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Application of Fractal Dimension to Trabecular Bone and its Implications with PathologiesRelated to Aging

Aplicación de la Dimensión Fractal al Trabeculado Óseo y sus Implicaciones con Patologías Relacionadas con el Envejecimiento

Dª Yolanda Guerrero Sánchez

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TESIS DOCTORAL

APPLICATION OF FRACTAL DIMENSION TO TRABECULAR BONE AND ITS IMPLICATIONS WITH PATHOLOGIES RELATED TO AGING (*Aplicación de la dimensión fractal al trabeculado óseo y sus implicaciones con patologías relacionadas con el envejecimiento*)

Yolanda Guerrero Sánchez

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La investigación en odontología es la historia de un avance permanente. Por tanto, también es un desafío emocionante para quien decide orientar su futuro profesional por ese campo. Ya lo dejó escrito Plutarco: "El conocimiento no es una vasija que se llena, sino un fuego que se enciende". La formación en odontología es la herramienta precisa para alcanzar el grado de especialización requerido. Un odontólogo que conoce las técnicas de vanguardia es un profesional en búsqueda constante de la excelencia.

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Resumen

La densidad ósea es un concepto relacionado con la calidad ósea. Está determinada por el nivel máximo de masa ósea existente y la cantidad de pérdida ósea que se produce. La densidad ósea se expresa en gramos de mineral por área o volumen. La calidad de la misma se refiere a su macro y microarquitectura, recambio óseo, tamaño, daño acumulado (por ejemplo, micro fracturas) y mineralización. La resistencia ósea refleja fundamentalmente la integración de la densidad y la calidad ósea.

La densidad ósea juega un papel clave en muchos trabajos de investigación. Se debe a que mide de forma adecuada los cambios que se producen en la estructura ósea. Se sabe que todos los procesos que afectan a la arquitectura trabecular podrán ser estudiados a través de ella. En nuestro trabajo jugará un papel principal.

Existen muchas patologías relacionadas con la edad que afectan a la densidad ósea, en particular a la calidad del hueso y de su estructura trabecular. Las matemáticas son una herramienta fundamental para analizar multitud de problemas procedentes de diversos campos, modelizar la naturaleza y realizar predicciones a futuro. La literatura está llena de buenos ejemplos de esto, en particular, la aplicación de las matemáticas a la odontología es cada vez más frecuente y necesaria.

Motivados por este problema de gran calado y usando una herramienta matemática sofisticada vamos a realizar diferentes estudios, en los que analizaremos la calidad ósea, este va a ser nuestro objetivo principal a lo largo de toda a tesis.

El envejecimiento es un proceso que está directamente relacionado con los cambios en el nivel del hueso, entre otras muchas cosas. El hueso es un tejido dinámico. Durante la infancia y la adolescencia, la formación ósea domina sobre la reabsorción (fase de modelado). Sin embargo, durante el envejecimiento en ambos sexos y después de la menopausia en las mujeres, existe un desequilibrio entre la formación del hueso y su reabsorción, predominando esta última. Las cargas sufridas en el

esqueleto causan microfracturas, que son reemplazadas por un mecanismo de remodelación ósea. Este proceso está mediado por hormonas, factores de crecimiento y citoquinas. Se lleva a cabo en las superficies del hueso cortical y especialmente a nivel del hueso trabecular. Estas alteraciones ocurren en todo el esqueleto óseo, siendo los huesos maxilares una de las partes más susceptibles del organismo, cuando hay una disminución de la densidad ósea a nivel sistémico. Para el diagnóstico de ciertas patologías que afectan al hueso a nivel oral, la radiología convencional (radiografías periapicales, ortopantomografías,...) no es muy sensible para evaluar la densidad ósea. Solo proporciona una estimación burda y subjetiva de la misma, detectando disminuciones en la masa ósea solo superiores al 30%.

Sin embargo, las nuevas pruebas, como la tomografía computarizada de haz cónico (CBCT), permiten obtener una imagen clara de las estructuras y son extremadamente útiles para evaluar los cambios a nivel del hueso. En particular, los datos de la CBCT son susceptibles de ser reformados en un volumen en lugar de un corte, proporcionando así información tridimensional. Las imágenes resultantes son útiles para evaluar características morfológicas específicas, como la altura y el ancho del hueso alveolar.

A lo largo de la presente tesis doctoral exploramos un invariante matemático, llamado dimensión fractal, de las imágenes radiográficas de tipo CBCT que pretendemos correlacionar con la calidad de la estructura ósea trabecular tanto de maxilar como de mandíbula de los sujetos que componen la muestra de estudio en cada momento.

Históricamente, el primer método para evaluar la masa ósea fue el estudio histológico. Los métodos de cuantificación de la masa ósea que se han impuesto son indirectos. Lo más común, pero impreciso, es la lectura cualitativa de una placa radiológica. La radiología simple ha sido y es, por su difusión, la herramienta de diagnóstico más utilizada en la evaluación de la densidad ósea. Pero también ha sido estudiada en pruebas radiológicas mucho más complejas, tales como:

- La TC de haz cónico (CBCT) es una modalidad de imagen relativamente nueva, de la que hoy en día disponemos para examinar **tejidos duros** en las regiones dental y maxilofacial.

- La CBCT ofrece una representación tridimensional de la anatomía y la patología, que es similar a la TC médica y utiliza dosis similares a las de una panorámica.

El acrónimo CBCT, tiene su origen en el inglés Cone Beam Computed Tomography, o lo que es lo mismo Tomografía Computerizada de Haz Cónico, haciendo mención a la forma de cono que tiene la fuente de emisión del haz de Rayos X, y que es la diferencia fundamental con el TAC convencional. En el TAC convencional la emisión del haz de Rayos X es en forma de abanico, obteniéndose así una Òespiral Ó de 1 mm de grosor en el plano axial de la cabeza del paciente, (aunque el tamaño podrá variar sensiblemente según el sistema utilizado o de la configuración del colimador seleccionado).

Sin embargo con la tecnología CBCT, al emitir el haz de Rx en forma cónica, con una única rotación de 360 grados, se expone toda la zona a explorar y se consiguen todas las proyecciones necesarias para crear finalmente la reconstrucción tras el proceso de computerizado. Las proyecciones las recibe un sensor plano (Flat panel) y de su calidad depende significativamente la imagen resultante. Además la resolución de la imagen resultante es isotrópica, es decir que el voxel, unidad mínima de información, es igual en dimensión en los 3 ejes del espacio, dando lugar a imágenes sin distorsión ni magnificación (escala 1:1).

Así pues los **beneficios de los escáneres 3D CBCT** serán:

- **Baja dosis de radiación**: la dosis efectiva recibida sería parecida a la recibida en una panorámica, y hasta un 90% más baja que la que se produce en un TAC convencional.
- Através de ella podemos deducir que la dosis recibida en un TAC equivale a la recibida en 75 CBCT.
- **Posición cómoda para el paciente**: la prueba se realiza con el paciente sentado o de pie en un ambiente no claustrofóbico, y en un aparato similar al ortopantomógrafo.
- **Rapidez en la realización**: las imágenes se obtienen en unos 15 segundos y se procesan en 30 segundos.
- **Calidad y compatibilidad de las imágenes procesadas**: las imágenes obtenidas en los 3 ejes del espacio, producen reconstrucciones tridimensionales de alta calidad a tamaño real y con resolución sub-milimétrica. Además compatibles con los programas informáticos más importantes de planificación de cirugía guiada de implantes.

De tal manera, y usando las matemáticas como herramienta de apoyo en este trabajo se ha probado que la dimensión fractal calculada por vez primera de un modo matemáticamente riguroso es un buen invariante para medir los cambios que se producen en la densidad osea a nivel oral y relacionarlo con patologías asociadas al envejecimiento y que afectan a la calidad del hueso. Estamos seguros que esta técnica desarrollada en el presente trabajo de tesis doctoral será de inspiración en futuros trabajos en la línea que proponemos.

La dimensión fractal, calculada a través de tres enfoques distintos, nos proporcionó valores precisos de normalidad con respecto a la densidad radiográfica de este tipo de huesos y nos permitirá establecer comparaciones con respecto a la dimensión fractal de pacientes con diferentes patologías que pueden afectar la densidad ósea de los huesos trabeculares en ambos maxilares.

Todos los sujetos que participaron en nuestros estudios se ajustaban a los criterios de inclusión y exclusión establecidos al respecto. La edad media de los sujetos en la muestra varía en función del estudio realizado y siempre elegimos la misma ventana radiológica para estudiar basándonos en una serie de referencias anatómicas en función del objetivo planteado.

La dimensión fractal y, específicamente, la dimensión box-counting, es la principal herramienta aplicada en muchos campos, entre ellos la odontología, para detectar patrones fractales aplicados al estudio de la calidad ósea. Sin embargo, el cálculo efectivo de tal invariante no se ha llevado a cabo con precisión en la literatura previa, es por ello que hablábamos anteriormente de tres enfoques diferentes. En nuestros tres artículos de investigación publicados todos ellos en revistas con índice de impacto, proponemos un nuevo método para calcular correctamente la dimensión fractal de un subconjunto del plano e ilustrarlo mediante el análisis de la dimensión box-counting del hueso trabecular en ambos maxilares a través de una tomografía computarizada cone beam (CBCT).

En el primer y segundo artículo realizamos cálculos en pacientes con un estado sistémico y dental saludable y comparamos estos resultados con el estudio sobre un paciente con enfermedad periodontal en estadío avanzado, donde ya sabíamos que a nivel clínico presentaba pérdida de inserción y afectación a nivel óseo.

En el primer trabajo, publicado en Journal of intelligent & Fuzzy Systems, desarrollamos la novedosa idea de computar la dimensión box-counting analizando los puntos de corte con las cajas que reticulan los subconjuntos del plano de una curva recubridora modelizada mediante un una función unidimensional. Remarcamos que esto permite el cómputo de la dimensión box-counting de una manera mucho más precisa que hasta la actualidad en donde se venía realizando el conteo de una manera más rudimentaria. Como una aplicación de nuestros resultados matemáticos teóricos en este trabajo, exploramos la naturaleza fractal de un paciente con periodontitis cuya estructura trabecular puede variar con respecto a sujetos sanos. Seleccionamos a este paciente en concreto porque su CBCT era de muy alta calidad y resolución. Realizamos un preciso análisis de tiempos de cómputo entre los tres métodos que proponemos para computar este invariante.

En el segundo trabajo, publicado en la revista Discrete and Continuous Dynamical Systems S, proporcionamos todas las herramientas matemáticas que aplicamos para llevar a cabo el estudio clínico sobre las muestras recogidas. Más específicamente, este trabajo contenía los conceptos básicos sobre la dimensión box-counting y describía el concepto de estructura fractal (en el que se basan nuestros resultados teóricos). En particular, definimos la estructura fractal natural en el plano euclideo. Dado que estábamos interesados en el cálculo de la dimensión box-counting para imágenes CBCT planas, todo nuestro desarrollo teórico se encuentra en el contexto de los subconjuntos del plano. Sin embargo, vale la pena mencionar que todos ellos pueden extenderse a cualquier espacio euclideo de dimensión arbitraria, si fuese necesario. También proporcionamos algunos resultados teóricos que permiten el cálculo de la dimensión box-counting de las imágenes CBCT en términos de la dimensión box-counting de los subconjuntos unidimensionales a través de una función determinada α aunque los resultados teóricos en esta línea los desarrollamos en nuestro segundo trabajo. Presentamos una sección donde se comentan nuestros resultados computacionales. De hecho, explicamos cómo los cálculos con respecto a la dimensión box-counting de las imágenes CBCT se han llevado a cabo a través de tres enfoques diferentes, a saber, el algoritmo estándar de la box-counting y dos enfoques novedosos basados en nuestros teoremas.

En el tercer trabajo, publicado en Symmetry, el objetivo fue describir todas las consideraciones anatómicas que rodean el foramen nasopalalatino, relacionándolas con el estudio de la densidad ósea, a través de la dimensión fractal, en esa misma área. Seleccionamos consecutivamente una muestra de 100 pacientes, todos con CBCT realizadas por necesidades de tratamiento. Elegimos una ventana específica (ROI), que coincide con un corte axial al nivel de la salida del agujero naso-palatino. Analizamos diferentes medidas antropométricas junto con el análisis de la dimensión fractal. La muestra inicial fue subdividida en tres grupos: grupo 1 (sin pérdida de dientes), grupo 2 (ausencia de algunos dientes) y grupo 3 (edéntulos totales). Aplicamos la prueba de Mann-Whitney y la prueba de la t de Student para obtener los resultados estadísticos. La muestra de los pacientes que cumplieron los criterios de inclusión finalmente consistió en un total de 77 pacientes, de los cuales 63 son mujeres (81.8% del total). un total de 60 sujetos se asignaron al grupo 1, 10 al grupo 2 y 7 al grupo 3. La edad media de los pacientes en esa muestra fue de 53,2 años con una desviación estándar de 9 años.

Este fue un estudio clínico observacional y transversal, en el que seleccionamos una muestra de 100 pacientes consecutivamente de la clínica dental de la universidad de Murcia (España). El estudio fue aprobado por el Comité de Bioética de la universidad de Murcia. Todos los individuos dieron su consentimiento informado por escrito antes de participar. Se aplicaron los criterios de inclusión: pacientes en condiciones de salud tanto sistémicas como dentales, no embarazadas, que no contengan artefactos. De estos 100 pacientes iniciales, teníamos 77 que cumplían con todos los criterios descritos anteriormente (5 se descartaron porque se sometieron a tratamiento con bifosfonatos y 18 desde el inicio).

Las imágenes que presentaron artefactos o no se consideraron con la calidad suficiente para poder aplicar el algoritmo matemático de cómputo de la dimensión fractal fueron descartadas. Todas las CBCT se realizaron con el mismo equipo Planmeca, Planmeca ProMax 3-D Max (Planmeca Oy, Helsinki, Finlandia) calibrado de acuerdo con consideraciones técnicas. Las radiografías se obtuvieron con el paciente en la misma posición (posición prona). Los parámetros de emisión del haz fueron kV = 96, mA = 8, tiempo de exposición de 12 segundos (11.94s) con un tamaño de imagen de $501 \times 501 \times 466$ voxels (cada voxel es equivalente a 200 μm). El software de evaluación utilizado fue Romexis 2.5. Programa (Planmeca Oy, Helsinki, Finlandia), que permitía observar la imagen en una ventana múltiple donde los planos axial, coronal y sagital se pueden visualizar en intervalos de 0,2 mm, además de una visión 3D. Procedimos a seleccionar un ROI específico que se obtuvo en el plano axial, visualizando el foramen nasopalatino y los mamelones caninos en ambos lados. Puesto que este agujero esta en la línea media analizamos a ambos lados de él varias medidas antropométricas junto con el análisis de la dimensión fractal y establecimos rasgos de simetría entre la mayoría de los valores.

Gracias al tercer artículo podemos concluir que la dimensión fractal es un invariante matemático que se comporta simétricamente para imágenes binarias del escáner de cada sujeto de nuestra muestra de estudio para el contorno del foramen

nasopalalatino. También concluimos que no hubo diferencias significativas entre todas las medidas antropométricas utilizadas ni en los sujetos mismos ni en los diferentes grupos. Por lo tanto, se aprecia un patrón de simetría en todos los niveles.

1

Introduction

1.1 Bone density

1.1.1 Definition

Bone density is a notion linked with the bone quality. It is determined by the peak of bone mass and the amount of bone loss. Bone density is expressed in grams of mineral by area or volume. Quality refers to macro and microarchitecture, bone turnover, size, accumulated damage (e.g., micro fractures) and mineralization. Bone resistance fundamentally reflects the integration of density and bone quality.

1.1.2 Why bone density is useful?

Bone density is a notion which plays a key role in many studies. It is because it measures in a very accurate way the changes in the bone structure. It is known that all processes which affect the trabecular architecture will be able to be studied through it. In our study it will play a main role.

1.1.3 Applications

Historically, the first method of assessing bone mass was the histological study. Although it could be considered histology / histomorphometry as a gold standard in the assessment of bone mass, its limitations regarding being a restricted method, bloody, slow and expensive, they have practically relegated it in research studies. The methods of quantifying bone mass that have been imposed are indirect. The most common, but imprecise, is the qualitative reading of a radiological plate. The simple radiology has been and is, by its diffusion, the diagnostic tool most used in the evaluation of bone density.

1.2 Mathematical tools

1.2.1 Fractals

The word *fractal* (that means “to break”) has become a very important concept in mathematics. The study of fractal patterns plays a key role in economics, physics, and statistics, where fractals appear. It is also worth mentioning that there is a special interest in regard to the application of fractals to social sciences.

1.2.2 Fractal dimension

Fractal dimension constitutes the key tool to explore fractals. In fact, it is their main invariant and displays useful information regarding the complexity of a set when it is examined with enough level of detail. Fractal dimension has been applied in several areas such as dynamical systems, diagnosis of diseases, ecology, earthquakes, and ophthalmology, just to name some of them.

Hausdorff and box dimensions are the two classical models of fractal dimension. Thus, while the former is “better” from a theoretical viewpoint, the latter results more appropriate to deal with empirical applications. In this way, almost all applications of fractal dimension have been carried out in the Euclidean setting by box dimension. Indeed, popularity of box dimension is due to the easiness of its empirical estimation.

In 1914, Carathéodory contributed a method to define a measure by coverings of certain subsets (c.f. [17]). Later (1919), Hausdorff applied that procedure and proved that the middle third Cantor set has a positive and finite measure with a dimension equal to $\log 2/\log 3$ (c.f. [14]).

On the other hand, the origins of box dimension go back to the twenties, when some research was done by the pioneers of Hausdorff measure and dimension in regard to such a model. In the thirties, the standard definition of the box dimension was contributed by Pontrjagin and Schnirelman (c.f. [15]).

1.2.3 Fractal structures for fractal dimension calculation

The introduction of fractal structures has allowed to formalize some topics on fractal theory from both theoretical and applied points of view (c.f. [16, Section 2.6]). A fractal structure is a countable collection of coverings of a given set which provides better approximations of the whole space as we go deep in further stages, called *levels* of the fractal structure (c.f. [16, Definition 2.6.1]). As such, if the definition of box dimension is analysed, then we can observe that fractal structures provide an ideal context where new models of fractal dimension could be posed. Furthermore, the use of fractal structures leads to connect several topics on topology like transitive quasi-uniformities, non-Archimedean quasi-metrization, metrization, topological and fractal dimensions, self-similar sets and space-filling curves. Self-similar sets provide a special kind of fractals which always have a fractal structure on a natural way, which allows us studying them from the viewpoint of fractal structures (c.f. [16, Definition 2.6.3]).

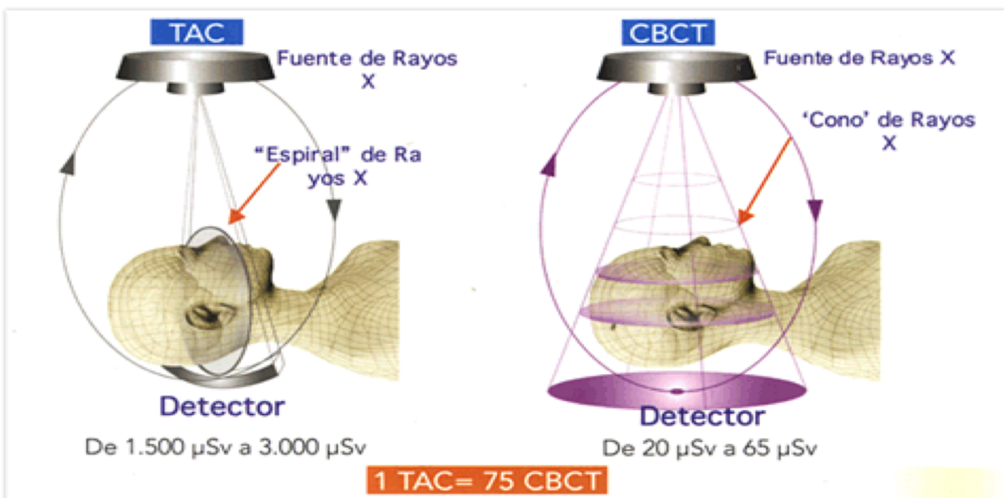
One of the goals of this thesis is to apply a novel mathematical model to calculate the effective fractal dimension of a given set by fractal structures. In this way, it is desirable that the fractal dimension model to be considered presents useful theoretical properties (as it is the case of Hausdorff dimension), but could be also calculated with easiness (like box dimension). In this way, appropriate discretizations for both Hausdorff and box dimensions will lead to new fractal dimension models for fractal structures which inherit some of their properties and advantages (c.f. [16, Sections 3.6, 3.8, 4.3, 4.11, and Chapter 5]). It is worth pointing out that our approach combines [18, Theorem 23] with [35, Algorithm 3.1].

1.3 Aging, bone density and fractal dimension

1.3.1 Interconnections among the previous three concepts

Most evolutionary biologists define aging as an age-dependent or age-progressive decline in intrinsic physiological function, leading to an increase in age specific mortality rate (i.e., a decrease in survival rate) and a decrease in age-specific reproductive rate (Barton, 1996; Tatar, 2001; Promislow and Bronikowski, 2006; Flatt and Schmidt, 2009). Aging is a process that is directly related to changes at the bone level, among many other things. The bone is a dynamic tissue. During childhood and adolescence, bone formation dominates over resorption (modeling phase). However, during aging in both sexes and after menopause in women, there is an imbalance between the formation of bone and its resorption, predominating the latter. The loads suffered in the skeleton cause microfractures, which are replaced by a mechanism of bone remodeling. This process is mediated by hormones, growth factors and cytokines. It takes place on the surfaces of the cortical bone and especially at the level of the trabecular bone. These alterations occur throughout the bone skeleton, with the maxillary bones being one of the most susceptible parts of the organism, when there is a decrease in bone density at a systemic level.

Since Dr. Frederic Otto Walkhoff first took a dental radiography in 1896, the radiological field has widely evolved, not only from the viewpoint of the apparatus but also due to the exposure times and the radiation doses. At the same time, William Herbert Rollins built the first dental X-ray unit. However, it was William J. Morton who really used this device, who also contributed to the scientific basis regarding the use of X-rays in the field of dentistry. Several years later, the intraoral radiographic film was used by Dr. Frank Van Woert. In 1913, William D. Coolidge created the first X-ray tube with tungsten filament, a revolution. In 1980, Fred M. Medwedeff, throughout the technique of collimation, managed to reduce exposure significantly. The devices have been improved over the years until the Cone Beam Computed Tomography (CBCT, hereafter) was introduced in 1996 in the European market. Such a method considerably reduces the dose of radiation and exposure and provides high resolution images, as well. For the diagnosis of certain pathologies that affect bone at the oral level, conventional radiology (periapical radiographs, orthopantomographies, ...), is not very sensitive to assess bone density. It only provides a gross and subjective estimation of the same, detecting decreases in bone mass only greater than 30%. However, new tests such as cone-beam computed tomography (CBCT) allow to obtain a clear image of structures and is extremely useful to evaluate changes at the bone level. In particular, the data of the CBCT are susceptible to being reformed in a volume instead of a cut, thus providing three-dimensional information. The resulting images are useful for evaluating specific morphological characteristics, such as the height and width of the alveolar bone [38, 39, 40]. In 1998, Mozzo et al. introduced a new type of CT in dentistry and maxillofacial radiology, the CBCT, also called cone beam image (CBVI) or cone beam volumetric tomography (CBVT), the result of the search to obtain a reduction in radiation doses to which the patient was exposed, to achieve a high spatial resolution and to achieve a reduction of the economic costs that traditional medical CT implied.



Subsequently, in the year 2000, the CBCT developed widely in the United States (USA) and despite an initial period of limited interest between the years 2000-2002, it resurfaced again to the present day with at least 14 different types of CBCT scanners. Conical beam CT (CBCT) is a relatively new imaging modality, which we now have to examine hard tissues in the dental and maxillofacial regions. The CBCT offers a three-dimensional representation of anatomy and pathology, which is similar to medical CT and uses doses similar to those of a panoramic. The European Radiology Academy DentoMaxilloFacial recognizes that dentists receive training in two-dimensional dental images as university students, but most of them have received little or no training in the application and interpretation of three-dimensional cross-sectional images. To assess bone density in the jaws traditionally, the Lekholm-Zarb and Misch classifications have been used, empirical and subjective techniques based on personal appreciation and experience. But the appearance of these new tools in radiodiagnosis has revolutionized the image of the cranio-facial complex, offering an alternative to the conventional image that avoids overlapping and problems of image distortion. This technology, which emerged at the end of the nineties, presents another added advantage that is a lower radiation dose than the conventional TAC. And depending on the CBCT model we can even get doses close to those of an orthopantomography. The acronym CBCT, has its origin in the English Cone Beam Computed Tomography, or what is the same Computerized Tomography of Conic Beam, mentioning the cone shape that has the emission source of the X-ray beam, and that is the fundamental difference with the conventional TAC. However, with the CBCT technology, when emitting the beam of Rx in a conical shape, with a single rotation of 360 degrees, the entire area to be scanned is exposed and all the projections necessary to create the reconstruction after the computerized process are finally achieved. The projections are received by a flat sensor and its quality depends significantly on the resulting image. In addition, the resolution of the resulting image is isotropic, meaning that the voxel, the minimum unit of information, is equal in dimension in the 3 axes of the space, giving rise to images without distortion or magnification (scale 1:1), see [38, 39, 40].

In the conventional CT, the emission of the X-ray beam is in the form of a fan, thus obtaining a “spiral" of 1 mm thickness in the axial plane of the patient’s head, (although the size may vary considerably depending on the system used or of the selected collimator configuration).

Fractal objects (from Latin, “frangere”, *to break*) are mathematical objects characterised by their irregular nature and self-similarity properties. Several scientific areas have experienced significant advances by detecting fractal patterns including the analysis of the human retina and the study of capillaries, as well. In particular, certain types of tissues, such as the trabecular one, resemble a fractal.

As such, important consequences from the viewpoint of diagnostic and prevention at oral level would follow whenever an accurate value for the fractal dimension of a trabecular tissue is provided. In fact, that quantity throws useful information in regard to the existence, complexity, and evolution of fractal patterns. In this way, fractal dimension could be a *good* candidate to accurately *measure* the bone density structure in trabecular tissues.

There are many systemic diseases that may affect the quality of dental bones. Different studies appeared in the literature try to measure the effect of a particular disease on the trabecular structure. To deal with, the main tool applied in this context is the fractal dimension throughout the box-counting model. Such a quantity allows to detect self-similarity patterns. Thus, if some kind of disease destroys that internal structure, its fractal dimension may vary providing a measure regarding this fact. See, e.g., [3, 4, 7, 10, 12] and [13].

However, the effective calculation of box dimension has not been carried out in the most accurate manner in empirical applications. In most cases, the analysed images have been treated by a hand computation inspired by the "Archimedes' exhalation method", [1, 5, 6, 8, 9] and [11]. It is worth pointing out that box dimension may be underestimated for great values of the scale (c.f. [37]).

In this thesis, we develop a detailed study from high quality CBCT images based on the analysis of their fractal dimensions. Unlike other approaches used in the literature, we test a novel approach, completely different from the standard methods usually applied to estimate fractal dimension in the medical field. We should mention here that the so-called box dimension constitutes the par excellence method to explore fractal patterns in radiographic projections (c.f. [1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13]).

2

Global summary of objectives and final conclusions

Our Ph.D. work has three published papers as can be seen in the next section. Here we shall describe in detail the global objectives and final conclusions of each work developed in a brief way. Note that the order of authors appearance followed in our publications is the alphabetical one.

2.1 Objectives

The main objectives of this Ph.D. work are the following:

1. To use and develop an accurate mathematical tool for computing fractal dimension on self-similar structures.

2. To explore fractal dimension of CBCT images to analyse the trabecular bone structure of healthy subjects.

3. To explore fractal dimension values from a computed tomography scan images from a periodontitis patient in order to show that fractal dimension is a good measure to describe the effects of this disease.

4. To describe all the anatomical considerations that surround the nasopalalatine foramen, relating them to the study of bone density, through the fractal dimension, in that same area.

5. To show that the fractal dimension is a good tool to measure bone density and therefore to state it as a good tool for analysing pathologies related with agin which potentially affect the bone quality.

2.2 Material and Methods

We underline that the statement of the mathematical tools for developing our algorithm for computing, a in novel way, the fractal dimension has been stated along the three papers published but the main machinery is showed in Papers 1 and 2 describe in the sequel.

2.2.1 Paper 1 (objectives 1 and 2)

We explore the fractal dimension of CBCT images to analyse the trabecular bone structure of healthy subjects. That quantity, computed throughout three distinct approaches, provided us accurate values of normality concerning the radiographic density of this kind of bones and will allow us to establish comparisons with respect to the fractal dimension from patients with different pathologies that may affect the density of trabecular bones.

All the subjects taking part in our study were in general and oral health good conditions. They did not present any kind of dental or systemic pathology. They did not take any type of medication that could affect their bone density nor had they taken it in the past. The mean age of the subjects in the sample was 45 years and the same section of the bone, located according to the mental hole in the jaw bone, was analyses in all the cases.

2.2.2 Paper 2 (objectives 1 and 3)

Fractal dimension and specifically, box dimension, is the main tool applied in many fields such as odontology to detect fractal patterns applied to the study of bone quality. However, the effective computation of such invariant has not been carried out accurately in literature. In this paper, we propose a novel approach to properly calculate the fractal dimension of a plane subset and illustrate it by analysing the box dimension of a trabecular bone through a computed tomography scan.

In this work we analyse the fractal dimension of a computed tomography scan images from a periodontitis patient. It is worth pointing out that, the effects of that disease in the bone quality were studied through the box dimension although the conclusions reported no connections between periodontitis and bone density, likely due to a large margin of error in the box method.

2.2.3 Paper 3 (objectives 1 and 4)

The aim of this work was to describe all the anatomical considerations that surround the nasopalalatine foramen, relating them to the study of bone density, through the fractal dimension, in that same area. We consecutively selected a sample of 100 patients all of them with CBCTs performed for treatment needs. We chose a specific window (ROI), which coincides with an axial cut at the level of the anterior nasal spine. We analysed different anthropometric measurements together with a novel analysis of the fractal dimension. In turn, our initial sample was subdivided into three groups: group 1 (without loss of teeth), group 2 (absence of some teeth), and group 3 (total edentulous). We applied both Mann-Whitney test and Student's t-test to obtain the statistical results. The sample consisted of a total of 77 patients, of which 63 are women (81.8% of the total). A total of 60 subjects were assigned to group 1, 10 to group 2, and 7 to group 3. The mean age of the patients in that sample was 53.2 years with a standard deviation of 9 years.

This is a cross-sectional and observational clinical study where we selected a sample of 100 patients consecutively from the dental clinic of University of Murcia (Spain). The study was approved by the Bioethics Committee of the University of Murcia. All individuals gave their informed consent in writing before participating. The inclusion criteria were applied: patients in health conditions both systemic and dental, not pregnant, images that do not contain artifacts. Of these 100 initial patients we had 77 that met all the criteria described above (5 were discarded because they were submitted to treatment with bisphosphonates and 18 since the images presented artefacts or were not considered with enough quality to be able to apply the algorithm). All CBCTs were performed using the same Planmeca®

equipment, Planmeca ProMax 3-D Max (Planmeca Oy, Helsinki, Finland) calibrated according to technical considerations. X-rays were obtained with the patient in the same position (prone position). The beam emission parameters were kV = 96, mA = 8, exposure time of 12 seconds (11.94s) with an image size of $501 \times 501 \times 466$ voxels (each voxel being equivalent to 200 μm) The evaluation software used was the Romexis 2.5.1® program (Planmeca Oy, Helsinki, Finland), which allowed observing the image in a multiple window where the axial, coronal and sagittal planes can be visualized in 0.2 mm intervals, in addition to a 3D vision. As indicated above, the sample was divided into three groups. We proceed to select a specific ROI that was obtained in the axial plane at the height of the nasal spine, visualising the nasopalatine foramen and the canine mamelons on both sides.

We proceed to make the following measurements: distance anterior wall nasopalatine hole to anterior nasal spine (DCV), distance back wall foramen (NF) to border palate bone (DCP), distance right side wall NF to right canine mamelon (DVD), distance left lateral wall NF to left canine mamelon (DVI), area of the NF and other series of values provided by the software itself. All measurements were made by a single examiner duly trained for the purpose. The measurements were repeated by the examiner one month after performing the first ones and if there was a discrepancy in any measurement, the average of both is obtained and the kappa index was used. Once all the results were obtained, a database was created, and the necessary Mathematica® code was written to perform all the statistical analyses.

Objective 5 has been obtained as a corollary of our three published papers.

2.3 Results

2.3.1 Paper 1

In this paper we provide all the mathematical tools we applied to carry out the present study. More specifically, it contains the basics on the box dimension (box dimension, hereafter) and describes the concept of fractal structure (which our theoretical results are based on). In particular, we define the natural fractal structure on the Euclidean plane. Since we are interested in the calculation of the box dimension for plane CBCT images, all our theoretical development lies in the context of subsets of $\mathbb{R}^2$. However, it is worth mentioning all of them can be extended

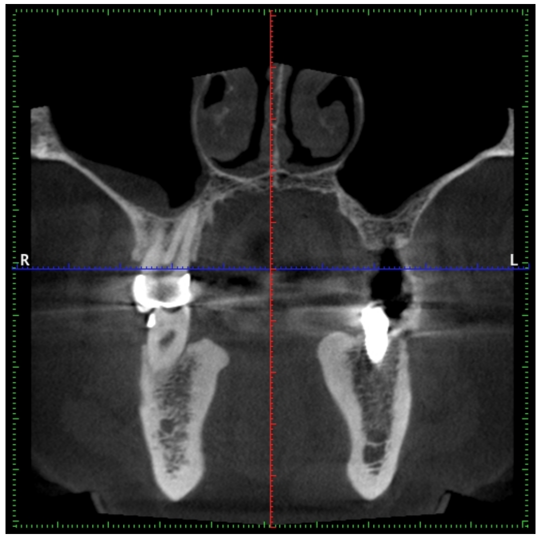


Figure 2.1: CBCT scan from a periodontitis patient (left) and detailed view of a trabecular bone from that scan where it can be identified the fractal nature of periodontal tissues.

to any Euclidean space, if needed. We also provide some theoretical results allowing the calculation of the box dimension of CBCT images in terms of the box dimension of 1−dimensional subsets via a certain function α. Interestingly, a constructive approach to define that function is also contributed at the end of that section. We present a section where are commented our computational results. In fact, we explain how the calculations regarding the box dimension of CBCT images have been carried out via three different approaches, namely, the standard box dimension algorithm and two novel approaches based on our theorems, as well.

2.3.2 Paper 2

As an application of our mathematical results, we explore the fractal nature of a dental tissue. It is known that periodontal tissues do possess a self-similar nature whose structure may vary between patients having periodontitis disease to healthy subjects. (c.f. Fig. 2.1). For illustration purposes, the box dimension of a trabecular bone from a periodontitis patient was analyzed. To deal with this, we considered a high-resolution caption from a CBCT scan.

Self-similarity patterns were detected in a range of $1-10$ levels by a correlation coefficient equal to 0.97801. The box dimension of the trabecular bone in Fig. 2.1 (right) calculated according was found to be equal to 1.95251.

2.3.3 Paper 3

We conclude that the mathematical invariant *fractal dimension* behaves symmetrically for binary images from the scanner of each subject of our study sample for the surround the nasopalalatine foramen. We also conclude that there were no significant differences between all the anthropometric measures used neither in the subjects themselves nor in the different groups. Therefore, a pattern of symmetry was appreciated at all levels.

2.4 Conclusions

2.4.1 Paper 1

Historically, the box dimension was used to stated a measure of the bone quality. The box dimension is a very hand-made computation which introduce big error in the results. Our approach, via a novel mathematical algorithm, allows to compute the real mathematical invariant indicate to make these studied, the so called fractal dimension. In this first paper we state all mathematical tools for this aim and we explore fractal dimension of CBCT images to analyse the trabecular bone structure of healthy subjects.

2.4.2 Paper 2

It is known that periodontal tissues do possess a self-similar nature whose structure may vary between patients having periodontitis disease to healthy subjects. Fractal dimension is a good tool for measuring this fact.

2.4.3 Paper 3

Fractal dimension is an accurate tool to measure symmetry of the surround the nasopalalatine foramen which is also proved via the non presence of no significant differences between all the anthropometric measures computed neither in the subjects themselves nor in the different groups. So, therefore we can conclude that a pattern of symmetry was appreciated at all levels from the surround the nasopalalatine foramen.

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Published and submitted papers

In this section we present the reprints of the published papers or papers submitted for possible publication. We recall the highlight of them:

1. **PAPER 1**. *An intelligent system to study the fractal dimension of trabecular bones.*

   Paper published in the journal: Journal of Intelligent & Fuzzy Systems **35**, (2018), 4533–4540, DOI:10.3233/JIFS-169772 by M.Fernández–Martínez, F.J. Gómez–García, Y. Guerrero–Sánchez and P. López–Jornet. JCR impact (2017): 1.426.

   URL: https://content.iospress.com/articles/journal-of-intelligent-and-fuzzy-systems/ifs169772

   Abstract:In this paper, we explore the fractal dimension of Cone Beam Computed Tomography images to analyze the trabecular bone structure of healthy subjects. That quantity, computed throughout three distinct approaches, provided us accurate values of normality concerning the radiographic density of this kind of bones and will allow us to establish comparisons with respect to the fractal dimension from patients with different pathologies that may affect the density of trabecular bones.

2. **PAPER 2**. *A novel approach to improve the accuracy of the box dimension calculations: applications to trabecular bone quality.*

   Paper published in the journal: Discrete and Continuous Dynamical Systems S **12(4-5)**, (2019), 4533–4540, DOI:10.3934/dcdss.2019105 by M. Fernández–Martínez, Y. Guerrero–Sánchez and P. López–Jornet. JCR impact (2017): 0.561.

   URL: https://www.aimsciences.org/article/doi/10.3934/dcdss.2019105

   Abstract:Fractal dimension and specifically, box-counting dimension, is the main tool applied in many fields such as odontology to detect fractal patterns applied to the study of bone quality. However, the effective computation of such invariant has not been carried out accurately in literature. In this paper, we propose a novel approach to properly calculate the fractal dimension of a plane subset and illustrate it by analysing the box dimension of a trabecular bone through a computed tomography scan.

3. **PAPER 3**. *On the symmetry of the bone density over the nasopalalatine foramen via a mathematical fractal dimension analysis.*

   Paper published in the journal: Symmetry **11(202)**, (2019), 202–2017 DOI: 10.3390/sym11020202 by M.M. Bornstein, M. Fernández–Martínez, J.L.G. Guirao, F.J. Gómez-García, Y. Guerrero–Sánchez and P. López–Jornet. JCR impact (2017): 1.256.

   URL: https://www.mdpi.com/2073-8994/11/2/202

   Abstract: The objective of the present paper is to describe all the anatomical considerations surrounding the nasopalatine foramen by relating them to the study of bone structure density via an accurate fractal dimension analysis in that area. We consecutively selected a sample of 130 patients, all of them with cone beam computed tomography (CBCT) images performed for treatment needs. We chose a specific window (ROI), which coincides with an axial cut at the level of the anterior nasal spine. Different anthropometric measurements were analyzed and a novel fractal dimension analysis was performed. Our sample consisted of 130 patients and was divided into two groups: group one (consisting of 65 subjects without loss of teeth) and group two (consisting of 65 patients with the absence of some teeth). In the sample, 52.31% were women (68 people). Mann–Whitney tests were applied to obtain the statistical results.

The mean age of the patients in that sample was 53.67 years with a standard deviation of 8.20 years. We conclude that fractal dimension, a mathematical invariant, behaves symmetrically for binary images from the CBCT scanners of each subject of our sample of study. We also conclude that there were no significant differences between all the anthropometric measures used neither in the subjects themselves nor in the different groups. Therefore, some patterns of symmetry were appreciated at a complete range of levels.

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