM) format. It does not require a large amount of time to treat the source image in the preprocessing CEUE analysis nor in the RDI iteration-processes until it reaches the phase where calculation of the fractal dimension from the regression slope of log-log power law plot is made. It could be useful for pulmonary research centers interested in applying such a tool for lung diseases diagnosis in addition to studying the changes in disease severity especially during evaluation and follow up of novel and current therapies.

This work benefits from the Fractal geometry to reveal the self-similarity properties (Fractal feature) of the detected Region of Interest (ROI) histogram by the developed software. It reflects precisely the fractal geometry in lung medical images. The presented tool is a try to analyze the density distributions of air within lung airways by non-linear approach.

⁴ Joint Photographic Experts Group is a group of experts on graphics and photography who developed a standard for compressing photographic data.

The intention of this method is to create a model applicable in clinical practice. The only equipment necessary is computer software for quantitative CT measurements and linear regression analysis.

Fractal approach is a unifying concept integrating scale-dependence and complexity, both of which are central to our understanding of biological patterns and processes.

The statistical power of the current study will be able to perceive sensation when applying it on large number of lung specimens.

Better mathematical characterization of the lung airways helps to provide more efficient delivery of inhaled medications, and to a better understanding of the effects of specific pollution materials, smoke, suspected industrial activities, and respiratory diseases.

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REFERENCES

- [1] Rabe KF, Hurd S, Anzueto A, et al. (2007). "Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary". *Am. J. Respir. Crit. Care Med.* 176 (6): 532–55. doi:10.1164/rccm.200703-456SO. PMID 17507545.
- [2] Sullivan SD, Ramsey SD, Lee TA. "Economic burden of COPD". *Chest* 2000; 117(2 Suppl):5S–9S.
- [3] Pen a VS, Miravittles M, Gabriel R, Jimenez-Ruiz CA, Villasante C, Masa JF, Viejo JL, Fernandez-Fau L. "Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study". *Chest* 2000; 118:981–989.
- [4] Miravittles M, Ferrer M, Pont A, Luis Viejo JL, Masa JF, Gabriel R, Jimenez-Ruiz CA, Villasante C, Fernandez-Fau L, and Sobradillo V. "Characteristics of a population of COPD patients identified from a population-based study: focus on previous diagnosis and never smokers." *Respir. Med* 2005; 99:985–995".
- [5] Rennard S, Decramer M, Calverley PM, Pride NB, Soriano JB, Vermeire PA, Vestbo J. "Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey". *Eur Respir J* 2002; 20:799–805.
- [6] David M. Mannino¹ and Sidney Braman². "The Epidemiology and Economics of Chronic Obstructive Pulmonary Disease". *Proc Am Thorac Soc Vol 4*. pp 502–506, 2007.
- [7] Tawhai, M. H., Hunter, P., Tschirren, J., Reinhardt, J., McLennan, G., and Hoffman, E. A., 2004. "CT-based geometry analysis and finite element models of the human and ovine bronchial tree". *Journal Applied Physiology*, 97(6): 2310-2321.
- [8] M.L.Valarmathi, Dr.K.Anbumani. "Non Iterative Fast Fractal Codec Using Local Fractal Dimension". *GVIP Journal*, Volume 6, Issue 3, December, 2006.
- [9] Lorimer, N.D., R.G. Haight and R.A. Leary. 1994. "The fractal forest: fractal geometry and applications in forest science". U.S. Department of Agriculture, Forest Service. NorthCentral Forest Experimental Station, General Technical Report NC-170. 43 pages.
- [10] Sayers BM (1973) "Analysis of heart rate variability". *Ergonomics* 16: 17-32.
- [11] Goldberger AL. (1996) "Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside". *Lancet* 347: 1312-1314.
- [12] Peng CK, Havlin S, Stanley HE, Goldberger AL. (1995) "Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series". *Chaos* 5: 82-87.
- [13] Yamamoto Y, Hughson RL. (1991) "Coarse-graining spectral analysis: new method for studying heart rate variability". *J Appl Physiol* 71(3): 1143-1150.
- [14] Pincus SM, Goldberger AL. (1994) "Physiologic time-series analysis: what does regularity quantify?" *Am J Physiol* 226: H1643-H1656.
- [15] Iyengar N, Peng CK, Morin R, Goldberger AL, Lipsitz LA. (1996) "Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics". *Am J Physiol* 271: R1078-R1084.
- [16] Fleisher LA, Pincus SM, Rosenbaum SH. (1993) "Approximate entropy of heart rate as a correlate of postoperative ventricular dysfunction". *Anesthesiology* 78: 683-692.
- [17] Goldberger AL, West BJ. (1987) "Applications of nonlinear dynamics to clinical cardiology". *Ann New York Acad Sci* 504: 155-212.
- [18] Babyloyantz A, Destexhe A. (1988) "Is the normal heart a periodic oscillator?" *Biol Cybern* 58: 203-211.
- [19] Lewis, M. and D.C. Rees. 1985. "Fractal surfaces of proteins". *Science* 230: 1163-1165.
- [20] Wagner, G.C., J.T. Colvin, J.P.Allen and H.J. Stapleton. 1985. "Fractal models of protein structure, dynamics and magnetic relaxation". *J. Am. Chem. Soc.* 107: 5589-5594.
- [21] Takahashi, M. 1989. "A fractal model of chromosomes and chromosomal DNA replication". *J. Theor. Biol.* 141: 117-136.
- [22] Xu, J., Y. Chao and R. Chen. 1994. "Fractal geometry study of DNA binding proteins". *J. Theor. Biol.* 171: 239-249.
- [23] Smith, T.G., W.B. Marks, G.D. Lange, W.H. Sheriff and E.A. Neale. 1989. "A fractal analysis of cell images". *J.Neurosci. Meth.* 27: 173-180.
- [24] L. S. Liebovitch. 1998. "Fractals and Chaos Simplified for the Life Sciences". Oxford University Press, New York.
- [25] Zeide, B., and Gresham, C.A. 1991. "Fractal dimensions of tree crowns in three loblolly pine plantations of coastal South Carolina". *Can. J. For. Res.* 21:1208-1212.
- [26] Tawhai MH and Hunter PJ. "Multibreath washout analysis: modelling the influence of conducting airway asymmetry". *Respir Physiol* 127: 249–258, 2001.
- [27] Kitaoka H, Takaki J, Suki B. "A three-dimensional model of the human airway tree". *J Appl Physiol* 1999;87(6):2207–17.
- [28] Schlesinger RB and McFadden LA. "Comparative morphometry of the upper bronchial tree in six mammalian species". *Anat Rec* 199: 99–108, 1981.
- [29] American Thoracic Society. 1962. "Chronic bronchitis, asthma, and pulmonary emphysema: a statement by the committee on diagnostic standards for nontuberculous respiratory diseases". *Am. Rev. Respir. Dis.* 85:762–768.
- [30] Mohanalin, Prem Kumar Kalra, Nirmal Kumar. "Tsallis Entropy based Microcalcification Segmentation". *ICGST-GVIP Journal*, ISSN 1687-398X, Volume (9), Issue (I), February 2009.
- [31] Kenkel, N.C. and D.J. Walker. 1993. "Fractals and ecology". *Abst. Bot.* 17: 53-70.
- [32] Loehle, C. and L. Bai-Lian. 1996. "Statistical properties of ecological and geologic fractals". *Ecol. Modeling* 85: 271-284.
- [33] Nowak N, Kakade, PP, and Annapragada AV. "Computational fluid dynamics simulation of airflow and aerosol deposition in human lungs". *Ann Biomed Eng* 31(4): 374-390, 2003.
- [34] Sera, T., H. Fujioka, H. Yokota, A. Makinouchi, R. Himeno, R.C. Schroter, and K. Tanishita, 2003. "Threedimensional visualization and morphometry of small airways from microfocal X-ray computed tomography". *Journal of Biomechanics*, 36:1587-1594.
- [35] Hausdorff JM, Peng CK, Ladin Z, Wei JY & Goldberger AL (1995) "Is walking a random walk? Evidence for long-range correlations in stride interval of human gait". *J Appl Physiol* 78: 349-358.
- [36] Goldberger AL, Kobalter K, Bhargava V. "1/f-like scaling in normal neutrophil dynamics: Implications for hematologic monitoring". *IEEE Trans Biomed Eng* 1986;33:874-6.
- [37] B. B. Mandelbrot, J. V. Ness. "Fractional Brownian Motion, fractional noises and applications". *SIAM Rev.* 10(4):78-79, 1968.