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Classification of micro-CT images using 3D characterization of bone canal patterns in human osteogenesis imperfecta

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Abstract

Few studies have analyzed the microstructural properties of bone in cases of Osteogenesis Imperfecta (OI), or 'brittle bone disease'. Current approaches mainly focus on bone mineral density measurements as an indirect indicator of bone strength and quality. It has been shown that bone strength would depend not only on composition but also structural organization. This study aims to characterize 3D structure of the cortical bone in high-resolution micro CT images. A total of 40 bone fragments from 28 subjects (13 with OI and 15 healthy controls) were imaged using micro tomography using a synchrotron light source (SR μ CT). Minkowski functionals - volume, surface, curvature, and Euler characteristics - describing the topological organization of the bone were computed from the images. The features were used in a machine learning task to classify between healthy and OI bone. The best classification performance (mean AUC – 0.96) was achieved with a combined 4-dimensional feature of all Minkowski functionals. Individually, the best feature performance was seen using curvature (mean AUC - 0.85), which characterizes the edges within a binary object. These results show that quantitative analysis of cortical bone microstructure, in a computer-aided diagnostics framework, can be used to distinguish between healthy and OI bone with high accuracy.

Keywords

Minkowski functionals; texture analysis; support vector machine classifier; bone; osteogenesis imperfecta

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1. MOTIVATION/PURPOSE

Osteogenesis imperfecta (OI) is a common skeletal disease caused by mutations of genes primarily encoding type I collagen [1]. Also referred to as ‘brittle-bone’ disease, such mutations significantly affect the properties of bone matrix, osteoblast function and bone remodeling, which can result in impaired bone quality. Due to the heterogeneous nature of the disease, OI is generally classified into different types (Type I – VIII) based on the severity as well as the gene/protein that is affected/targeted [1]. The deformities shown by Types I, III and IV can be distinguished readily using radiological features and hence are commonly used in most studies. For individuals affected, skeletal deformity is a common symptom during childhood, whereas fracture risk remains high throughout life. Due to the high importance of collagen in various functions in the body, OI can also be accompanied with a wide range of other problems, such as impaired lung function, spine deformities, heart valve abnormalities, etc.

In most cases of OI, the common paradigm for bone quality assessment is via the measurement of bone mineral content. Given the complex nature of the bone, it has been understood that its micro-structural organization plays an important role in modulating its properties. Accurate visualization of such micro-architecture is not possible using standard clinical imaging techniques due to limited resolution. Additionally, radiation exposure in X-ray based imaging techniques is also a concern as pediatric subjects suffering from this disorder undergo repeated imaging during the course of treatment. With the advent of ex-vivo imaging techniques, such as micro-computed tomography (μ CT), micrometer resolution scanning of bone specimens has made it possible to explore small structures (such as osteocyte lacunae, vasculature, etc.) in the interior of the bone. This has also paved way for complex analysis of bone porosity using direct and indirect 3D measurements. We have previously demonstrated the potential of using morphometric measurements for accurate characterization of the cortical bone network. Characteristics such as cortical porosity, canal diameter, and canal connectivity undergo significant changes in OI bone compared to a pediatric control group. In this study, we investigate the use of advanced textural characterization and an application of such features in a computer aided diagnosis framework for predicting the presence or absence of OI in bone samples.

We use Minkowski Functionals (MF), which provide a detailed topological and geometrical description of the underlying patterns within the images, for high dimensional characterization of the μ CT images. We have previously demonstrated the applicability of such features to other clinically relevant imaging-based computer-aided diagnostics tasks, specifically for characterizing lesions on dynamic breast MRI and pathological patterns indicative of interstitial lung disease as revealed by CT [2,3]. This work is embedded in our group’s endeavor to expedite ‘big data’ analysis in biomedical imaging by means of advanced machine learning and pattern recognition methods for computational radiology and radiomics, e.g. [9–39].

2. DATA

2.1 Subject recruitment

A total of 21 samples harvested from 13 children who underwent osteotomies for surgical correction of limb deformities caused by OI. In addition, a total of 19 specimens from 15 (healthy and pediatric) cadavers who had no history of bone pathology were harvested. All tissue samples were collected with written IRB approval (Rush University Medical Center and Marquette University). Specimens were fresh frozen prior to imaging.

2.2 Synchrotron radiation μ CT (SR μ CT) imaging

All bone fragments were imaged (continuous mode, 1025 projections, 180° rotation) on the tomography beamline at the Advanced Light Source (BL 8.3.2, Berkeley, CA) using a monochromatic X-ray energy of 17 keV. To reduce phase contrast effects and improve resolution, we used the beamline's newly commissioned Optique Peter X-ray microscope (Lentilly, France), which allows for closer (i.e., <5mm) scintillator-to-objective distances. Further details of the setup can be found in [5]. A combination of the 4× and 10× objective lenses was used, with resulting nominal pixel sizes of 1.7 μ m and 0.6 μ m, respectively. After flat field correction, subsequent reconstructions were performed using a filtered back projection algorithm in Octopus commercial software (Octopus 8.6, inCT, Ghent, Belgium) to generate scaled, 16-bit TIF stacks. The linear scaling equation was embedded in the header file such that floating-point gray values could be recovered for composition measurements.

3. METHODS

3.1 Texture analysis

Minkowski Functionals (MF) are used to characterize morphological properties of binary images i.e. shape (geometry) and connectivity (topology) [7]. Four MF features namely volume, surface, curvature and Euler characteristic can be calculated from binary 3D image data as follows

$$\begin{aligned}\text{Volume} &= n_c, \\ \text{Surface} &= -6n_c + 2n_f, \\ \text{Mean Breadth} &= 3n_c - 2n_f + n_e, \\ \text{Euler Characteristic} &= -n_c + n_f - n_e + n_v,\end{aligned}$$

where n_c is the number of cubes, n_e is the number of edges, n_f is the number of faces and n_v is the number of vertices, if image voxels are represented as 3D cubes.

MFs are defined for binary patterns, and hence the μ CT images require a thresholding step before these features can be computed. In previous studies [6] we have used a range of thresholds, which capture information in high dimensional features. Having high dimensional feature representations is an advantage as can be seen here in Figure 1. We can see a good distinction between the features when the represented as a function of their thresholds. This is an additional advantage of using MF.

In this analysis, however, because of the high signal-to-noise ratio and enhanced spatial resolution of the μ CT, the images have a clear bimodal histogram (Figure 2, central column) indicating a high contrast between bone tissue and background voxels. Hence these images can be binarized using a threshold that is biologically motivated. This reduces an additional parameter to optimize for the analysis. The threshold chosen here specifically captures the fine lacunae and canal network of the bone as can be seen in (Figure 3, right column), hence the characterization performed using MFs can be considered to describe specific properties related to it.

3.2 Classification

The extracted vectors are divided into training and test data sets and used as inputs to a Support Vector Machine (SVM) classifier. We follow a sub-sampling cross-validation strategy ensuring that samples from the same subject are not a part of the training as well as test set. The free parameters of the SVM are optimized using the training set only. Subsequently, during the testing phase, the trained SVM is used to classify the image data of the independent test set. A Receiver Operating Characteristics (ROC) curve is generated and used to compute the Area Under the Curve (AUC), as a measure of the diagnostic accuracy of the classification. This process is repeated 50 times, i.e. 50 different training/test splits, to obtain a robust estimate of classification performance.

4. RESULTS

Figure 2 shows the classifier performance obtained based on 3D MF feature vectors extracted from the image data. The highest AUC values are observed with the combined MF feature (mean AUC = 0.96), which is a 4D vector of all four MF features, which is better than using individual MFs. The best performance among the individual features is observed for the MF “curvature” (mean AUC = 0.85), which characterizes the edges within a binary object. This suggests that topological properties can accurately capture differences in the bone canal network micro-architecture.

5. DISCUSSION

There has been surprisingly little data examining the effects of OI on bone development. Fewer studies have performed a detailed analyses of bone micro-architecture in OI. Most studies explore the use of histomorphometric parameters for characterization of bone structure. Although efforts have been made the results so far have not been very conclusive. Part of the difficulty in studying this disease in human beings is the difficulty in obtaining bone specimens for ex-vivo analysis. Additionally, current clinical imaging techniques have limited resolution to study micro-structure in detail. Researcher have recently explored the use of high-resolution peripheral quantitative computed tomography (HR-pQCT) to analyze bone composition and structure in vivo. One such study [8] reported decreases in OI volumetric bone mineral density and several trabecular parameters; however, the study was limited as only at the ultra-distal radius and ultra-distal tibia could be images and also the limited resolution restricted the accurate visualization of the canal network. In the case of our study, the use of SR μ CT allows for simultaneous analysis of cellular and tissue level properties describing bone structure, as well as bone mineral characteristics assessed using

monochromatic X-rays. Using μ CT, the canal networks can be visualized with micrometer resolution, allowing for detailed study of cortical bone micro-architecture. We have previously shown that using such data; degenerative changes in OI can be quantified. Increases in porosity, canal diameter and connectivity [4] were noted in subjects with OI implying that the bones tend to lose their compact and organized canal network.

In this preliminary study, we investigated the use of advanced texture characterization methods to quantify OI induced differences and classify between images of healthy and OI bone samples. The individual features show adequate performance in the classification task, with AUCs ranging from 0.73 to 0.85. This shows that each of these features is able to capture subtle underlying properties of the 3D micro-patterns of the canals. It is interesting to note that Minkowski Functionals are particular efficient at capturing underlying topology. Hence based on the threshold chosen, it can be concluded that the properties of the bone canal network can be used a potential biomarker in cases of OI. Interestingly, a combination of the individual features produces the best results suggesting that the features may capture complimentary information regarding the images. This implies a better characterization is obtained when the properties captured by each of these individual features are leveraged in conjunction. Topological characterization of bone using MF features is able to capture such difference accurately, as evidenced by the high AUCs obtained. Our results suggest that characterization of micro-architecture using such methods can be an initial point to develop novel imaging biomarkers for detecting the presence and potentially quantify the severity of OI. This aspect however warrants more in-depth analysis in future research.

6. CONCLUSION

The results presented in this work show that 3D characterization of cortical bone using MF features can be used to classify images of healthy and OI bone with high diagnostic accuracy. In conjunction with previous work on morphometric characterization of OI bone in 3D, we can conclude that SR μ CT imaging combined with advanced image analysis can be used as a tool for developing a better understanding of the pathophysiology of OI. Although, there are methodological limitations that need to be resolved, our results here, suggest that topological features can be potentially useful to further serve as quantitative imaging biomarkers for evaluating the presence or progression of OI.

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Figure 1.

Minkowski Functionals plotted as a function of thresholds over the images. The mean values of each functional for each group are plotted here. Some of the functionals capture differences across thresholds. Specifically it observed that Curvature and Euler Characteristic have different trends for healthy and diseased subjects.

Figure 2.

Sample images from a subject with osteogenesis imperfecta (top row) and a healthy subject (bottom row) demonstrating bi-modal histograms (central column images). The last column on the right shows the effect of applying a gray level thresholding based on the histogram to the original images. This represents a porosity mask (of lacunae as well as canals) with bones represented in white. Minkowski functionals can capture the topological properties such of binary patterns. The images in this figure represent only single slices of a multi-stack image dataset obtained from micro-computed tomography.

Figure 3.

Comparison of classification performance for different Minkowski functionals in the task of classifying image data as healthy or affected by osteogenesis imperfecta. The error bars (light blue) represent the standard deviation of the mean AUCs. A 4D feature vector obtained from combining all four MFs perform best at the classification task.

Table 1

AUC values obtained for each MF features over 50 iterations of the cross-validation scheme. The 4d 'combined' feature of all the MF performs best at the classification task

3D Minkowski Functionals	AUC
Volume	0.732 ± 0.180
Curvature	0.813 ± 0.164
Surface	0.854 ± 0.149
Euler	0.731 ± 0.136
<i>Combined</i>	0.955 ± 0.088