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SERVICES FOR SCIENCE AND EDUCATION

Characterization of Alzheimer's Disease Development Using Complexity Index

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ABSTRACT

Human brain is the most dynamic and varied system of the body. The brain is composed of neuron and glia. But how do they interact to generate emergent properties like memory, learning, emotion and sleep is little understood. Many such complex systems that exist in non-linear dynamics are characterized by the fractal nature. The fractal dimension (FD) is a quantitative parameter that has been extensively used to analyse the complexity of structural and functional patterns of the human brain. The fractal dimension (FD) of the human brain quantifies the inherent complexity. Evidences strongly suggest that fractal properties of a biologic system might be related to entropy and metabolism. In several pathologies of the brain such as Alzheimer's, Epilepsy and Stroke, fractal dimension (FD) is altered. FD in combination with other features is emerging as a powerful diagnostic approach at the hands of a clinician. Alzheimer disease (AD) is a progressive neurodegenerative disease that destroys memory and cognitive skills. Aging is the biggest risk factor for AD. The central quest of research on AD is to identify the steps in its pathogenesis that, if inhibited, would slow or prevent the disease. All AD patients develop neuritic plaques in brain areas subserving memory and cognition. These plaques consist of extracellular masses of Aβ filaments intimately associated with dystrophic dendrites and axons, activated microglia, and reactive astrocytes. In this study we are focused to understand the changes in fractal properties (FD) of human brain as a whole in glioma during the states of AD. Our primary goal is to investigate FD to assess whether it can discriminate between different states of AD. According to our results, the fractal dimension decreases with developing Alzheimer disease (AD).

INTRODUCTION

Alzheimer disease (AD) is a progressive neurodegenerative disease that destroys memory and cognitive skills (see Figure 1). Aging is the biggest risk factor for AD. The central quest of research on AD is to identify the steps in its pathogenesis that, if inhibited, would slow or prevent the disease. All AD patients develop neuritic plaques in brain areas subserving memory and cognition. These plaques consist of extracellular masses of Aβ filaments intimately associated with dystrophic dendrites and axons, activated microglia, and reactive astrocytes.
Many researchers have put great efforts into this field of fractal geometry, and many methods for estimating fractal dimensions of certain objects have been proposed since the establishment of fractal geometry theory. We talk about the fractals if all the occupied squares of equal size at any stage have the same amount of mass. It is in this sense we say that the mass is evenly distributed [1–3]. However, in the case of a cut and paste model the mass is not distributed evenly rather it is distributed unevenly. Therefore, the fractal dimension of the object

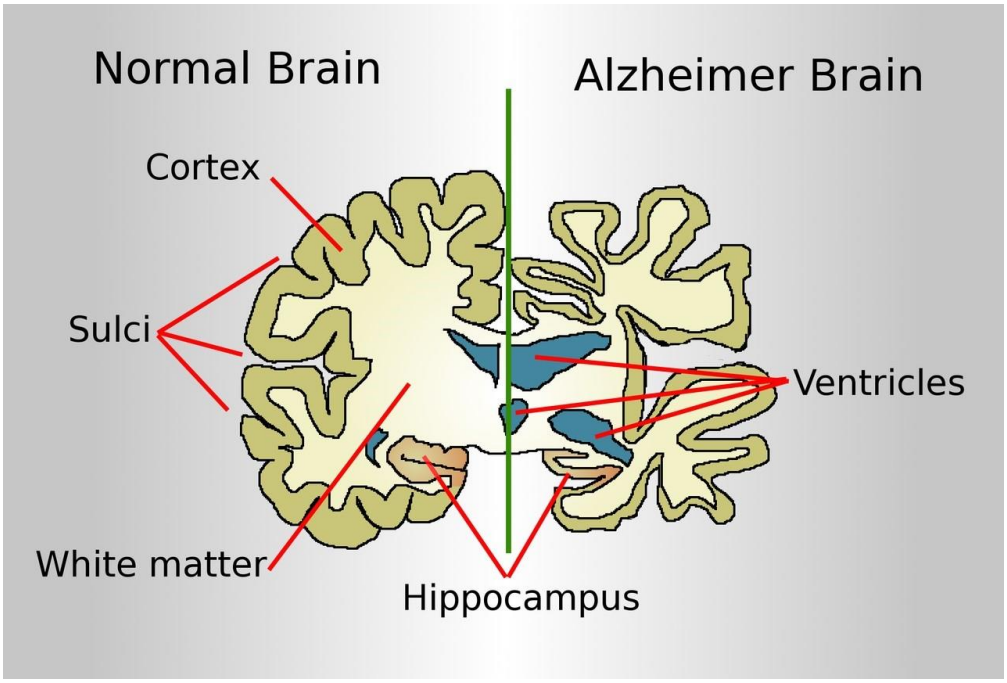


Figure 1: Diagram of a normal brain compared to the brain of a person with Alzheimer's (Wikipedia).

will still be the same even if the content is diluted to change the density of the content and then distributed throughout the space exactly in the same way as before revealing that it tells us nothing about the distribution of the content. There are situations in which physical quantities are unevenly distributed over the space. That is, the distribution may not be homogeneous and instead heterogeneous in the sense that the density of the content over the occupied regions only are different. We therefore have to invoke the idea of multifractality which tells us about the uneven or heterogeneous distribution of the content on a geometric support. The dimension of the support may itself be a fractal or not [3–6].

MATHEMATICAL PLAYGROUND

A "measure" is a mathematical way of identifying a given set with a numerical value, so that, if we divide the set into a countable number of smaller parts, the measure of all smaller sets sum up to the measure of the whole set.

Definition 2.1 (External measure). Let X by a set and P(X) be the set of all subsets of X. The External measure is a function of the form μ: P(X) → [0, +∞) that satisfies:

1. $\mu(\emptyset) = 0$.
2. $\mu(A) \leq \mu(B), \quad A \subseteq B \subseteq X$.
3. $(\mu(\bigcup_{i=1}^{\infty} A_i \leq \Sigma_{i=1}^{\infty} \mu(A_i)$ if $A_i \subset X, \quad i = 1..., N$.

Definition 2.2 (σ-algebra). A family A, of subsets of X, is called a σ-algebra, if it satisfies:

1. $\emptyset \in A$.
2. If $E \in A$, then $E^c \in A$.
3. If $E_i \in A$, $i \in \mathbb{N}$, then $\bigcup_{i=1}^{\infty} E_i \in A$

Definition 2.3 (measure). Let A be a σ-algebra. Then any function $\mu^*: A \to [0, \infty)$ that satisfies:

1. $\mu^*(\emptyset) = 0$.
2. $\mu^*(\cup_{i=1}^{\infty} E_i) = \Sigma_{i=1}^{\infty} \mu^*(E_i)$, if $Ei \in A$ and $Ei \cap Ej = \emptyset, i \neq j$.

is called a measure.

Remark 1.

1. Using the Lebesgue measure, we measure volumes using unit-cubes of $\mathbb{R}^{\mathbf{k}}$. In particular, to measure the volume of any given set in $\mathbb{R}^{\mathbf{k}}$, we cover the set with parallelepipeds in the cheapest way possible.
2. In order to do so, we need a system of coordinates in a finite vector space. The Lebesgue measure works well for the typical sets of classical geometry, which are usually convex, and at the same time it provides information about their dimension.
3. In the case of more complex sets, such as the Cantor set and the Sierpinski triangle, Lebesgue measure gives only a rough estimate1. We may view this as measuring the weight of an object using a balance scale. If we have standard masses of 1 kilo only, it is hard to distinguish a soccer ball from a table tennis ball.

This is the motivation underlying the introduction of the more specific Hausdorff measure, which can be used to measure fractal sets, as well as sets the lie in more general spaces.

Remark 2.

1. The measuring unit in the Hausdorff measure is the volume of the s-ball (for $s \in R$, $s \geq 0$).
2. The volume of a ball in $\mathbb{R}^{\mathbf{k}}$ is a function of only one variable (the radius), hence its measure doesn't require a vector-space structure. The only requirement is the existence of a metric.
3. We define the volume of an s-ball, with radius δ, as δ_s.
4. To measure the s-volume of a specific set, we cover it with s-balls (with increasingly smaller radius) in the cheapest way possible.
5. In contrast to the Lebesgue measure, where s is an integer, in the Hausdorff measure s can, even, take real values. Hence, it ensures a more accurate measure of the volume of the specific set.
6. If the object that we want to measure lies in the Euclidean space $\mathbb{R}^{\mathbf{k}}$, then its Lebesgue measure is proportional (in some sense) to its Hausdorff measure. Hence, the sets of 0 or ∞ measure are the same for both cases.

Definition 2.4 (External Lebesgue measure). In the space $\mathbb{R}^{\mathbf{k}}$ we define the External Lebesgue measure, λ_k as follows: Consider the orthogonal parallelepiped $B = [a_1,b_1] \times \cdots \times [a_K,b_K] \subseteq \mathbb{R}^{\mathbf{k}}$, where $[a_i,b_i] \in R$, i = 1,2,...,K, and define the K-volume of B as

$$Vk(B) = (b_1 - a_1)(b_2 - a_2) \ldots (b_k - a_k)$$

For an arbitrary set $E \subseteq \mathbb{R}^{\mathbf{k}}$ we define

$$V_k(E) = \inf\{\sum_{i=1}^{\infty} V_k(B_i) : E \subseteq \bigcup_{i=1}^{\infty} B_i \quad , B_i \text{is an orthogonal parallelepiped, } i \in \mathbb{N}\}$$

It turns out that λ_k is an external measure and that λ_k (B) = V_k (B), if B is an orthogonal parallelepiped.

Moreover:

$$\lambda_k(E + x) = \lambda_k(E), \alpha \in \mathbb{R}^{\boldsymbol{k}}$$

$$\lambda_k(\alpha E) = \alpha^k \lambda_k(E), \alpha > 0$$

Remark 3. If we restrict λ_k to the σ-algebra, M, of the λ_k-measurable sets, then this restriction is a Lebesgue measure of dimension K. λ_k is also called as K-volume. M contains all open and closed subsets of $\mathbb{R}^{\boldsymbol{k}}$. The Hausdorff measure can be defined on an arbitrary metric space similarly

Definition 2.5 (External Hausdorff measure). Consider the Euclidian space <$\mathbb{R}^{\boldsymbol{k}}$,d >. We define the external Hausdorff measure H^s, for s ∈ ℝ, s ≥ 0, as follows: Let δ(A) = sup {|x − y|: x, y ∈ A} be the diameter of a set A ⊆ $\mathbb{R}^{\boldsymbol{k}}$ and for any e> 0 we set

$$H_{\epsilon}^{s}(E) = inf\{\sum_{i=1}^{\infty} \delta^s(U_i) : E \subset \bigcup_{i=1}^{\infty} U_i, 0 < \delta(U_i) \leq \epsilon, i \in \mathbb{N}\}$$

where $E \subset \mathbb{R}^{\boldsymbol{k}}. For\ 0 < \epsilon_1 < \epsilon_2$ we have that $H_{\epsilon_2}^{s}(E) \leq H_{\epsilon_1}^{s}(E)$. The external Hausdorff measure is given by:

$$H^s(E) = sup\{H_{\epsilon}^{s}(E), \epsilon > 0\} = lim_{\epsilon \to 0+} H_{\epsilon}^{s}(E)$$

Moreover, we have that:

$$H^s(E + x) = H^s(E), x \in \mathbb{R}^{\boldsymbol{k}}$$
$$H^s(\alpha E) = \alpha^s H^s(E), \alpha > 0$$

Fractal Dimensions; Hausdorff-Besicovitch Dimension and the Box (or Minkowski) Dimension

According to what we know from elementary Euclidian geometry, line segments and lines have dimension 1, polygons and circles have dimension 2, while pyramids, cubes and spheres have dimension 3.

Definition 2.6 (Hausdorff-Besicovitch dimension). For every E ⊂ $\mathbb{R}^{\boldsymbol{k}}$, there is exactly one real number s_0,

$0 \leq s_0 \leq K$, such that

$$H^t(E) = \begin{cases} 0, t > s_0 \\ +\infty, t > s_0 \end{cases} \tag{2.1}$$

The number

$$s_0 = sup\{t \geq 0 : H^t(E) = +\infty\} = inf\{t \geq 0 : H^t(E) = 0\}$$

is called Hausdorff-Besicovitch dimension of E and it is denoted by $\dim_H E$.

WHY WE DO NOT USE HAUSDORFF-BESICOVITCH DIMENSION?

1. The computation of the Hausdorff-Besicovitch dimension is quite tedious and unattainable in many cases, using existing mathematical tools.
2. For example, the dimension of the Weierstrass functions (which are continuous but nowhere differentiable) hasn't been compute yet, despite the fact that they are studied since the 18-th century.
3. The wide utilization of computers imposed the need for a more convenient fractal dimension, which, in addition, would be possible to be computed in an algorithmic manner by a machine.
4. This led to the introduction of the Box-counting dimension. For classical geometrical objects as well as many popular fractal objects (i.e., Cantor set, Sierpinski triangle, e.t.c.), the box-counting dimension and the Hausdorff dimension give identical results.
5. Moreover, it can be easily approximated using a computer.

Box (or Minkowski) dimension; Steps

Its definition emerges from a simple observation:

1. Consider that we have a line segment AB with length equal to 1.
2. The minimum number of line segments of length $\epsilon = 1/n$, which are needed to cover AB is $N_1(\epsilon) = n$.
3. Observe that $1 = \epsilon N_1(\epsilon)$.
4. We can work in a similar fashion for a unit square, and cover it with $N_2(\epsilon) = n^2$ smaller squares of ϵ side.
5. We get the equation $1 = \epsilon^2 N_2(\epsilon)$.
6. For the cube we take $1 = \epsilon^3 N_3(\epsilon)$.
7. The dimension of the typical geometrical objects appears as an exponent of ϵ. 8. Hence, the dimension of a set A satisfies

$$dimA = \frac{ln\, N\, \epsilon}{-\, ln\, \epsilon}$$

Definition 2.7 (Box counting dimension). Let A be a bounded set of $\mathbb{R}^k$. Let N (A, ϵ) be the minimum number of ϵ-radius balls that are needed to cover A. If the limit

$$D(A) = \lim_{\epsilon \to \infty} \left\{ \frac{ln(N(A, \epsilon))}{ln \frac{1}{\epsilon}} \right\}$$

exists, then $D(A) = \dim_B A$ is called the Box counting dimension of A.

Multi-Fractal Analysis

Fractals only tell us about an object in which a certain physical quantity is distributed evenly wherever it is found in the embedding space. The multifractal analysis utilizes a spectrum of singularity exponents to provide a detailed and local description of complex scaling behaviors. Here, we present the multifractal analysis:

1. We describe set S of points, describing an object which can be divided into boxes labeled by an index i.
2. Such that i^{th} box has N_i points of total N points of the set.
3. These points are sample points describing the content of the underlying measure.
4. These points are sample points describing the content of the underlying measure.
5. We use the "mass" or "probability" $\mu_i = \frac{N_i}{N}$ in the i-th cell to construct weighted d-measure which we write

$$M_d(q,\delta) \;=\; \sum_{i=1}^{N} \mu_i \; \delta^d \;=\; Z(q,\delta)\delta^d \tag{2.2}$$

6. The "mass exponent" τ(q) for the set depends on the "moment":

$$Z(q,\delta) \;=\; \sum_i \mu_i^q \tag{2.3}$$

of order q. It is also known as the "partition function" as it behaves in a similar manner when one tries to find an analogy of multi fractal formalism with thermodynamic phase transition.

7. Like N(δ) of d measure the "partition function" Z (q, δ) often exhibits "power law" distribution

$$Z(q,\delta) \;\sim\; \delta^{-\tau(q)} \tag{2.4}$$

8. The "exponent" τ(q) is called the "mass exponent" not the "fractal dimension" if it is non-linear in q.

   The mass exponent is more revealing than the simple fractal dimension.

$$\tau(q) = \lim_{\delta\to\infty} \frac{ln(Z(q,\delta))}{ln(\delta)} \tag{2.5}$$

9. Using (2.4) and (2.5) we can write

$$Md(q,\delta) \;\sim\; d^{(d-\tau(q)} \;= \delta \to 0 \tag{2.6}$$

$$\to \begin{cases} 0, d > \tau(q) \\ \infty, d < \tau(q) \end{cases} \tag{2.7}$$

This "weighted d-measure" has a critical mass exponent d = τ(q) for which the measure neither vanishes nor diverges as $\delta \to 0$ analogous to the definition of "Hausdorff-Besicovitch" dimension for the bare dmeasure.

The "weighted measure" is characterized by a whole sequence of "exponents" τ(q) that controls how the "moments of the probabilities" $\{\mu_i\}$ scale with δ.

10. If q = 0 then $\mu_i = 1$, Z (q = 0, δ) = N(δ). This number Z (0, δ) = N(δ) is the number of boxes needed to cover the support and therefore τ (0) = D is the Hausdorff-Basicovitch dimension of the support and tells nothing about the content in it.

11. On the other hand, probabilities are normalized: $\mu_i = 1$ and τ (1) = 0.

12. Choosing "Large values of q" in Z (q, δ) = $\sum_i \mu_i^q$ favours contributions from cells with relatively high values of μ_i since $\mu_i^q \gg \mu_j^q$ with $\mu_i > \mu_j$ if $q \gg 1$.

13. Conversely, $q \ll -1$ favours the cells with relatively low values of the measure μ_i on the cell. These limits are best discussed by considering the derivatives $\frac{d\tau(q)}{dq}$ given by:

$$\frac{d\tau(q)}{dq} = -\lim_{\delta \to 0} \frac{\sum_i \mu_i^q \ln(\mu)}{(\sum_i \mu_i^q) \ln(\delta)} \tag{2.8}$$

14. Let μ_{min} be the min value of μi in the sum. Then, we find

$$\frac{d\tau(q)}{dq} | q \to -\infty = -\lim_{\delta \to 0} \frac{\Sigma_i' \mu_{min}^q \ln(\mu_{min})}{(\Sigma_i' \mu_{min}^q) \ln(\delta)} \tag{2.9}$$

where the prime on the sum indicates that only cells with μi = μmin contribute.

15. The expression may be written as

$$\frac{d\tau(q)}{dq} | q \to -\infty = -\lim_{\delta \to 0} \frac{\ln(\mu_{\min})}{\ln(\delta)} = -\alpha_{\max} \tag{2.10}$$

16.

$$\frac{d\tau(q)}{dq} | q \to -\infty = -\lim_{\delta \to 0} \frac{\ln(\mu_{\max})}{\ln(\delta)} - \alpha_{\min} \tag{2.11}$$

where μ_{max} as the largest value of μ_i leads to the smallest values of α.

17.

$$\mu_{\min} \sim \delta_{\max}^{\alpha} \text{ a nd } \mu_{\max} \sim \delta_{\min}^{\alpha}$$

18.

$$\mu \sim \delta^{\alpha}$$

19.

$$\alpha(q) = -\frac{d\tau}{dq} \tag{2.12}$$

20. q = 1 we find that $\frac{d\tau}{dq}$ has an interesting value

$$\frac{d\tau(q)}{dq}|q = 1 = -\lim_{\delta\to 0}\frac{\Sigma_i \mu_i \ln(\mu_i)}{\ln(\delta)} = \lim_{\delta\to 0}\frac{S(\delta)}{\ln(\delta)} \tag{2.13}$$

where S(δ) denotes " information entropy" of the partition of the measure which we write as

$$S(\delta) = -\sum_i \mu_i \ln(\mu_i) \sim -\alpha(1)\ln(\delta) \tag{2.14}$$

$$\alpha(1) = -\frac{d\tau}{dq}|q = 1 = ds \tag{2.15}$$

where the "exponent α (1)" is also the fractal dimension of the set onto which the measure concentrates and describes the scaling with the box size δ of the entropy of the measure.

21. The "partition entropy S(δ)" at "resolution" δ is given in terms of the entropy S of the measure by S(δ) = −S ln(δ).

Legendre Transformation of τS(q): f(α)

We have a function $\tau = \tau(q)$ which is non-linear in q and hence its slope depends on q. Legendre transformation of τ(q) means a method whereby its derivative $\frac{d\tau}{dq} = -\alpha$ can be considered as an independent variable instead of q itself. The curve given by $\tau = \tau(q)$ can be presented by the relation $f = f(\alpha)$ that describes a family of tangent lines as a function of slope α without sacrificing any of the mathematical content of the parent equation. The slope of τ vs q should be different at each value of q. From the curve we can draw tangent for a given value of q and write down the equation for the resulting straight line. If we denote α as the slope and intercept f which should depend on the slope itself then the equation for the straight line is

$$\tau = -\alpha q + f(\alpha) \tag{2.16}$$

The function f(α) is the "Legendre transform" of the function τ(q).

$$\frac{d\tau}{dq} = -\alpha \Rightarrow d\tau = -\alpha dq$$

$$d\tau = -\alpha dq - q d\alpha + q d\alpha$$

$$d(\tau + \alpha q) = q d\alpha$$

We can define new function

$$f(\alpha) = \tau + \alpha q$$

where the new function f is a function of α.

Data

Imaging [18F]AV-1451 and [18F]AV-45 in acute and chronic traumatic brain injury authored by Dara Dickstein, Mariel Y. Pullman, Corey Fernandez, Jennifer A. Short, Lale Kostakoglu, Karin Knesaurek, Laili Soleimani, Barry Jordan, Wayne Gordon, Kristen Dams-OConnor, Bradley N. Delman, Edmund Wong, Cheuk Y. Tang, Steven T. DeKosky, James R. Stone, Robert C. Cantu, Mary Sano, Patrick R. Hof, Sam Gandy. Alzheimer's Disease and Healthy Aging Data; 2015-2019. This data set contains data from BRFSS (see Figures 2 and 3).

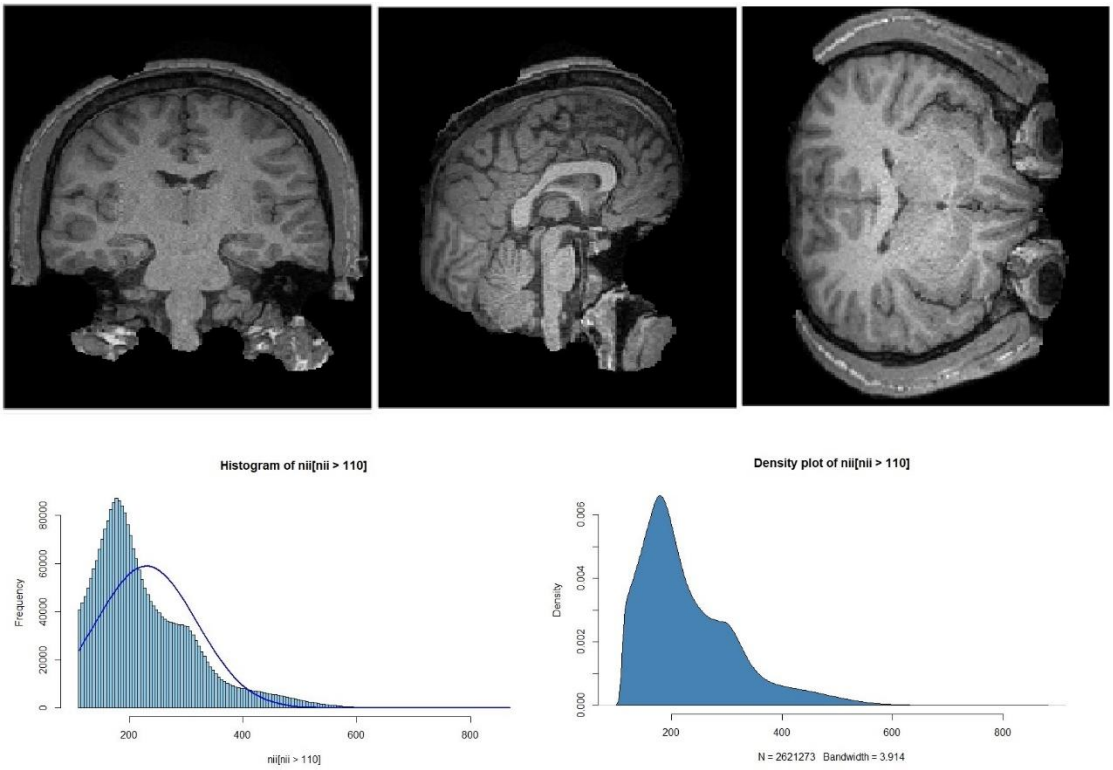


Figure 2: anatT1.nii MRI images year 2011.

1. The Alzheimer's Disease Drug Foundation; NIH grants NINDS 5U01NS086625 and NICHD K01HD07465101A; The Werber Family Foundation.
2. This data was obtained from the OpenfMRI database. Its accession number is ds000204.
3. https://healthdata.gov/w/i2i7-abim/default?cur=OQBOBS0gtcG
4. Available Modalities: MRI https://chronicdata.cdc.gov/Healthy-Aging/Alzheimer-s-Disea hfr9-rurv

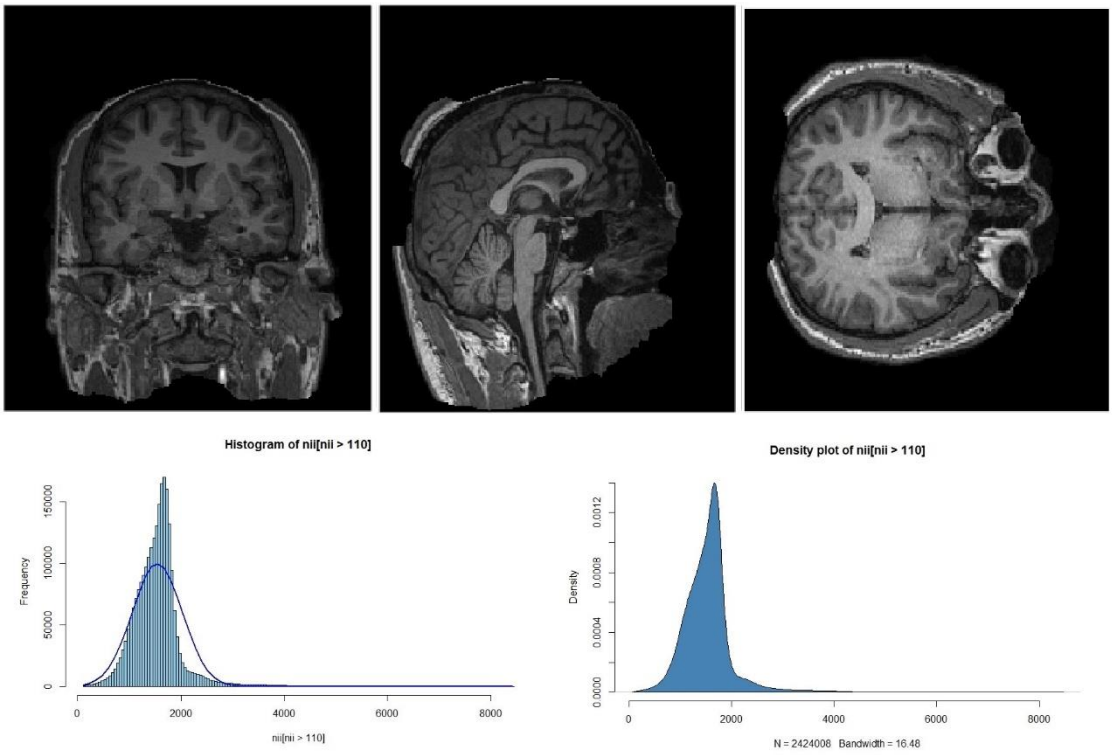


Figure 3: anatT1.nii MRI images year 2015.

Fractal Analysis

In 1983, Benoit Mandelbrot, the founder of fractal geometry, presented the amazing world of fractals to the world. Fractals are infinitely complex objects which are self similar in different scales. FD in combination with other features is emerging as a powerful diagnostic approach at the hands of a clinician.

According to our analysis in Figures 4 and 5, we have a wide range of exponents for AD fMRI images, which indicates different states of Alzheimer's disease have multi-fractal structure. As a result, fractal geometry can be considered as a computational framework to characterize different stages of AD and with further analysis, it can be used as a diagnostic tool to fight against Alzheimer's disease.

CONCLUSION

In this study we focused to understand the changes in fractal properties (FD) of human brain as a whole in glioma during the states of Alzheimer disease (AD). A non-linear analysis called the Fractal Dimension (FD) was performed to quantify the fractal complexity of AD. Our primary goal was to investigate FD to assess whether it can discriminate between different states of AD. From FD analysis, we noticed that the fractal dimension decreases with developing the AD, i.e. the complexity and self similarity of brain structure decreases. We performed multi-fractal analysis to discover whether AD and its states belong to class of multi-fractal object for which a large number of scaling exponents are required to characterize their scaling structures.

The computed multi-fractal spectra of the fMRI images displayed the changes in the width of the scaling exponent for each spectrum.

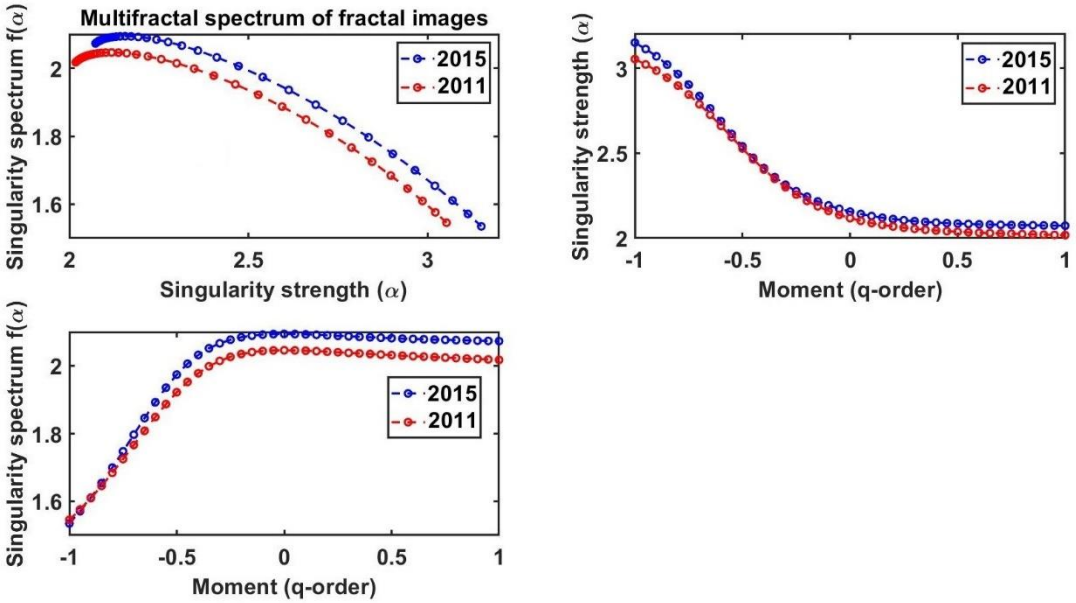


Figure 4: The multi-fractal spectrum analysis of MRI images years 2011 and 2015.

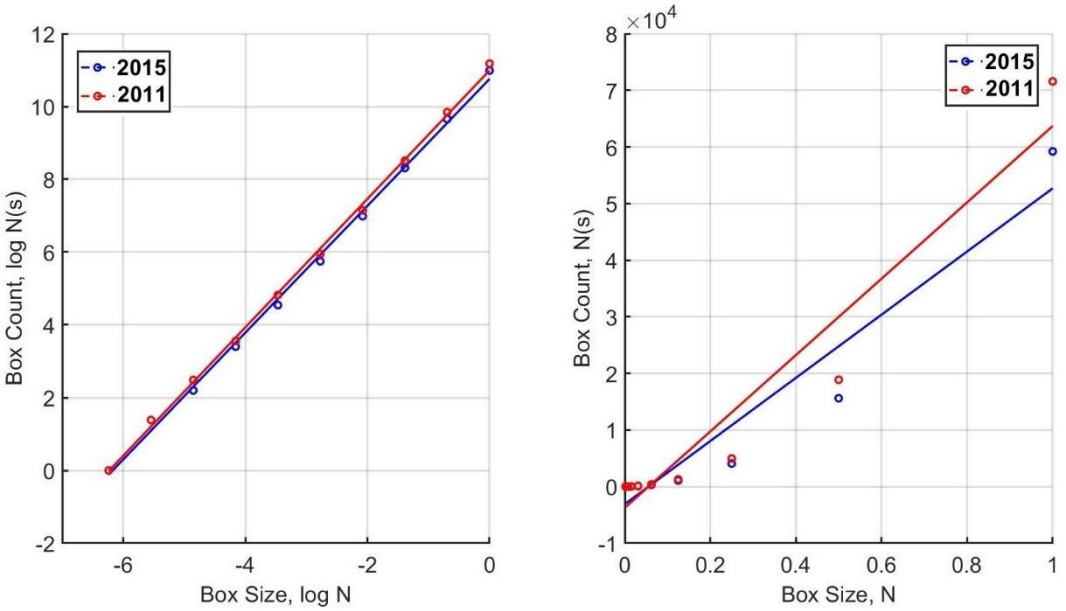


Figure 5: The fractal analysis of MRI images years 2011 and 2015. Reduced in the fractal dimension as AD develops.

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