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Research Article

Fractal Approaches to Image Analysis in Oncopathology

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Abstract

Fractal analysis is an objective approach that in pathology we have one of the most important fields of application. Here we review and present fractal methodologies at histological level that have been successfully applied to characterize pathological features and able to perform differential diagnosis and prognosis in cancer.

Keywords: Fractal geometry; Fractal analysis; Oncopathology; Differential diagnosis; Prognosis

Introduction

Mandelbrot's concept of fractal geometry [1] is a powerful approach in order to precisely characterize natural structures, structures that follow geometric laws not in common with the classic Euclidean rules.

The term "fractal" is related to highly irregular shapes, with non-integer, or fractional, dimensions, and a property known as self-similarity. Unlike a smooth Euclidean line, a fractal line is irregular or wrinkly, it owns a non-integer dimension: values placed between 1 and 2 observing a 2D image. If we imagine observing this fractal line with the lens of a microscope with increasing power of magnification we look smaller wrinkles that resemble the wrinkles of the larger ones. Further magnification shows yet smaller wrinkles and so on [2].

In a theoretical (mathematical) fractal that behavior is repeated toward the infinite, in a natural fractal this is only true for few scales, at least for two order of magnitude: the object presents subunits that resembles the larger scale structure, maintaining the same, shape, at least statistically, if observed at various magnification: a property named self-similarity, that give us an index called fractal dimension. Fractal dimension may be explained as a statistical index of complexity, able to characterize the space-filling capacity of a pattern [3].

Fractal analysis has become in recent years very powerful to study many phenomena in astrophysics, economics, agriculture as well in biology and medicine.

In biology: Fractal structures are present in a variety of biological structures: the ramifying tracheo-bronchial tree, where the self-similar tracheobronchial tree provides an enormous surface area for exchange of gases at the vascular-alveolar interface, coupling pulmonary and cardiac functions [4], the cardiopulmonary structures, the His-Purkinje network, as well the cardiac muscle bundles and the aortic heart valve leaflets [5,6], or the placenta's arterial tree [7]. The meaning of these fractal structures in the human body is profound. We can recall, for example, the fractal branching of the vasculature that provides a rich network for the distribution of nutrients and oxygen, as well for the collection of metabolic waste products [8].

In medicine: We can recall works regarding bacteriology, human pathology and medical imaging [9-14], as we have also shown [15-20]. It has been affirmed that network structures and scaling laws, developed in quantitative, mathematical, approaches, must to be characterized in medicine to understand health and disease [21].

In particular, fractal analysis is emerging as a powerful tool to perform differential diagnosis and prognosis of the patients in cancer and other malignancies as well to improve the effectiveness and safety of patient care. In effect, today there is a growing emphasis on differential diagnosis tools, in order to apply the best therapy to the patient.

Also in the present "molecular days", imaging is the actual cornerstone: X-rays radiodiagnostics or radiochemical tracers, magnetic resonance imaging, positron-emission tomography (a functional imaging technique, particularly useful to explore the presence of cancer metastasis), and all techniques that are in the pathology lab: microscopies such as light microscopy, performed on biopsy and cytology specimens (by the routine hematoxylin-eosin staining, special staining, and antibody staining) and transmission electron microscopy. Morphometry, the measure of shapes, can be added to every imaging technique in order to obtain objective indexes. In this field, fractal geometry has been applied to histopathology, cytopathology, and other biomedical domains with great success [22-25].

Performing fractal analysis of tissue samples, it's possible to make differential diagnosis between the early stage of tumors and flogosis [15] or among the different types of Basal Cell Cancer, as well as to investigate the subtle alterations of the nuclear patterns in human breast tumors [26] or evaluate brain tumors [27]. Fractal analysis shows a high ability for automatic classification of cancer cells in urinary smears [28] as well as to identify prostate cancer cells [29]. In our hands, fractal analysis has been able to distinguish diagnostic/prognostic classes in the basal cell carcinoma as well in myelodysplastic syndromes [30,31].

In the present paper we present a possible approach to fractal analysis of histological specimen in order to obtain quantitative parameters able to distinguish among diagnostic classes or to perform prognosis in oncopathology.

Fractal Geometry Analysis in Human Oncopathology

To perform computerized image analysis and to obtain morphometric fractal indices, the first challenge is the tissue/cell/

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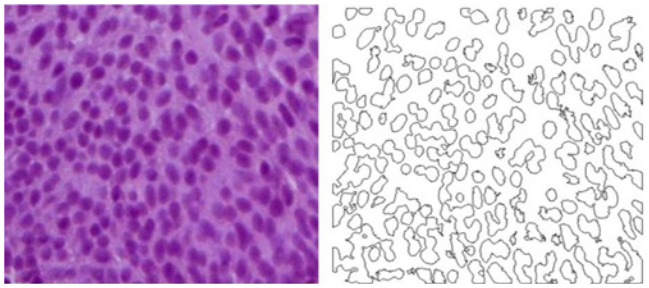

Figure 1: a) Hematoxylin-eosin stained urothelial carcinoma (left); b) Its contours obtained after segmentation (right.); original magnification x 100. JMicroVision software1.2.7 & Image analyzer 1.37.1.

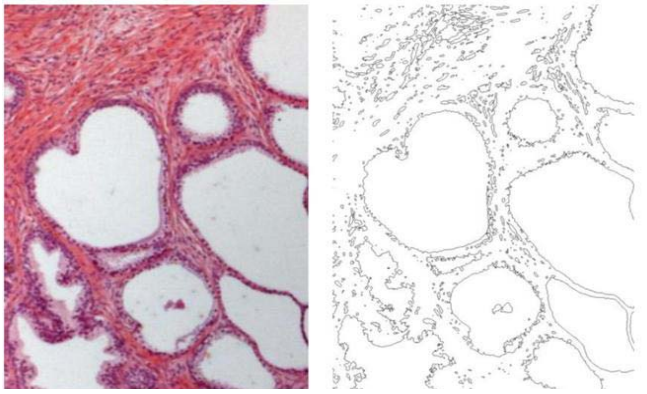

Figure 2: a) Hematoxylin-eosin stained prostate (adenoma) (left); b) Its contours obtained after segmentation (right); original magnification x 40. JMicroVision software1.2.7 & Image analyzer 1.37.1.

nucleus segmentation, to separate noise and biological features. The second step is the feature selection to isolate the tissue, the cells, or the nuclei of interest. The last important challenge is the system of evaluation, e.g. the log-log plot in order to determine the fractal dimension of the skeletonized tissue/cell/nucleus, being the fractal dimension(s) the exponent of a log-log plot, meaning the self-similarity of the biological structure [26].

In a possible approach, images are digitized, while aperture settings and conditions of illumination and magnification are kept constant. Single pixel outlines of the contours of the image are automatically obtained by using grey-level threshold segmentation. X 40 magnification may be suitable to evaluate tissue, X 100 magnification to analyze the distribution of nuclei. Free software like Jmicrovision (https://www.jmicrovision.com/) and Image Analyzer (http://meesoft.logicnet.dk) can be used to obtain the skeletonized images (Figures 1a,b and 2a,b).

Now we can start with the evaluation of the geometric complexity presents in those single-pixel specimen outlines. It may be performed by following the nuclei distribution in the tissue in order to perform a mass dimension technique [25], or by using the box-counting technique over the tissue outlines in order to evaluate the geometric complexity [11,15,19,31] or the entropy [32,33] of the sample.

Mass Dimension, Dm

When calculating the mass dimension, we draw a circle of radius

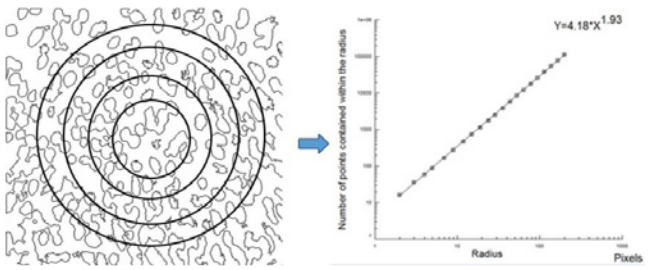

Figure 3: a) Concentric circular regions on the skeletonized images to assess the "mass" within circles in an histological image of urothelial cancer (left, the same of figure. 2a,b) and b) Its log-log plot (right). Mass dimension is the exponent of the logarithmic straight line (radius *vs*. number of points contained within the radius). Benoit 1.3 software.

r on a data set of points (for example, nuclei) distributed in a two-dimensional plane (the skeletonized images), and we count the number of points in the set that are inside the circle, M(r). If there are M points in the whole set, one can define the "mass" m(r) in the circle of radius r, m(r) = M(r)/M. Consider a set of points lying on a smooth line, or uniformly distributed on a plane: the mass within the circle of radius r will be proportional to r and r2 respectively. The mass dimension, Dm, is the exponent of the relationship: m(r) ≈ r Dm.

We measure the mass m(r) in circles of increasing radius starting from the center of the set and plotting the logarithm of m(r) versus the logarithm of r. If the set is fractal, the log-log plot will follow a straight line with a positive slope equal to Dm.

It may be performed by a cheaper software as Benoit 1.3 (http://www.trusoft-international.com/benoit.html). See (Figure 3a,b)

Geometric Complexity, D0

Briefly, the skeletonized image is covered by nets of square boxes, from 1 pixel to 100 pixels wide, for example, and the amount of boxes containing any part of the outline is counted. A log-log graph is plotted on the side length of the square against the number of outline-containing squares. If our image is fractal, a logarithmic linear segment appears: the slope of the linear segment of the graph represents the local fractal dimension of the image (Figure 4a,b). In our example, a prostate adenoma, the log-log plots used to calculate the local fractal dimension of the images shows a log-log line (from 10 to 300 pixels; 1 pixel = 1 micrometer) with high correlation coefficient, always above a value equal or greater than 0.99, thus justifying our fractal approach.

Entropy (Information Dimension, D1)

To evaluate the information (entropy) present in the pattern, information dimension, D1, a robust estimate from a finite amount of data that gives the probability of finding a point in the image, is calculated. Briefly, the set is covered with boxes of linear size, d (as above), but now keeping track of the mass, mi (the amount of pixels) in each box, and the information entropy I (d) is calculated from the summation of the number of points in the i-th box divided by the total number of points in the set multiplied for its logarithm. The slope of the log-log plot of information entropy vs. box side length represented the information dimension of the distribution. The log-log plot used to calculate the information dimensions in a case of

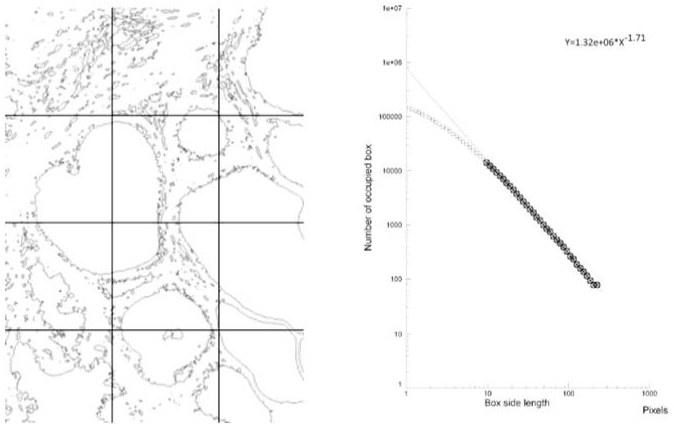

Figure 4: a) Log-log plot of the single-pixels outlines of a prostate histological sample (adenoma) in order to determine its geometric complexity, D0. b) The histological feature is fractal (a straight line is present in the log-log plot: the structure is statistically self-similar), its slope is the fractal dimension at the chosen scales. Benoit 1.3 software.

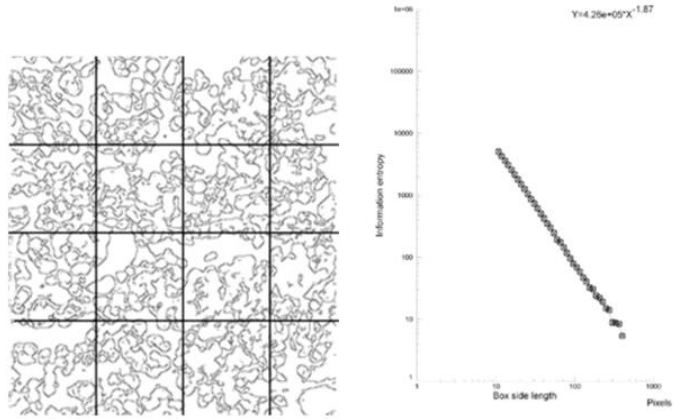

Figure 5: a) Log-log plot (right) of the single-pixels outline (left)s in a case of acute myeloid leukemia in order to determine its entropy, D1. b) The image is fractal (a straight line is present in the log-log plot: the structure is statistically self-similar), its slope is the information dimension at the chosen scales. Benoit 1.3 software.

acute myeloid leukemia shows a line from 10 to 500 pixels with high correlation coefficient, always above a value equal to 0.99 (Figure 5a,b), thus justifying our fractal approach.

Fractal Analysis: Diagnosis and Prognosis in Oncopathology

Fractal dimension gives an objective number that is able to characterize quantitatively a lesion close to a 100% correct classification.

In effect, since many years, neoplasms in organs have been studied by fractal analysis for demonstrating differences between normal, dysplastic and neoplastic cells and tissues [27-31, 33-38], also by X-ray [39-41], estimating angiogenesis [42], evaluating the response of anticancer therapy [43] as well as in order to determine the prognosis of the patient, in the squamous cell carcinomas of the larynx, the first work that used fractal dimension to perform prognosis [44], studying the fractal characteristics of chromatin observed in light and electron microscopy [45], or studying MR images of glioma tissues, being the fractal indexes able to differentiate the malignant grades of that tumor [46], as well in radiomic approaches in order to predict pathological response after chemo-radiotherapy in rectal cancer [47].

Also in our hands, fractal analysis has been very able to distinguish among diagnostic classes linked to prognosis in cancer, studying bioptic samples in mycosis fungoides [15] as well in oral cancer [30] and myelodysplastic syndromes [31].

See below, the ROC curve analysis in normal prostate vs. prostatic cancer ("mild" cancer: Gleason index = 6) in histological images in order to determine sensitivity and specificity of D0: sensitivity and specificity resulted very high (Figure 6 a,b,c).

Discussion

Since one hundred years the pathologist examines under a microscope the histopathological images of bioptic samples removed from patients, and makes judgments based on their personal experience. Pathologists typically assess the change in the distribution of the cells across the tissue under examination and the deviations in the cell structures themselves. However, this judgment is subjective, and often leads to considerable variability, sometimes with low levels of concordance among the pathologists. To improve the reliability of diagnosis, it is important to develop computational tools for quantitative diagnosis that operate on quantitative measures. Such computerized diagnosis facilitates objective mathematical judgment

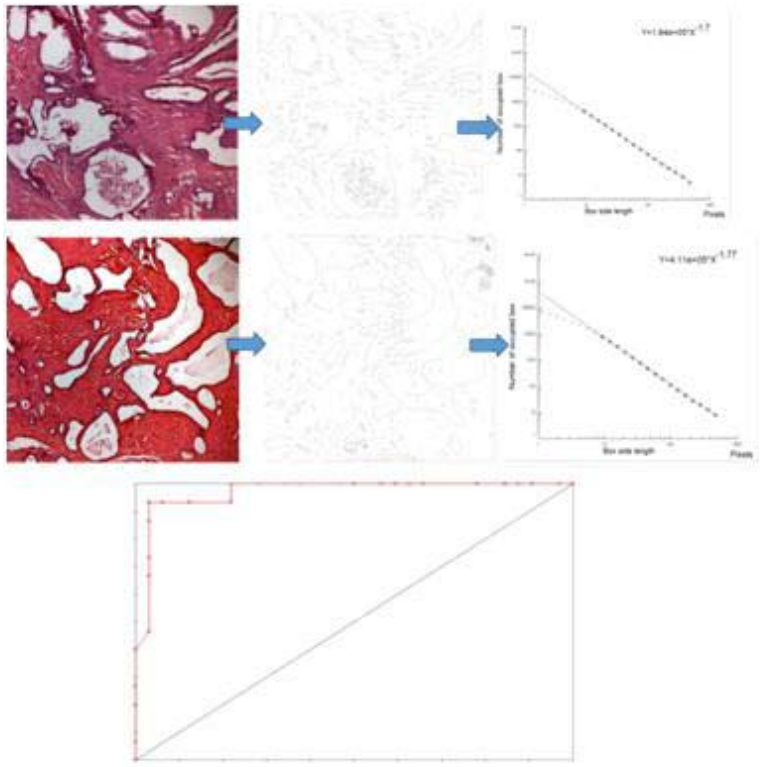

Figure 6: a) Histologic images, theirs single-pixels outlines and b) Their log-log plots(from left to right). c) Healthy prostatic tissue, top; prostatic cancer, Gleason score = 6, below. Bottom: corresponding ROC curve, geometric complexity, D0: prostatic cancer (n=15) *vs*. healthy prostate (n=30), sensitivity = 0.93, specificity = 0.96).

complementary to that of a pathologist, providing objective "numbers". Today, following Mandelbrot's work, nonlinear, fractal, approaches grow in importance. Fractality, the geometric concept related to highly irregular shapes, that originates from simple iterated function with non-integer, or fractional, dimensions and a property known as self-similarity, give to the pathologist a powerful method to support diagnosis and prognosis of the patients.

Nowadays, the role of the fractal indexes to support differential diagnosis and prognosis in oncopathology is undoubtful. If we consider that Evidence-Based Medicine (EBM) is the fundamental element to evaluate the effects of drugs, surgery or other interventions, on health outcomes and that EBM itself requires randomized controlled trials, the need to have quantitative, reproducible, indexes to perform patient diagnosis and prognosis is mandatory: one can be certain that the use of fractal analysis will be a field with a very promising future.

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