Fractal analysis of neuroimaging: comparison between control patients and patients with the presence of Alzheimer’s disease

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Abstract. Alzheimer’s disease is a neurodegenerative cognitive, affective, and behavioral disorder aligned to the aging process and other coronary diseases. To contribute to the early diagnosis of the disease, a neuroimaging treatment is implemented through a preprocessing to subsequently calculate the fractal dimension associated with these images in order to propose an alternative to the one proposed in medical physics through positron emission tomography. In this work, a comparative analysis is made of a previous work using the Box Counting methodology versus the calculation of the fractal dimension by means of software developed by the researchers based on the same method. The differences between the fractal dimensions of the neuroimages of control patients and patients with the presence of the disease are maintained showing a lower value of fractal dimension in patients with the disease due to the physical deterioration of the brain.

1. Introduction
Dementia is a syndrome characterized by cognitive impairment that generates a gradual loss that affects the overall functioning of the person and involves behavioral and psychological symptoms [1]. However, one of the most prevalent dementias is Alzheimer’s disease (AD), a neurocognitive disorder that causes a progressive and degenerative deterioration that affects between 60% and 70% of cases with a diagnosis of dementia, which is one of the main consequences of disability in older adults worldwide [2].

Currently, the alterations found as a result of the disease are varied, for example, alterations in semantic memory, which do not necessarily occur in the early stages [3-6], but even to more advanced stages (moderate and severe phases), this being one of the typical alterations of AD [7]; other alterations found are those mentioned by Muñoz, et al. [8] who explored and found alterations in attentional functions, memory, visuospatial aspects, arithmetic skills and alterations directly related to genetic functioning in people with AD. The tools oriented to the diagnosis of Alzheimer’s disease are mainly focused on medical follow-up and diagnostic tests to know the general health status of the older adult.

In addition, neuropsychological tests are performed to measure cognitive function through standardized and endorsed instruments such as mini-mental, Montreal cognitive assessment (MoCA), among others. On the other hand, using neuroimaging it is possible to analyze the presence of the disease, since this type of imaging shows a structural representation of the brain by means of computed tomography (CT) or magnetic resonance imaging (MRI), which allows observing the deterioration of the brain in patients with the presence of the disease. These kinds of examinations allow the exclusion of other brain diseases and help to establish the subtype diagnosis unless clinical judgment indicates...
ineffectiveness [9]. Updates in the tools implemented for diagnosis reflect current advances or developments [10]. *i.e.*, more reliable diagnoses are provided as new theories and computational developments are implemented.

From the above, the relationship between neuroimaging analysis and neuropsychological assessment becomes indispensable, as the latter determines cognitive impairment by implementing fast, sensitive, and easy-to-apply tools [11,12]. Despite these evaluation tools, Alzheimer’s disease and its understanding continues without a detailed characterization or identification, since some mechanisms involved are recognized, but there are no prevention, treatment, or diagnosis programs with standardized and exclusive criteria for this disease [13]. Alzheimer’s disease has been classified over time as a purely clinical diagnostic disease, due to the difficulty of specialized tests to identify the disease in its early stages, and no specific and standardized criteria for its exact diagnosis or exclusively oriented to this disease have been established [14].

Currently, one of the most widely used tools to establish a possible diagnosis of Alzheimer’s disease is structural neuroimaging, which focuses especially on the hippocampus and its volume [15]. Within neuroimaging, magnetic resonance imaging is indispensable for filtering and establishing diagnoses, since neuroimaging makes it possible to identify the causes of symptomatology possibly linked to Alzheimer’s disease or dementias, which, when subjected to protocols based on detailed brain imaging, are ruled out by other medical diagnoses [16].

The results in neuroimaging are of importance for diagnosis, since they allow detecting brain changes, and generating predictions as in the case of patients with mild cognitive impairment showing a high probability of developing Alzheimer’s disease, establishing precedents focused on providing relevant information for the classification of the progression of dementias and their development over time [17].

Medical physics has developed research that has made significant contributions to the early detection of Alzheimer’s. One of these recent contributions has been the development of positron emission tomography (PET). This technique determines the distribution of the radioligands used, which makes it possible to obtain structural and kinetic information about the molecule being analyzed [18], *i.e.*, it makes it possible to evaluate different neurotransmission pathways, inflammatory and metabolic changes at the cerebral level [19]. In addition to the above, PET has a greater technical capacity with respect to the quantification of cerebral blood flow and neurotransmitter receptor density [20].

Nowadays, in the field of Alzheimer’s disease analysis, research is focused on the use of brain imaging with technological development, which has allowed detection and monitoring based on neuroanatomy, focusing on structures, tissues, or regions, which not only allow visualization, but also become statistical inputs to be analyzed [21].

The new diagnostic trends demand methodologies channeled in the development of technological tools. One of the most widely used tools is MATLAB® [22], with which it has been possible to develop software [16] that performs an anatomical cortical and subcortical reconstruction of each participant in certain regions [23] from data processing. Then scientific research has been favored with the emergence of new technologies and their implementation in the diagnosis and treatment of diseases as well as psychiatric disorders, but in general neuroimaging allows to understand new knowledge and implement them in the clinical aspect [24].

Therefore, there is an increasing need to develop differential criteria for Alzheimer’s disease based on evidence and neuroimaging findings, based on specific techniques such as those based on mathematical models of fractal geometry that provide the expansion of knowledge in diagnosis and early identification to contribute to the improvement of quality of life [25,26].

The main objective of this study is to show a computational tool, built by the researchers, based on the Box Counting methodology, which allows relating the fractal dimension (FD) with the neurocognitive disorder in magnetic resonance images or neuroimaging. A comparison is made with data from a database endorsed by Massachusetts Institute of Technology (MIT) to observe the reliability of the software and to propose additional features that can help to improve the tool to contribute significantly to the members of the health sector in the early diagnosis of this disease.
2. Mathematical method

The present study presents a quantitative approach with a non-experimental cross-sectional design and a descriptive comparative scope with double-blind analysis. There are different computational methods with which it is possible to calculate the fractal dimension associated with an image or a signal. To obtain the fractal dimension, different procedures have been implemented, however, the method Box Counting or entropy of Kolmogorov, is the most used technique to calculate the fractal dimension of certain objects that are represented in a plane, thanks to its ease of mathematical calculation and empirical estimation [27].

Since neuroimages or magnetic resonance images can be obtained in 2D, it is possible to calculate the fractal dimension by means of an application developed within the research project which seeks to obtain the fractal dimension as an additional feature in a learning machine whose objective is to determine whether Alzheimer’s disease is present in a patient.

Due to the self-similarity, a property presents in fractals, the Box Counting methodology exposes the importance of analyzing images from the relationship between the variable-length grid, which covers the chosen image, and the number of boxes that contain said image. The Box Counting method is based on the slope of the linear fit between the number of boxes containing the image and the size of the grid that satisfies the Equation (1).

\[
D = \frac{\ln(N)}{\ln(k)}
\]

where, \(N\) is the number finite subfigures, \(k\) is congruent with the numerical value \(r = 1/k\), and \(r\) is a shrinkage factor. The iteration is observed as the number of boxes, of equal length, in the grid that cover the image, increases as the length of the boxes decreases. By repeating this process as the length decreases, more boxes will be needed to cover the image.

Finally, the limit is calculated when the length of the boxes tends to zero of the quotients between the natural logarithm of the number of boxes over the natural logarithm of the reciprocal of length [28]. This limit value matches the fractal dimension. To perform the analysis, a data of images found in [23] will be available.

In this paper, regarding the preprocessing of the neuroimages, initially a segmentation procedure is performed using FreeSurfer software [29] to estimate the cortical ribbons automatically, then a motion correction is performed together with an intensity normalization to finally remove atypical voxels. Then, a segmentation of the gray matter from the white matter is performed by means of intensity difference and difference between the geometrical structure between the union of both.

The surface is generated by means of an outward deformation, between the surface of both matters, with a second order smoothness constraint, whereby applying this constraint it was possible to avoid ambiguity between certain areas.

Regarding the methodology used in the project, with respect to neuroimaging, this is divided into two stages of preprocessing based on the method of Edge Detection and morphology. For the first part of the preprocessing the black and white image is inverted, then the edges of the image are estimated by means of the Canny method [30] which uses a multi-step algorithm to find a range width of the edge of an image.

Subsequently, the image is dilated with a diamond kernel, to finally make a small filling of the image so far. In the second part of the preprocessing, the above mentioned is repeated adding then a binary operator, OR, between the image and its inverse so that only the part of the brain remains for the estimation of the fractal dimension, a small smoothing is applied by means of an erosion. For the estimation of the fractal dimension, the image is divided into each of the grids.

The image being binary, its pixels have only ones and zeros. In this way each pixel of the box is traversed looking for the presence of those two-pixel values, if there is a difference, the edge of the image is found, and the box is counted. The process is repeated depending on each grid, thus obtaining the fractal dimension.
3. Results and discussion
By using the software, it was possible to compare the fractal dimensions of the Axial 2-slice MRI images of the 15 patients without the presence of the disease and the 9 with the presence of the disease; the data obtained by using the software and those shown in [23] (FD paper) (Table 1). Table 1 shows the gender, age, and fractal dimensions of 15 patients with and without the presence of Alzheimer’s disease. The fourth and ninth column show the data analyzed in article [23] and in the fifth and tenth column the data obtained with the implementation of the software. In this case, there are 7 men and 8 women with a mean age of 75 years for control patients and 76 years for patients with the disease.

The average fractal dimension of the reference article is 1.639 with a standard deviation of 0.02 in the control patients and an average of the fractal dimension evidenced in the work is 1.618 with a standard deviation of 0.018. On the other hand, the fractal dimension obtained with the software under construction is 1.430 with a standard deviation of 0.18 in control patients and a fractal dimension of 1.424 with a standard deviation of 0.075 for patients with the disease.

An outlier was found in Table 1, which was analyzed by reducing the dimension of the grid, however, the data is still less than 1, this due to the number of cuts taken for patient 131_S_1301. Table 1 shows a significant difference in the calculation of the fractal dimension that may be associated with the image preprocessing method. However, it is possible to show that the fractal dimension of the neuroimaging of control patients was greater than that of the neuroimaging of patients with the presence of the disease.

The use of the methods with which neuroimaging is generated is a determining factor in calculating the fractal dimension. Through the magnetic field and radio waves, magnetic resonance imaging is a minimally invasive method in the delivery of radioactive material since PET could better identify changes at the cellular level and therefore an image with greater reliability. Being able to relate the fractal dimension to the images produced by either of these two methods constitutes a great contribution to medical physics, in the strict sense of providing useful elements for the diagnosis of any disease, particularly Alzheimer’s.

### Table 1. Results of fractal analysis patients control and patient with Alzheimer.

| Patient control | Gender | Age  | FD Paper | FD software | Patient with Alzheimer | Gender | Age  | FD Paper | FD software |
|-----------------|--------|------|----------|-------------|------------------------|--------|------|----------|-------------|
| 141_S_1094      | M      | 76   | 1.632    | 1.548       | 009_S_1354             | F      | 59   | 1.599    | 1.321       |
| 131_S_1301      | F      | 72   | 1.596    | 0.846       | 012_S_0689             | M      | 64   | 1.627    | 1.427       |
| 002_S_1261      | F      | 71   | 1.637    | 1.547       | 011_S_0053             | M      | 80   | 1.609    | 1.409       |
| 002_S_1280      | F      | 70   | 1.632    | 1.460       | 011_S_0183             | F      | 73   | 1.621    | 1.281       |
| 002_S_0413      | F      | 76   | 1.667    | 1.483       | 002_S_0938             | F      | 82   | 1.64     | 1.409       |
| 002_S_0295      | M      | 84   | 1.645    | 1.464       | 002_S_0619             | M      | 78   | 1.633    | 1.490       |
| 002_S_0559      | M      | 79   | 1.651    | 1.291       | 011_S_0003             | M      | 81   | 1.607    | 1.451       |
| 002_S_0685      | F      | 89   | 1.597    | 1.435       | 005_S_0221             | M      | 68   | 1.596    | 1.474       |
| 003_S_0907      | F      | 88   | 1.635    | 1.613       | 012_S_0720             | F      | 78   | 1.612    | 1.375       |
| 003_S_0931      | F      | 86   | 1.617    | 1.564       | 002_S_0955             | F      | 78   | 1.605    | 1.386       |
| 003_S_0981      | F      | 84   | 1.624    | 1.519       | 002_S_1070             | M      | 74   | 1.593    | 1.494       |
| 011_S_0016      | M      | 66   | 1.654    | 1.325       | 007_S_0316             | M      | 82   | 1.642    | 1.486       |
| 011_S_0022      | M      | 63   | 1.65     | 1.372       | 006_S_0653             | F      | 74   | 1.621    | 1.515       |
| 020_S_1288      | M      | 60   | 1.675    | 1.404       | 007_S_1339             | F      | 80   | 1.614    | 1.476       |
| 073_S_0089      | M      | 65   | 1.679    | 1.504       | 027_S_0404             | F      | 89   | 1.656    | 1.324       |

4. Conclusions
From the results obtained, it is possible to show that the value of the fractal dimension of the people with the presence of the disease is lower than that of the people in the control group. Regarding the implementation of the software that has been developed, the difference between the fractal dimensions of patients with the disease and those belonging to the control group is observed in the same way.
However, it is necessary to improve the image preprocessing stage to obtain the closest values to those presented in the guide document and to include a new indicator in the software that allows a more evident differentiation at the time of comparison. The methods used for the generation of neuroimaging, such as nuclear magnetic resonance, from a magnetic field, and recently positron emission tomography, using small amounts of radioactive material, generate images that allow detecting early manifestations of any disease.

However, it is necessary that there are alternative methods that allow the correlation of the images with the disease under study and thus achieve a more reliable diagnosis. Similarly, it is considered appropriate to implement learning machines to further guarantee the reliability of the results from the images.

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