INT. J. BIOL. BIOTECH., 8 (4): 463-467, 2011.

MODELING OF BRAIN CANCER DEVELOPMENT USING FRACTAL GEOMETRY

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ABSTRACT

This investigation attempts to analyze the growth of brain cancerous tissue employing the technique of fractal geometry, specifically computing the fractal dimensions. The fractal dimensions were determined using a box-counting method. The earliest stage showed lowest fractal dimension (D), 1.6541. The intermediate stage showed maximum fractal dimension of 1.7016 while the last stage available showed slightly lower D value of 1.6847. These results were found to be in agreement with those of previous studies on certain cancer types. The use of fractal analysis in the diagnosis of cancer is discussed. It has been shown that the fractal dimension of 2D microvasculature networks can discriminate between normal versus tumor tissue. Fractal dimensions also differed between various stages of malignancy.

Key Words: Fractal Geometry, Brain Cancer

In the past four decades spatial analysis has been mainly performed using a group of modeling techniques that focus on the understanding of biological phenomenon associated with their occurrence in space, yet they almost completely ignore the geometry of the spatial form.

Fractals can be employed to analyze varied patterns, including density, diversity, geometrical shapes, size distribution of islands, boundary of islands, and the spread of various types of carcinoma (malignant tumors). Fractal geometry can be conceived as a unifying (and recurrent) theme in biology, because it integrates scale related phenomenon and complexity which provides understanding of scale dependent patterns in nature (Mandelbrot, 1983, 1997; Kenkel and Walker, 1996; Halley *et al.*, 2004). Fractals are geometric structures that can be used to model many biological structures that are not amenable to conventional analysis. The term fractal was introduced by Mandelbrot (1983), derived from the Latin word *fructus* , meaning 'broken', to characterize spatial or temporal phenomenon that are continuous but not differentiable (Kenkel and Walker, 1996; Brown and Liebovitch, 2010).

The key properties of fractals are scale independence, self similarity across a range of scale, complexity, and infinite length or detail (Kenkel and Walker, 1996; Halley *et al*., 2004). Thus fractals have the potential to provide a novel way to gain understanding and analyze such natural spatial or temporal phenomenon, which are not smooth but rough and fragmented to self-similarity or self-affinity at all scales. The concept of fractals extends the usual ideas of classical geometry beyond those of point, line, circle, square and so on into realm of irregular disjoint and singular structures (Li, 2000). Therefore, the fractals generally have fractional or non-integer dimensions as opposed to Euclidean objects which can have integer dimensions (e.g., 1 for line, 2 for plane, etc.). Fractal models represent fractal objects in terms of a fractal dimension D, which measures the objects ability to fill the Euclidean space E in which it is embedded (Mandelbrot, 1983, 1997; Halley *et al*., 2004). Fractal analysis techniques are common tools in physics and image process and also being applied in ecology and biology (Kenkel and Walker, 1996).

Cancer is often characterized as chaotic, poorly regulated growth. Not surprisingly, the irregular shapes of cancerous cells, tumors, and vasculature defy description by the classical Euclidean geometry. For instance, it is an established fact that tumor vasculature is more chaotic than the normal vasculature. This constitutes one of the most critical development in cancerous growth, the angiogenesis. One established facts in the study of malignant tumors is that they differ remarkably from one patient to other even though they may be of the same general type (Wheldon, 1988). For the purpose of diagnostics of malignancies the pathologists generally rely on the qualitative and empirical parameters of cells in biopsies or cytological parameters. Tumor growth has been studied in detail and its pathological morphology has been described using Euclidean parameters such as size, diameter and volume but these structures do not fully provide diagnostic results in this manner. However, paying greater attention on the irregular shapes of cancerous growth rather than focusing on diameter or volume of the tumor, the fractal analysis offers a more profitable alternative modeling approach for the development of various types of cancerous growths (Baish and Jain, 2000). Fractal geometric analysis, in particular, the determination of fractal dimensions is amore valid method for quantification and is more likely to provide discrimination between various fractal objects. Thus fractal geometry has great potential utility in the analysis of cancerous tissues (Baish and Jain, 2000) such as the detection and diagnosis of various types of carcinoma (Sedivy and Thurner, 2002; Dey and Rajesh, 2004; Loasa and

Castelli, 2005; Jayalalitha and Uthayakumar, 2009). Spillman (2004) examined the potential of two measures of complexity, fractal dimension and percolation, for use as components of 'disease time' vector that more accurately quantifies disease state. A convenient alternative is to calculate fractal dimensions D which is scale independent. When D approaches 1 it implies that the object in focus is found in patches and is less space filling. Whereas, a D value approaching 2 suggests that the object is space filling and dispersed, such that the overall space is not patchy (Sugihara and May, 1990; Ross, 2005). This paper attempts to analyze the growth of brain cancerous tissue using the fractal technique, by determining the fractal dimensions.

MATERIALS AND METHODS

The images (angiographs) of brain cancer development in a patient were obtained from Kiran Cancer Hospital, Karachi. X-ray pictures were obtained for three different chronological stages. The fractal dimensions were calculated using a grid or box-counting method (Longley and Batty, 1989). Usually the method is employed to measure the fractal dimension of a simple plane curve (Longley and Betty, 1989; Kenkel and Walker, 1996). Nevertheless, the technique can be applied to more complex curves or other structures that do not conform to the relevant property of self-similarity (Peitgen *et al.,* 1992). The dimension derived from box-counting procedure is generally referred to as the fractal dimension describing habitat complexity in ecological literature (Kenkel and Walker, 1996 Halley *et al*., 2004). It involves counting the boxes (grid units or cells) of size δ to cover an object as a function of scale (δ). At the limits it provides an estimate of the Kolmogorov dimension, which is most often equal to (or slightly greater than the number of boxes covering the object in question a regular grid of pixel length δ is superimposed on the object and the number of pixels (N) that occupy the object or its parts are counted. The same procedure is then iterated with increasing values of δ (Peitgen *et al*., 1992; Foroutan-Pour et al., 1999; Falconer, 2003). The following equation describes this relationship:

$$N(\delta) = k\,\delta^{D} \qquad (1 < D < 2)$$

The fractal dimension D can be estimated using the following equation:

$$\text{Log}_e\, N(\delta) = \log_e k - D \log_e \delta + \varepsilon$$

Fractal dimension D can be obtained as the –slope of the straight line (regression line) plotted between $\log_e N(\delta)$ and $\log_e \delta$ which has a negative slope, while ε is the error term. Because varying only slightly the orientation of the grid results in a different value of $N(\delta)$, different placement of the grid at different angels was replicated for a total of 10 times , i.e., 10 replications for each grid unit size δ (Kenkel and Walker, 1996). The method has been shown to be accurate with errors of < 1.5% for objects with known fractal dimensions, and highly reproducible, with a reliability coefficient of 0.972 (95% confidence limits of 0.868-0.987 (Cross et el., 1994). The grids of various sizes δ were produced, the image of each of the cancer stage was superimposed and the boxes intercepted by the cancerous tissue (vasculature) counted for each image. However, the interceptions of the boxes were manually counted. The regression analysis was performed using a program REGRESS developed by one of us (SSS) in C++ which is available on request at a nominal cost.

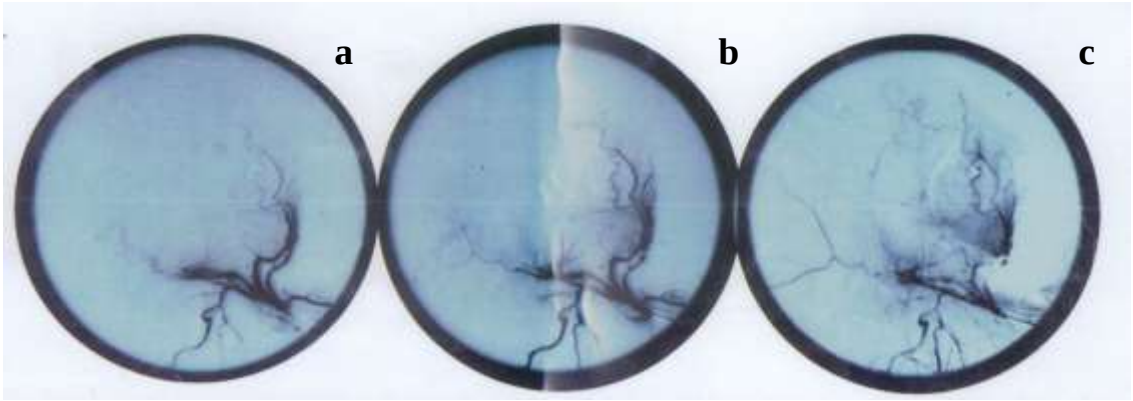
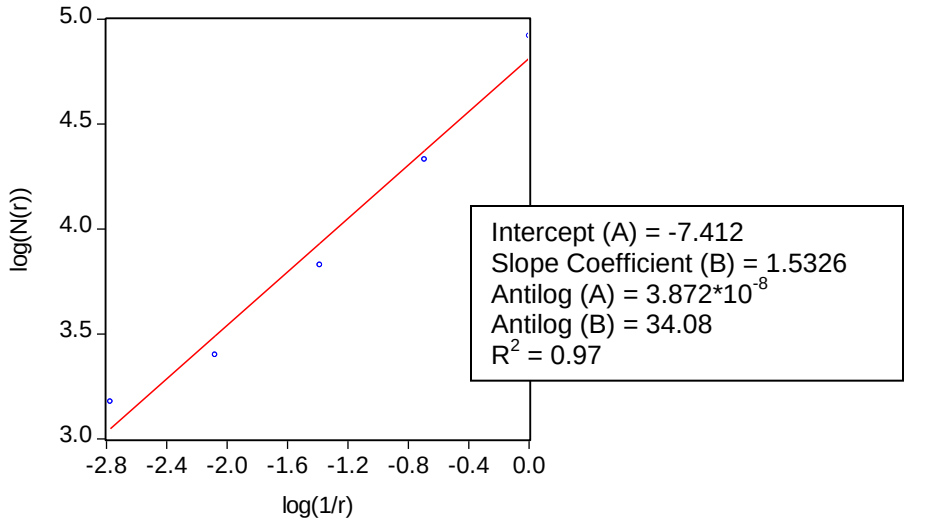
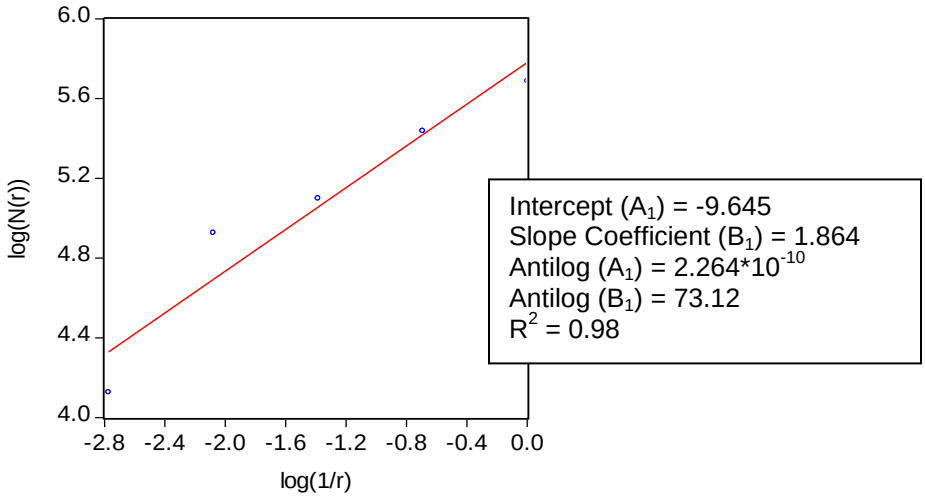


Fig. 1.a, b, c. Three stages of brain cancer showing microvasculature of the cancerous growth. (a) First stage, (b) Second stage and (c) Last stage (available to authors). Courtesy of the surgeons of Kiran Hospital, Karachi.





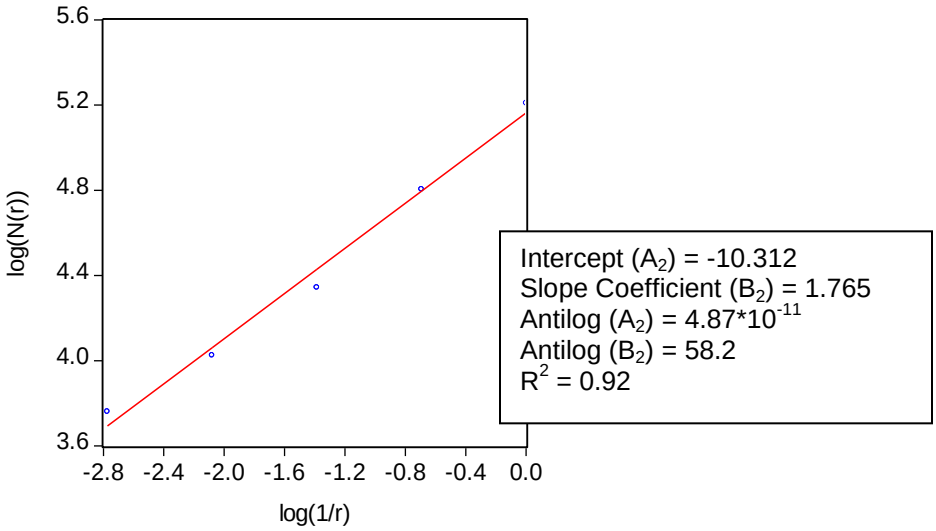


Fig.2a, b, c. The regression graphs of pixel size (δ) against the number of boxes N (δ). The pixel size in the graphs show actual values of δ as r. (a) first stage, (b) second stage and (c) last stage (available).

RESULTS AND DISCUSSION

The images of cancerous growth, in particular the vasculature are given in Fig.1. High density of blood vessels is quite apparent. The normal vasculature (not shown here) generally has low vasculature density. During tumor growth and regression, the vasculature in the tumor has scaling characteristics that reflect the changing state of the tissue. Growing tumors show vascular networks that progressively deviate from their normal pattern, in which they seem to follow diffusion-limited aggregation to a pathological condition in which they display scaling similar to percolation clusters near the percolation threshold (Gazit *et al.,* 1997; Bauer and Mackenzie, 2001). Tumor vessels are tortuous and sinuous, have increased vascular length and diameter compared to normal tissue, shunts, loops, variable intravascular distances, and the whole structure is heterogeneous (Dewhirst, 1993, Bullitt et al., 2007).The key determinants of tumor vascular architecture are local substrate properties rather than gradients of a diffusing substance, such as an angiogenic growth factor (Gazit *et al.,* 1997).

$Log_e(\delta)$ versus the log- number of boxes at size δ, that is $Log_e N(\delta)$ are plotted in Fig.2. All the graphs showed a positive linear relationship. The earliest stage showed the lowest fractal dimension D of 1.6541, the intermediate stage revealed a D value of 1.7016 while the third stage yielded a fractal dimension D of 1.6847. In comparison to the values of fractal dimensions, the value for normal vasculature was 1.520 (image not given). This accords well with the findings of Lin et al., (2008).

Experimental settings with mice have demonstrated that tumors have quite different vascular densities and growth characteristics. Moreover, the fractal dimension of tumor vessels has been calculated as 1.89±0.04 while the normal arteries and veins gave fractal dimension of 1.70±0.03. During tumor regression, the fractal characteristics of the vasculature return to an intermediate between those of growing tumors and those of healthy tissues (Gazit et al., 1995; Baish and Jain, 2000)

This pattern of change in fractal dimension was also observed in the present study. Normal arteriovenous networks display diffusion limited scaling, and normal capillary networks are compact structures. Gazit et al., (1995) suggested the mechanism involved in normal and tumor vascular networks using a growth model. The present study has demonstrated that the fractal dimension of 2D microvasculature networks can not only discriminate between normal versus cancerous tissue but also between various stages of malignancy.

ACKNOWLEDGEMENTS: We are grateful to the doctors and surgeons of Kiran Hospital, Karachi for providing the images (angiographs) of the brain cancer development. Special thanks are due to Prof. Dr. Javed Zaki, Chairman, Department of Botany, University of Karachi for his cooperation and moral support during this work.

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(*Accepted for Publication October 2011*)