FRACTAL ANALYSIS OF NEUROIMAGISTICS. LACUNARITY DEGREE, A PRECIOUS INDICATOR IN THE DETECTION OF ALZHEIMER'S DISEASE

Dragos BORDESCU[1], Maria-Alexandra PAUN[2], Vladimir-Alexandru PAUN[3], Viorel-Puiu PAUN[1*]

The fractal dimension and lacunarity measurements of neuro-images were leveraged to differentiate between benign, biphasic and lacunarity tissue samples. For various benign and malignant subtypes, using the program developed by the authors, the fractal dimension and lacunarity were calculated. The results were categorized and interpreted.

Keywords: fractal analysis, fractal dimension, lacunarity, brain diseases, Alzheimer's

1. Introduction

The healthy human brain contains tens of billions of neurons, specialized cells that process and transmit information via electrical/physical and chemical signals. Most neurons have three basic components: a cell body, multiple dendrites, and an axon, respectively.

The function and survival of neurons depend on several key biological processes. Neurons are a major player in the central nervous system, but other cell types are also key to healthy brain function. In fact, glial cells are by far the most numerous cells in the brain, outnumbering neurons by about 10 to 1. These cells, which come in various forms-such as microglia, astrocytes, and oligodendrocytes-surround and support the function and health of neurons [1].

The healthy brain is well studied, with reference works available to the general public. We will not deal with this in our article. We will study here a serious problem that arises when the brain gets sick, one way or another, and the nature of

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[1] Doctoral School, Faculty of Applied Sciences, University POLITEHNICA of Bucharest, Romania

[2] Department of Engineering, Swiss Federal Institute of Technology, (EPFL), Lausanne, Switzerland

[3] Computer Science and Systems Engineering Department Ecole Nationale Superiore de Techniques Avancées (ENSTA), ParisTech, Paris, France

[4] Physics Department, Faculty of Applied Sciences, University POLITEHNICA of Bucharest, Romania

*corresponding author: e-mail: viorel.paun@physics.pub.ro

the disease must be discovered and healed. And last but not least, whether it is a malign or benign disease, if it is curable with the existing therapeutic means or not, would also be investigated. A question in itself refers to the fact whether we can discriminate if the disease affects only isolated neurons, whole neurons or the brain, in its assemblage. The answer is obtained by the fractal analysis of the images taken on the brain, or the so-called neuroimagistics domain under discussion.

The development of magnetic resonance imaging (MRI) techniques has defined modern neuroimaging. Thereby, since its inception, tens of thousands of studies using techniques such as functional MRI and diffusion weighted imaging have allowed for the non-invasive study of the brain [2].

Fractal analysis is a way of measuring phenomena when the details of design are as important as gross morphology. It has been applied to fields as diverse as music, finance [3], materials technology [4-8], and search and rescue, in addition to topics such as signal processing (EEG/ECG), diagnostic imaging, tumor morphology, vasculature [9, 10] and overall brain structure [11, 12].

In particular, fractal analysis is the method by which we investigate medical images, respectively the MRI images. In this effort to obtain the fractal dimension [13] of the image and the degree of its lacunarity, we can draw firm conclusions about the disease and its stage of development. The disease that is the subject of our research is Alzheimer's disease and its manifestation through the presence of lacunarity, as a measure of its evolution or stagnation so easily evidenced.
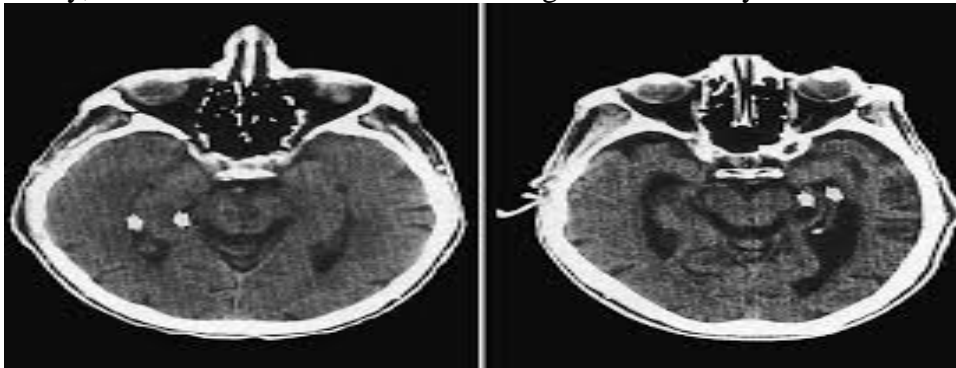

Fig. 1 Brain affected by Alzheimer's disease

As you can see, Alzheimer's appears in the brain images as a lacunar formation. This lacunarity in the brain takes time, and as it grows, leads to the anomalous functioning of the brain, and obviously of the human body.

2. The voxel and parameters of interest

A voxel analogous to a pixel represents image data values, depicted in a 3D space. In the case of medical imaging, the position is represented on the Ox and Oy

axes, while on the Oz it is represented in a gray scale the tissue resistance to the incident radiation. More precisely, the black color is being practically transparent to the radiation while the white color represents the reflectivity level.
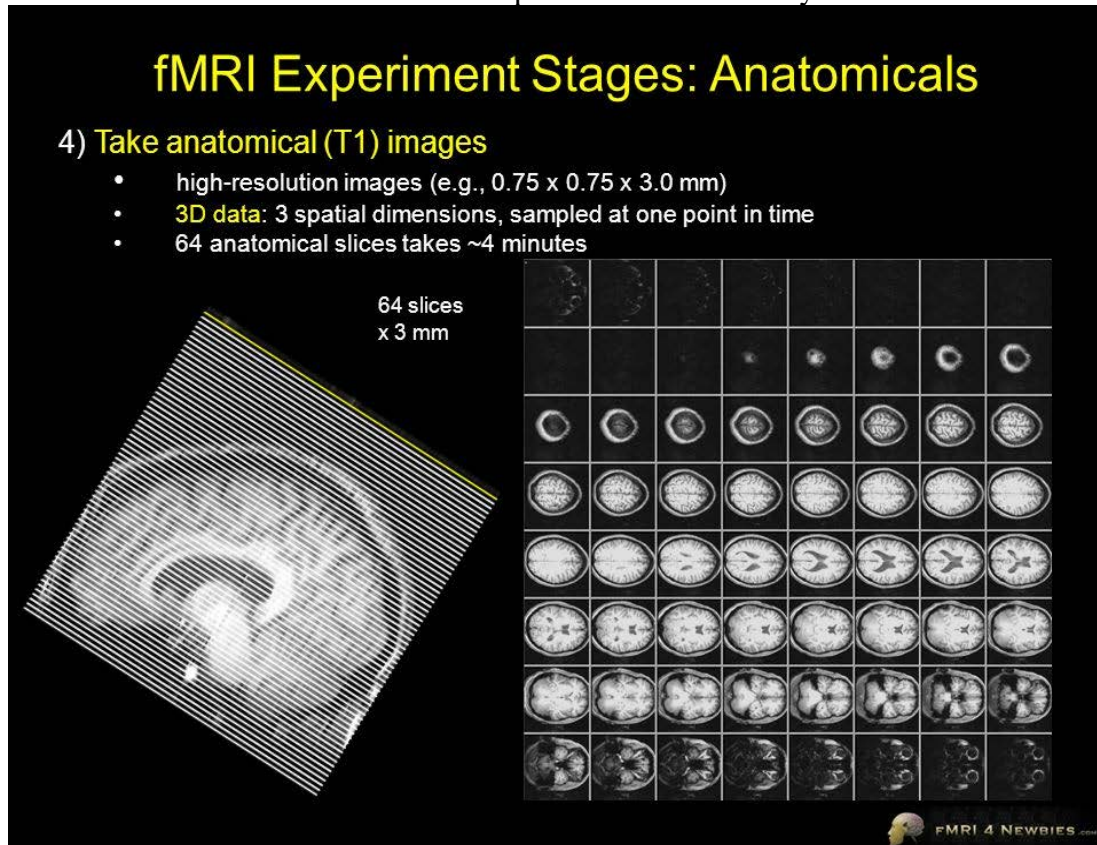

Fig. 2 The fMRI experimental stages. Those 64 anatomical slices take 4 minutes, approximatively

The medical imagining is not a continuous process, requiring a space of a few millimeters in between the scanned areas, in order to keep the image contrast. The smaller the space in between the images, the greater the informational density, but there is also the risk of cross-talk (the tissues previously radiated influence the new scanning area). Therefore, one of the essential parameters is the gap between scans, entitled scan density. To optimize the algorithm we have used the standard voxel size of 512x512x12 (the standard voxel size for MRI).

3. The box counting technique

Several methods to measure fractal dimensions and lacunarity have been used. As is well known, the box counting technique implemented in digital image analysis software is employed with priority [14]. As expected, box counting is a

way of assessing the distributions of background and non-background pixels in binary digital images representing extracted patterns from the real context of the original image.

3.1 The differential box-counting method

The differential box-counting (DBC) method is one of the frequently used techniques to estimate the fractal dimension (FD) of a 2D gray-level image. Undoubtedly, this is a serious development of the classical box counting method, which takes into account the gray scale of the voxels, through the height of the « boxes » which it computes. The parameters introduced are the length, width and height of the boxes, respectively, which are being counted by the algorithm under discussion. Below, we will propose an improved differential box counting method.

In their work from 2014, Y. Liu et al. suggested improved DBC method for computing FD of grey scale image [15]. For this reason authors took into account the difference of boxes where the greatest and least intensity value falls. In this regard they took grey scale image of range $M \times M$ in a three dimensional surface plane, where x and y plane represents the pixel location and third plane called z indicates grey level of an image. Then the entire number of pixels has been scaled down to block of size $l \times l$ where $M/2 \geq l \geq 1$ and l is an integer denoting box size. Afterwards we have to compute $r = l/M$. For every scaled down block, there is a pillar of boxes of size $s \times s \times s'$, where s' represents height of each box, $G/s' = M/s$ and G is the entire amount of grey levels. Let the least and greatest grey levels be denoted by I_{min} and I_{max} respectively in the (i, j)th block. Then the total quantity of boxes essential to cover up in z direction is $n_{r\text{old}}$ and after shifting the δ positions from $n_{r\text{old}}$, $n_{r\text{new}}$ is calculated [16]. Maximum of $n_{r\text{old}}$ and $n_{r\text{new}}$ is taken as n_r. $n_r = \max(n_{r\text{old}}, n_{r\text{new}})$. $n_{r\text{old}}$ or $n_{r\text{new}}$ is calculated as follows:

$$n_r(i, j) = ceil \left(\frac{I_{max} - I_{min}}{s'} \right) \text{ if } I_{max} \neq I_{min} \tag{1}$$

$$n_r(i, j) = 1, \text{otherwise} \tag{2}$$

and N_r will be calculated as

$$N_r = \sum n_r(i, j). \tag{3}$$

The fractal dimension (D_{IDBC}) is calculated with the regression plot between $\log(N)$ versus $\log(1/r)$.

3.2 Measure of Lacunarity

In overlapping or "sliding" box counting, the number of pixels per box is assessed using for each caliber, rather than a fixed grid, a single element that is

systematically moved over the entire image such that the element may overlap with a previous placement at the next placement. The distribution is determined from the number of pixels per box as a function of box size or scale (ε), which is inversely proportional to the box size. Lacunarity at a particular ε is denoted as λ_ε calculated as the squared coefficient of variation, CV, for pixel distribution:

$$\lambda_\varepsilon = (CV)^2 = \left(\frac{\sigma}{\mu}\right)^2 \tag{6}$$

where σ is the standard deviation and μ the mean of the pixels per box at ε [17].

To arrive at a single number, the values for λ_ε can be summarized as the mean $\overline{\lambda}$ for the total number of calibers (E) used:

$$\overline{\lambda} = \frac{\sum \lambda_\varepsilon}{E} \ . \tag{5}$$

A normal limitation of box counting is that the pixel distribution depends on how an image is scanned. For some patterns more than others, placing the non-overlapping box counting grid at different orientations yields different results.

4. The convolutional neural network

The convolutional neural network (CNN) consists of an input layer, an output layer and many hidden layers in between. Convolutional Neural Networks are very similar to ordinary Neural Networks. They are made up of neurons that have learnable weights and biases. Each neuron receives some inputs, performs a dot product and optionally follows it with a non-linearity. The whole network still expresses a single differentiable score function: from the raw image pixels on one end to class scores at the other. In addition, they still have a loss function (e.g. SVM/Softmax) on the last (fully-connected) layer and all the tips/tricks developed for learning regular Neural Networks still apply [18].

- The **Convolution** passes the images through a set of convolutional filters which are being activated as function of some image particularities.
- The **Rectified linear unit (ReLU)** allows the training of the neural network in a more rapid and efficient way, by assigning all negative values to 0 and keeping the positive values. ReLU stands for rectified linear unit, and is a type of activation function. Mathematically, it is defined as *y=max(0, x)*. ReLU is the most commonly used activation function in neural networks, especially in CNNs. If you are unsure what activation function to use in your network, ReLU is usually a good first choice. This process is also called activation, for only the activated characteristics, which are being sent to the next layer.
- **Pooling** simplifies the output through the reduction of the number of parameters necessary for the learning of the network, by using a nonlinear

down sampling process. It is common to periodically insert a Pooling layer in-between successive Conv layers in a ConvNet architecture. Its function is to progressively reduce the spatial size of the representation to reduce the amount of parameters and computation in the network, and hence to also control overfitting. The Pooling Layer operates independently on every depth slice of the input and resizes it spatially, using the MAX operation. The most common form is a pooling layer with filters of size 2x2 applied with a stride of 2 down samples every depth slice in the input by 2 along both width and height, discarding 75% of the activations. Every MAX operation would in this case be taking a max over 4 numbers (little 2x2 region in some depth slice).

5. Algorithm of the fractal dimension and lacunarity degree determination

The input of the program is a set of medical images taken in 3 mm slices with a voxel of standard 512x512x12 size. The first step for diagnostic determination is the image processing through the differentiable box counting method (determination of the image fractal dimension as well as the lacunarity degree).

Once we have obtained a value for the image lacunarity, it is important to also see the diffusion/ clustering degree of the lacunar structure. Due to the fact that mathematically speaking the lacunarity is rotation variant, the box counting algorithms to obtain the image lacunarity as well as the diffusion/clustering degree of the lacunarity are ran 4 times with a 90 degrees offset between iterations. The obtained values are averaged to avoid the spikes.

After obtaining the diffusion/clustering degree of the lacunarity, we will isolate the lacunar structure in order to determine its self-standing fractal characteristics (we treat the lacunar structure as a fractal). This step practically allows us for subsequent refinement of the neural network classification process, the isolation allowing for a more rigorous comparison between the lacunar structure and other similar structures sampled from clearly diagnosed Alzheimer patients.

After the comparison of the lacunar structure to the database and the determination whether a similar structure has been generated in a patient carrying Alzheimer's disease, the data determined from the isolated lacunar structure is added to the data coming from the initial image.

With all the imaging data obtained, the lacunarity degree, the lacunarity diffusion/clustering as well as the fractal characteristics of the lacunar structure itself, the data is then taken by a convolutional neural network for final classification.

Functionally the algorithm starts with an MRI image and does a contour feature extraction. Then using the scale invariant property of the images fractal dimension, we can easily estimate to a certain degree the inner structures of the brain, after some more image processing. This allows us to detect lacunar structures that would normally be hard to detect by eyesight alone. As you can see even with contour feature extraction alone, the differences between the patients and the control subjects are more easily visible.
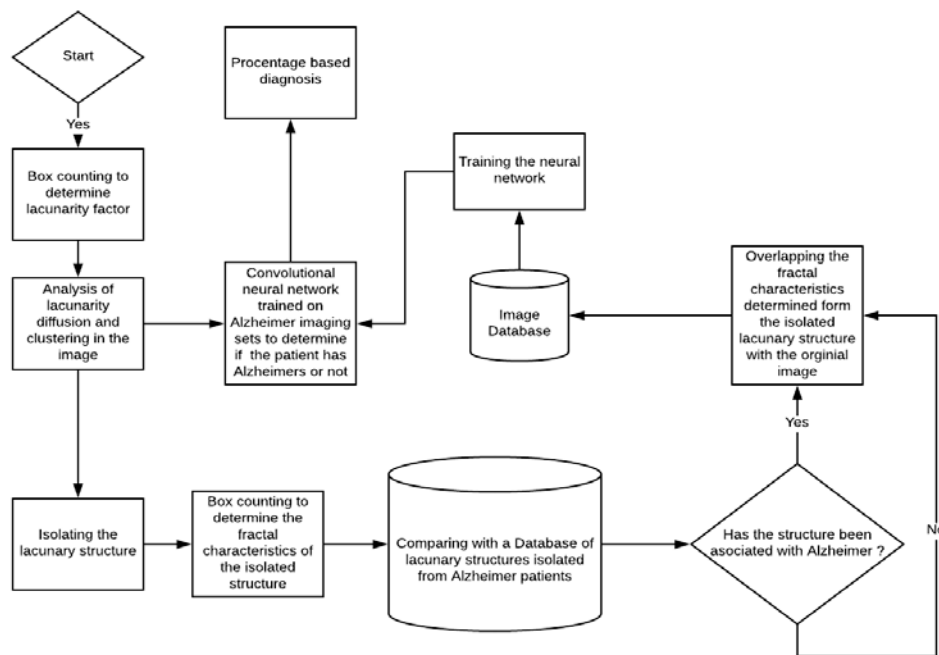

Fig. 3 Block schematic of the algorithm used to detect structures associated to Alzheimer disease

In Fig. 3 we present the block diagram of the algorithm used to detect structures associated to Alzheimer's disease, estimating the fractal dimension and the lacunarity, according to the program developed below.

Excerpt from the program we have developed
Start
Load image   // input the image
M = image.height ,N = image.width;
 s = 2; //the origin size of box
While(s ≤ M/2)
If (s < 13||M/s == 0) r = s/M; //define the r , r is the scale
For(i < M/s;j < N/s) nr(i, j) = (CMA × pa − CMI × pi)/s × s

Shift block in (x, y) plane with σ pixels nr(i, j) = max(nr old, nr shift)
End For
End If
 Nr old = P(nr);
 s + +;
Fit(log Nr, log(1/r)) //the least square method
Obtain FD ;
Lacunarity =((Fit(log Nr, log(1/r)))/ (mean(s,g)))^2; // g is the possile
lacunarity   orientations within the box of size s
Plot(Lacunarity)= Lacunarity + 1;
Load Plot(Lacunarity)   // input the image
M = image.height ,N = image.width;
 s = 2; //the origin size of box
While(s ≤ M/2)
If (s < 13||M/s == 0) r = s/M; //define the r , r is the scale
For(i < M/s;j < N/s) nr(i, j) = (CMA × pa − CMI × pi)/s × s
Shift block in (x, y) plane with σ pixels nr(i, j) = max(nr old, nr shift)
End For
End If
 Nr old = P(nr);
 s + +;
Fit(log Nr, log(1/r)) //the least square method
Obtain FD ;
End;

6. Results and Discussion

Lacunarity is another measurement often used in conjunction with fractal dimension to describe the texture of a shape or fractal [20, 21]. In this study fractal dimension and lacunarity measurements were leveraged to differentiate between benign and malignant tissues and to classify the different brain morphologies exhibited by formatted cell lines**.**

For various benign and malignant subtypes, the fractal dimension (Fig.4) and lacunarity (Fig. 5) of benign, biphasic and lacunarity tumor samples were calculated using the program described above.

We have considered the normal physiological brain zone as the benign area, the complete mixed zone as the biphasic area, and the tumor itself as the lacunarity area respectively, with a small margin taken from the rest of the tissue.

In the figures below, unique fractal evaluation and connected implications of brain morphology in malignant tissue are shown.
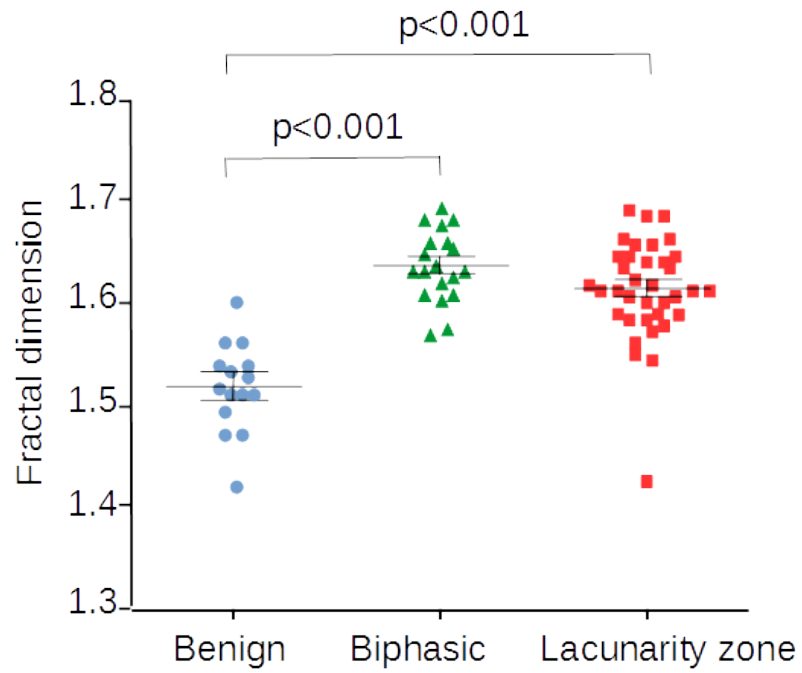
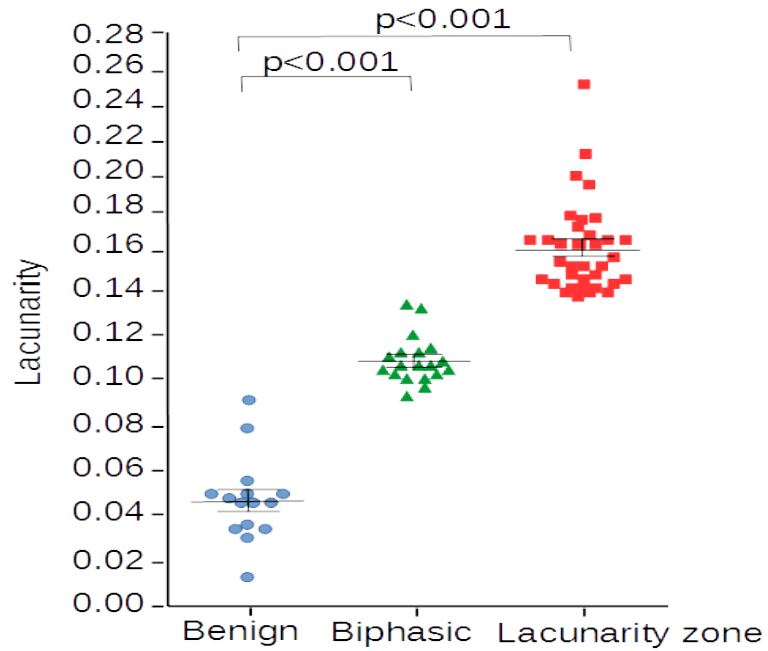Fig. 4 Fractal dimension for benign, biphasic and lacunarity tissues

Fig. 5 Lacunarity for benign, biphasic and lacunarity tissues

Due to some missing or damaged samples the resulting number of images analyzed was 36 with lacunarity, 19 biphasic and 15 benign controls. As shown in Fig. 4 and Fig. 5, biphasic and lacunarity tissue samples had significantly higher fractal dimension and higher lacunarity compared to benign tissue ($p < 0.0001$).

A low p-value (such as 0.01) is taken as evidence that the null hypothesis can be 'rejected'. Statisticians say that a p-value of 0.01 is 'highly significant' or say that 'the data is significant at the 0.01 level'.

Although the difference between biphasic and lacunarity tissue was not found to be statistically significant, lacunarity tissue tended to have a comparable fractal dimension, but it encountered higher lacunarity of lacunarity tissue than biphasic tissue. These results suggest that fractal dimension and lacunarity analysis may be a useful and rapid method to differentiate between benign and malignant tissues.

7. Conclusions and future work

In this paper, the brain radiographies were analyzed to find out the fractal dimension and lacunarity of benign, biphasic and lacunarity tumor samples. For this purpose, the radiographies were processed in the manner presented in a previous chapter of present work, to remove the noise and just keep the formatted cell lines. Then, the neuro-image was transformed into binary format and the differential box-counting (DBC) method was applied to reach the results.

The algorithm used to detect structures associated to Alzheimer's disease, estimating the fractal dimension and the lacunarity, has been developed by the authors.

Between the biphasic and lacunarity tissues a statistically significant difference was not found, as lacunarity tissue tended to have a comparable fractal dimension, but it encountered higher lacunarity of lacunarity tissue than biphasic tissue. These results suggest that fractal dimension and lacunarity analysis may be a useful and rapid method to differentiate between benign and malignant tissues.

Therefore, both fractal dimension and lacunarity demonstrated high accuracy as predictors of benign and malignant tumor and to classify the different brain morphologies.

The software developed in this paper can be fully integrated into a medical equipment, which can be used in detection and monitoring of brain diseases or other organs.

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