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Trabecular Bone Structure Analysis in the Limited Spatial Resolution Regime of In Vivo MRI

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Abstract

Rationale and Objectives—To develop a method for processing and visualization of trabecular bone networks on the basis of MR images acquired in the limited spatial resolution regime of *in vivo* imaging at which trabecular thickness is comparable to voxel size.

Materials and Methods—A sequence of processing steps for analyzing the topological structure of trabecular bone networks is presented and evaluated using three types of data sets: images of synthetic structures with various levels of superimposed Gaussian noise, micro-CT images of human trabecular bone downsampled to in-vivo resolution, and *in vivo* micro-MR images from a prior longitudinal study investigating the structural implications of testosterone treatment of hypogonadal men. The simulated images were analyzed at a voxel size of $(150\ \mu\text{m})^3$, the clinical MRI data had been acquired with $137 \times 137 \times 410\ \mu\text{m}^3$ voxel size. The technique is a modification to the virtual bone biopsy processing chain that involves a sinc convolution step immediately preceding binarization, and employs the Manzanera-Bernard thinning algorithm for obtaining the 3D skeleton prior to topological classification. The detectability of plate and rod bone elements was also analyzed theoretically.

Results—As compared with previously published techniques, the approach produced a more accurate bone skeleton in the micro-CT and simulation experiments, with clear improvement in preservation of rod and plate elements. Simulations suggest that rods are detectable down to a diameter of approximately 50% of the MRI voxel length, whereas plates can be detected at thicknesses of 20% or more of voxel length. For *in vivo* studies, it was shown that the method could recover the treatment response in terms of the ensuing topological changes in patients undergoing antiresorptive treatment.

Conclusion—The algorithm for processing of *in vivo* micro-MR images of trabecular bone is superior to prior approaches in preserving the topology of the network in the presence of noise.

Keywords

Trabecular bone; Virtual bone biopsy; 3D skeletonization; micro-MRI

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INTRODUCTION

The recognition of the role of architecture as a determinant of bone strength second in importance to density (1–3) has given substantial impetus toward the development of image-based methods for quantification of the three-dimensional structure of trabecular bone. Since trabecular bone remodels several times faster than cortical bone, it also responds faster to hormonal changes, such as loss of estrogen following menopause (4), or intervention with pharmacologic agents (5), cyclical loading (6), etc. Trabecular bone architecture is also altered in a characteristic manner in osteoarthritis (7). A number of programs, including the proclamation of the National Bone and Joint Decade by the US Government have fostered the development of capabilities for *in vivo* assessment of trabecular bone architecture in recent years.

Both micro-computed tomography (μ -CT) and micro-magnetic resonance (μ -MRI) have demonstrated their potential as modalities to provide quantitative information on the bone's microarchitecture in specimen studies at a resolution of tens of micrometers or better (8,9). In recent years, both modalities have evolved to the stage allowing *in vivo* imaging of the trabecular microarchitecture at peripheral skeletal locations such as the distal radius, tibia or calcaneus at voxel sizes on the order of 80–200 μ m (10–15).

Bone marrow in the distal extremities is all fatty and appears bright in MR images, whereas bone appears with background intensity. In principle, this is therefore a comparatively simple system to analyze. However, the currently achievable resolution (limited by detection sensitivity in MRI and radiation dose in CT) is not sufficient to fully resolve the trabeculae. Besides partial volume blurring, the intensity histogram is broadened by noise which prevents straightforward segmentation. Other difficulties result from subtle subject movement during the scan causing blurring and artifacts, which can be corrected in part by prospective motion correction techniques involving navigators (14), or retrospectively with methods such as autofocusing (16). Several approaches have been described for processing images as a means to compute bone volume fraction (BVF) and structural describing parameters of scale such as trabecular thickness (17) or topology from images acquired in the limited spatial resolution regime of *in vivo* μ -MRI (18,19). Another parameter of relevance to the bone's mechanical behavior is structural anisotropy, which is a consequence of Wolff's law that states that bone remodels in response to the stresses to which it is subjected (20). Of particular interest, however, is the topology of the network, for example, the knowledge of whether the bone is plate- or rod-like. A number of algorithms for quantifying such structure have been published, yielding parameters such as the structure model index (21) and digital topological parameters, include surface-to-curve ratio and erosion index (18).

In prior work from this laboratory *in vivo* images acquired in clinical studies have been processed by subjecting the data to a sequence of processing steps that comprise the *virtual bone biopsy*. These steps include motion correction (14,16), automatic region of interest segmentation (22,23), automatic 3D registration (24,25) (for longitudinal studies), correction for intensity inhomogeneity and bone volume fraction map (26,27), fuzzy distance transform (17) (for computing trabecular thickness), subvoxel processing (28), thresholding, and finally digital topological analysis in which each voxel in the bone network is classified as belonging to a surface, curve, or their intersections (18). While the method has been successful in distinguishing subjects with fractures from those without fractures (29) and quantifying the response to treatment (30), we encountered some difficulties and limitations of the current algorithms. Specifically, the thresholding step (i.e. converting from grayscale to binary data) is problematic, leading to artifactual branches in the 3D skeleton, and ultimately to errors in the measured topological parameters.

In this paper we introduce a new substantially improved processing cascade for the virtual bone biopsy, where the steps surrounding binarization are replaced by a more robust chain of operations. Subvoxel processing is replaced by simple 3D sinc interpolation, and we demonstrate how this approach results in a cleaner (and readily analyzable) binary volume input to skeletonization. Furthermore, we precede the digital topological analysis step by the Manzanera-Bernard skeletonization procedure (31), a robust thinning algorithm that has been shown to preserve topology as well as geometric features of the binary volume.

We show, by direct comparison with the original method, the qualitative improvement on the basis of simulated MR images obtained from synthetic plate and rod structures as well as high resolution μ -CT images of trabecular bone specimens. Furthermore, we derive a method for determining sensitivity of the technique, in terms of the size of the smallest detectable trabecular plates, rods, and perforations in plates. We apply the new processing to in vivo MR images and provide evidence that the virtual bone biopsy can accurately and reproducibly distinguish the 3D trabecular architecture in clinical situations. Finally we show, by reprocessing data from a previously published clinical study, that the new processing system is sensitive enough to detect small changes in trabecular architecture in response to drug intervention.

MATERIALS AND METHODS

All processing algorithms and simulations were implemented in C++ and executed using ChainLink (<http://chainlink.sourceforge.net>), a user interface for calling C++ code from Matlab-style scripts, developed by one of the authors (JFM).

A. Partial Volume Effects and Sinc Interpolation

Partial volume blurring occurs when the voxel size is on the same scale (or larger than) the underlying structure. In the case of trabecular bone MRI, it means that voxels cannot be strictly classified as containing either pure bone or pure marrow. Instead, most voxels have a grayscale value roughly representing the fraction of the voxel occupied by bone (unlike in CT, higher MRI signal indicates more marrow, and hence less bone). As mentioned in the introduction, existing algorithms for skeletonization and topological classification of trabecular bone networks require binary input data. It is therefore necessary for the grayscale MRI data to be converted into a 3D binary volume (i.e. consisting of zeros and ones). The simplest procedure to achieve this is by thresholding, so that voxels with signal intensity below a user-determined value are classified as bone. Due to artifactual intensity variations across the volume of interest (such as resulting from the inhomogeneous reception profile of surface coils), the threshold level should have a spatial dependence. Various local threshold methods exist to effectively deal with this problem (see, for example (26)).

Even in the ideal case (of no intensity variations or measurement noise), simple thresholding is not adequate for generating a binary volume because it results in loss of information and topological misclassification. The fallacy of arbitrarily setting an intensity threshold for binarization is illustrated in Fig. 1 with a simulated MR image of a synthetic structure consisting of two plates and three rods. While the resolution (150 μ m isotropic) is sufficient to resolve the individual elements, the thresholding step results in a very crude 3D representation of the object, notably a disconnection of two of the rods and breaking the object into two parts, thus altering the structure's topology.

An alternative to a simple threshold is the subvoxel processing technique (28). This procedure involves subdividing each image voxel into a number of smaller pieces, called subvoxels. The cumulative bone volume fraction (as given by the grayscale intensity) is preserved within each original voxel and is distributed among the subvoxels in a manner depending on the

surrounding grayscale values. In this way the compactness of the bone is used to effectively boost resolution. While subvoxel processing has been successfully applied to in-vivo MRI data in the authors' laboratory (see, for example (32) for a recent review), the technique has two major limitations. One is that it involves two rather arbitrary thresholding steps before subdivision to separate out the pure marrow voxels, and then again after subdivision to generate the binary volume. The second difficulty is that the theory of subvoxel processing relies on the assumption that the grayscale intensity is proportional to the amount of marrow in a voxel. Even in the noiseless situation this is not the case since the signal intensity in MRI is the result of a sinc convolution of the spin-density function.

Another method for dealing with the partial volume effect is sinc interpolation, also known as voxel shifting or zero padding in Fourier space (33). This technique has been used extensively to improve the appearance of MR images, particularly in the context of magnetic resonance angiography (34,35), where the blood vessels are sparse and typically thinner than voxel diameter. Vessels located at the center of a voxel are more detectable than those located toward the edge of a voxel. Because the reconstruction lattice is arbitrary, vessel detection can be enhanced by shifting the voxels, or by increasing the density of the reconstruction grid, typically by a factor of 2 in each direction. Practically, this is achieved by zero padding in Fourier space before reconstruction using the inverse discrete Fourier transform (IDFT). Apodization is generally used to reduce Gibbs ringing. In this study, a Fermi filter was used with 20% transition region in all three directions.

In the present context of structural analysis of trabecular bone, sinc interpolation has other advantages besides improved appearance of small trabecular elements. Indeed, whereas using sinc interpolation factors greater than 2 do not yield much additional improvement in terms of image appearance, the use of a higher interpolation factor (e.g. 3–6 in each direction) is expected to substantially improve the quality of 3D skeleton since skeletonization algorithms perform best with a very densely sampled binary volume as input. Furthermore, as the interpolation factor increases, we approach the continuum case, where we can think of the reconstructed image as a 3D continuous function. The advantage is that we then interpret the reconstructed image as a convolution of the underlying 3D spin-density function (i.e. the complement of the trabecular bone volume) with the point-spread function (or apodized sinc kernel). We note that in practice, sinc interpolation is actually only needed up to a factor of 2 or 3 in each direction, and then further interpolation can be achieved using simple linear interpolation without incurring significant error. We also note that other interpolation schemes may also produce visually good results, but the authors prefer to use apodized sinc interpolation so that the resulting image can be readily analyzed in terms of the detectability of ideal plates and rods, as described in Section C below.

B. VBB Processing Chain

The input to the new Virtual Bone Biopsy (VBB) data processing algorithm is a 3D grayscale image sampled at μ -MRI voxel size ($150 \times 150 \times 150 \mu\text{m}^3$ for simulations and $137 \times 137 \times 410 \mu\text{m}^3$ for in vivo examples). The **first step** is to correct intensity inhomogeneity as it occurs, for example, when surface coils are used for detection, so that each voxel contains a fractional grayscale value where 1=100% represents the intensity of pure marrow. This is achieved using a local threshold algorithm (26). In the **second step**, the image is interpolated using a 3D *sinc* function, usually by a factor of $3 \times 3 \times 3$ (although larger interpolation factors can be used, albeit at the expense of computation time and memory). Recall that this type of interpolation is natural for MRI, and we think of the resulting image as representing the original spin-density function convolved with an apodized 3D *sinc* kernel. The **third step** of thresholding yields a 3D binary volume that is the input to fourth step of 3D skeletonization. For this purpose we have selected an algorithm recently described by Manzanera et al (31) (henceforth referred to

as the *Manzanera-Bernard algorithm*). This robust thinning procedure has certain desirable properties, including the preservation of connectivity and symmetric thinning (in a sense described in (31)). For binarization, we have chosen threshold level at 80% of the marrow intensity because we have found empirically that this provides accurate skeletons. However, other values can be used, and, beyond the scope of this paper, the effect of varying the threshold can be analyzed using the method described in section C. **Finally**, digital topological analysis (DTA) is performed on the resulting skeleton to yield topological parameters such as surface-to-curve ratio and erosion index (18). Note that because DTA requires a skeleton of single-voxel thickness (and since the Manzanera-Bernard algorithm produces a skeleton having a thickness of up to *two* voxels) a further DTA skeletonization is required as part of the DTA classification. Skeletonization converts trabecular plates to surfaces and rods to curves under preservation of topology. Based on the inspection of a bone voxel's $3 \times 3 \times 3$ neighborhood most topological classes can be uniquely determined for each bone voxel as described in detail by Saha et al (18).

C. Synthetic Plate and Rod Simulations

We now return to the previously introduced synthetic structure consisting of two plates interconnected by three rods, mimicking a small portion of trabecular bone (see Fig. 1). It was created as a binary 3D array sampled at $20 \times 20 \times 20 \mu\text{m}^3$ resolution. Since in MRI marrow is the signal-producing entity, voxels inside the object were set to zero, those outside to one. Although not entirely realistic, plates (typically on the order of 100–150 μm thickness) were represented as thin (150 μm) parallelepipeds, the three rods as cylinders of diameter 150 μm , 85 μm , and 150 μm . Spacing between the plates was 880 μm . To simulate the MRI acquisition process, a 3D DFT was applied to obtain k-space samples. Then a central region of k-space was extracted, and inverse DFT applied to obtain a downsampled image at $150 \times 150 \times 150 \mu\text{m}^3$. To reduce Gibbs ringing, the k-space data were apodized using a 3D Fermi filter with a 20% transition region. Finally, the resulting images were subjected to various versions of VBB processing, including subvoxel processing and the new processing method.

To determine the sensitivity and accuracy of the interpolation and thresholding steps of the VBB procedure, a number of additional rod and plate structures were simulated. First, a rod was modeled as an infinite cylinder, and the diameter was varied between 0 and 450 μm . For each diameter, a MRI simulation was performed as above, and the resulting image was sinc interpolated and thresholded at 80% (as in the new VBB algorithm). For each cylinder size, the apparent diameter (after thresholding) was compared against the actual diameter. A similar procedure was performed for a plate, modeled as an infinite 2D sheet with thickness ranging between 0 and 450 μm . Finally, the simulation was performed on a plate of thickness 150 μm with a circular hole of diameter ranging from 0 and 450 μm . For each size, the apparent hole diameter (after thresholding) was compared to the actual diameter.

D. MRI Simulations Based on High-Resolution μ -CT Data

Beginning with a 3D μ -CT scan acquired from a specimen of human trabecular bone core (9 mm diameter and length of the distal radial metaphysis), a simulated μ -MRI data set was created. The downsampling (from approx. 22 μm to 150 μm isotropic) was performed using the technique described in the previous section, i.e. by cropping in spatial frequency space. The data was then processed using the procedure from section B, and the resulting 3D skeleton was compared qualitatively with the original high-resolution data set to determine to what extent the trabecular topology had been preserved. To evaluate the robustness of the algorithm with respect to measurement noise, the same experiment was repeated with Gaussian noise added to the simulated k-space data prior to image reconstruction. The noise level was chosen so that the image had a realistic signal-to-noise ratio of approximately 13:1 (somewhat higher than what is typically achieved in current clinical protocols). We note that despite the fact that

the simulated data was derived from an underlying μ -CT data set, the sinc kernel remains the natural choice for interpolation in the data processing chain, since downsampling was performed by cropping in Fourier space, thus mimicking acquisition in MRI.

E. In Vivo Analysis

Lastly, the performance of the new VBB processing procedure was tested by re-examining the data of a recently published clinical study (30). In brief, the original study was designed to evaluate structural implications on the trabecular bone in men with testosterone deficiency (also referred to as hypogonadism) as a result of pituitary disease and other conditions and whether the method had the sensitivity to quantify changes in architecture in response to testosterone supplementation. Ten subjects were studied at baseline, 6, 12 and 24 months of treatment and the results were compared with 10 age and body-mass index matched eugonadal men (i.e. men with normal testosterone levels). The data indicated the hypogonadal men to have significantly impaired trabecular structure compared to their eugonadal peers (36) and further that treatment significantly improved the structural integrity of the trabecular network (30). The data consisted of high-resolution 3D spin-echo images of the distal tibia (3D FLASE (37)) at a voxel size of $137 \times 137 \times 410 \mu\text{m}^3$ in a scan time of approximately 15 minutes. The purpose of the re-examination of this data was to evaluate the sensitivity of the new processing procedure to quantify the effect of intervention in the hypogonadal group and compare the results with those obtained previously.

RESULTS

The data processing steps of the algorithm are illustrated in Fig. 2 for a typical in vivo dataset obtained from the distal tibial metaphysis at 1.5 T with a modified 3D FLASE pulse sequence (38). The entire processing cascade requires virtually no user intervention. The key step prior to intensity normalization, *sinc* interpolation, thresholding and skeletonization that could possibly require some user interaction is the disconnection of the trabecular region from the cortex. But even this step has recently been automated (23).

Fig. 1(d–i) shows the results of applying subvoxel processing to the simulated data from Fig. 1 using interpolation factors 2, 4, and 6. Even at the highest factor ($6 \times 6 \times 6$), the resulting volume does not satisfactorily represent the original structure. This is in part due to the pre-thresholding step that is a necessary component of the subvoxel processing algorithm. In contrast, the method of *sinc* interpolation (Fig. 1(j–k)) largely preserves the circular shape of the thicker rods as well as the overall structure of the model, although the thin rod ($85 \mu\text{m}$ diameter) was lost. As discussed above, the resulting structure in this case is obtained from the original model via convolution by a 3D *sinc* kernel, and is therefore predictable. For example, it is noted that the thinnest (middle) rod is not detectable with the method, as predicted below.

The results of the simulations on individual rods, plates, and perforations are shown in Figs. 3 and 4. We note that for plates and rods with thickness on the order of the voxel dimension (i.e. $150 \mu\text{m}$ in our discussion), the apparent thickness exceeds actual thickness by approximately 75%. According to Fig. 4, rods become undetectable (i.e. are above the threshold) when the diameter falls below around half of the voxel size, whereas plates can be detected down to a thickness of 20% of voxel size.

Simulations based on downsampling μ -CT images are shown in Fig. 5. The data indicate that much of the trabecular structure can be recovered by VBB processing, even after adding noise and downsampling to $150 \mu\text{m}$ isotropic voxels. The interpolation step, preparatory to thresholding and skeletonization, is crucial for capturing the grayscale information contained in the simulated MR image. Fig. 6 demonstrates the improvement afforded by the new

processing algorithm in terms of reduction of artifactual branches in the skeleton caused by digitization and thresholding.

The ability of the virtual bone biopsy to reproducibly track the 3D structure of bone over time is illustrated in Fig. 7 with images from a 42 year-old female subject comparing baseline to six-month follow-up. The 3D structure at each site matches in the two scans, and the VBB parameters listed in Table 1 can distinguish between the two sites.

The results, in terms of two composite structural parameters (surface-to-curve ratio and erosion index), of applying the new processing algorithm to the previously published testosterone replacement study are shown in Fig. 8. The magnitude of the treatment effect increased as expected from 6 to 24 months, with statistically significant changes at the latest two time points. The p-values for 12 and 24 month changes are lower than those reported in (30) ($p=0.02$ at 12 months and $p=0.004$ at 24 months for both parameters), suggesting stronger associations than achievable with the prior processing method. The data for the (untreated) eugonadal group in whom previously no longitudinal changes were detected (30), has not been included in the present analysis.

DISCUSSION

There is compelling evidence that, compared to the reduction in bone mass and density, age and osteoporosis-related changes in the network's topology are disproportionately large (29, 39), leading to perforations of plates and disconnections of rod-like trabeculae. Such an etiology is commensurate with the notion that plate-like bone is gradually being converted to rod-like bone, as shown in μ -CT images from iliac crest bone biopsies (10,40). Further, *in vivo* image data suggest that a more plate-like architecture is biomechanically more competent than one characterized by a rod-like architecture when comparing patients with vertebral fractures with their unfractured peers (29,41,42). However, topological classification (e.g. the determination of whether a structure element pertains to a rod or plate) is sensitive to resolution. A narrow, ribbon-like plate may, after skeletonization be converted to either a surface or, at lower resolution, a curve. In the limit, as shown in this work, it may not be detected at all.

The robustness of the new algorithm is evident in the comparison of the downsampled and noise-corrupted images derived from a high-resolution μ -CT image of a specimen in Fig. 5, generated to mimic *in vivo* μ -MRI conditions. The data show that the VBB is able to recover the essential structural features. Moreover, the artifactual branches in the skeleton network (appearing in Fig. 6), which we ascribe to subvoxel processing, are not present with *sinc* interpolation performed in conjunction with the Manzanera-Bernard skeletonization algorithm. We expect the improved processing strategy to lead to greater accuracy in the topological counts, since such branches do not reflect true structural features.

The thinnest trabeculae typically encountered in diseased human trabecular bone may be less than 100 μ m thick (43). Based on our theoretical analysis (which predicts that rods are detectable down to 50% of the voxel length), we project that an isotropic resolution on the order of 160 μ m should be adequate to accurately recover the trabecular network. Of course these numbers are dependent on the chosen threshold, and the sensitivity to rods and plates could be enhanced by modifying this threshold. While Fig. 4c suggests that perforations (a common manifestation of high turn-over disease with excessive osteoclastic resorption (40)) are only detectable when their diameter exceeds 120% of the voxel length (assuming a plate thickness of 1 voxel), we expect to be able to detect a change in the VBB parameters resulting from only minor (i.e. sub-voxel) pitting throughout the volume of analysis. This is because the parameters represent a statistical average, and are therefore affected by slight variations in bone

thickness. In other words, in light of noise and other factors, we must consider the conditional probability that we observe a perforation given that one exists of a particular diameter.

Although the above analysis could be used to develop a method for measuring trabecular thickness, an average thickness can be directly quantified based on the grayscale bone-volume-fraction maps, as shown previously by resorting to the fuzzy distance transform algorithm (17). However, we are primarily interested in analyzing topology, rather than structural thickness, which is known to change little in postmenopausal osteoporosis (44).

The data in Fig. 7 and Table 1 lend further credence to the power of the algorithm, showing good agreement between baseline and six-month follow-up for some of the topological parameters at two randomly selected sites, both visually and numerically. Lastly, the data of Fig. 8 show that the method is able to detect the previously observed temporal changes with high statistical significance (considering the small number of subjects studied). While the absolute values differ somewhat from those reported in (30) they are in overall agreement with each other while the quality of the images is substantially improved over that achieved with the previous processing strategy.

Clearly, more work will be required to demonstrate the improved performance, in particular the algorithm's ability to detect small effects in response to intervention. To this end, further validation work is required to assess reproducibility and to further examine the sensitivity of the method to noise, particularly systematic or colored noise.

Currently, most imaging protocols for trabecular bone structure analysis performed in the various laboratories are based on anisotropic 3D imaging, typically performed such that the resolution along the axial direction is lower than in the transverse direction (see (32) for a review) even though isotropic resolution would be preferable. Unfortunately, the practically achievable SNR imposes limits on the voxel volumes that yield images of adequate quality in realistic scan times. Since trabeculae run preferentially along the axial (i.e. primary loading) direction, based on the present results, the algorithm is likely to accurately capture the longitudinal trabeculae, but the transverse structural elements are expected to be more prone to error. These transverse trabeculae play a crucial role in preventing fractures by acting as cross-ties between the plates, therefore their detection is important. Enhanced SNR as a result of improved coil technology and operation at higher field will likely make acquisition of images possible at isotropic resolution with a target voxel size on the order of 150 μ m, thus improving the detection of these transverse trabeculae.

Lastly, the algorithm is, of course, not limited to processing of MR images, although it should be noted that use of sinc interpolation is most natural in the context of MRI, and other interpolation strategies may be preferable for other modalities. The emergence of high-resolution peripheral quantitative CT (45) as well as multi-detector CT for structural imaging of vertebral trabecular bone (41), has substantially enlarged the field of *in vivo* bone structure analysis. Whereas in MR the practically achievable resolution is limited by scan time, the ultimate resolution in CT is primarily dictated by radiation dose considerations. Therefore, for both technologies there is a compelling need for improved methods to recover structural information in the regime of limited spatial resolution and SNR.

CONCLUSION

A data processing technique for analyzing 3D topology of trabecular bone images in the limited spatial resolution regime of *in vivo* MRI has been described. Using sinc convolution as a preparatory step to skeletonization, the method produces a well-defined and analyzable relationship between the original bone structure and the resulting 3D skeleton. The algorithm

has been shown to qualitatively preserve topology in synthetic, specimen, and in vivo situations, and to preserve statistical significance in a previously analyzed clinical study.

Future work will focus on quantitative validation, exploring how sensitive the technique is to small changes in bone, and determining an optimum threshold level for various types of analyses.

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Fig. 1.

(a) Synthetic structure mimicking trabecular bone. Two parallel plates (spacing of 880 μm) interconnected by three rods with thicknesses 150 μm (top and bottom) and 85 μm (middle); (b) Simulated (noiseless) image of a section parallel to the plates bisecting the object at a resolution $150 \times 150 \times 150 \mu\text{m}^3$. The slice is parallel to (and in between) the two plates. (c) 3D volume obtained by thresholding the simulated 3D MRI dataset at 80% of the marrow level, demonstrating that simple thresholding is not adequate for analyzing topological structure; (d), (f), and (h) are subvoxel processed image sections (parallel to and in between the two plates), and (e), (g), and (i) are the corresponding volumes obtained by thresholding at 80%; (j) Section of the data set sinc interpolated by $6 \times 6 \times 6$ and apodized using a 3D Fermi filter with 20% transition width; (k) 3D volume obtained from (j) using a threshold at 80%.

Fig. 2.

(a) In vivo μ -MRI of the distal tibia; (b) region of interest isolated using an automatic segmentation algorithm (23); (c) intensity normalized to remove coil shading using local threshold algorithm (26); (d) *sinc* interpolated by factor of $3 \times 3 \times 3$; (e) thresholded at 80% of marrow intensity; (f) skeleton map obtained with Manzanera-Bernard algorithm (31); (g) 3D core of skeleton; (h) DTA classification showing surfaces (resulting from skeletonization of plates) in red, and curves (resulting from skeletonization of rods) in blue.

Fig. 3. Simulated signal profiles for rods and plates of varying thicknesses using *sinc* interpolation. Dotted lines show the apparent thickness after thresholding at 80% of the marrow level; (a), (b), (c), and (d) show profiles for rods (cylinders of infinite length), and (e), (f), (g), and (h) show profiles for plates (2D-infinite sheets).

Fig. 4.

Simulated apparent thickness vs. actual thickness for rods, plates, and perforations in plates when thresholded at 80% of the marrow intensity. Note that rods become undetectable when the diameter falls below around half of the voxel size, whereas plates can be detected down to a thickness of 20% of voxel size, and perforations can be detected for diameters exceeding 120% of the voxel size. As noted in the text, these numbers depend on the chosen threshold.

Fig. 5.

VBB processing steps, with the starting point being a 3D micro-CT image dataset of trabecular bone in a tibia specimen (left), downsampled to μ -MRI resolution ($150\ \mu\text{m}$ isotropic), sinc interpolated, binarized, and skeletonized as described in the text (upper double row of images). Subsequently, gaussian noise was added to the simulated MRI data, to achieve SNR of approximately 13:1 (lower double row of images). Color coding of DTA classified images: surfaces (resulting from skeletonization of plates) are red, curves (resulting from skeletonization of rods) are blue. It is visually apparent that the topology of the structure is largely preserved after downsampling to *in vivo* MRI resolution and addition of noise.

Fig. 6. Skeletonized data set using (left) sub-voxel processing and DTA classification and (right) sinc interpolation and Manzanera-Bernard followed by DTA skeletonization.

Fig. 7. In vivo baseline (a) and six month follow-up (b) scans of the distal tibia of a 42 year-old woman. The 3D skeletons obtained at two different locations using the new VBB processing procedure. The trabecular bone at site #1 is considerably sparser. Note the visually apparent agreement between baseline and follow-up images.

Fig. 8.

Percent change in two composite VBB parameters for a group of ten hypogonadal men treated with testosterone over a period of two years. Both indicate an increase in surface/curve ratio as well as decrease in erosion index commensurate with an improvement in the trabecular network over time. The statistical significance for the new processing results is generally greater than that found for the previously published data (30) using the original processing algorithms.

Table 1

Topologic Classification Parameters for Cores Shown in Fig 7 Demonstrating Reproducibility from Baseline to Follow-up

	Site #1 BaselineFollow-up		Site #2 BaselineFollow-up	
Skeleton density	1.71%	1.74%	2.99%	3.14%
Plate density	1.48%	1.52%	2.62%	2.79%
Rod density	0.19%	0.18%	0.28%	0.26%
Junction density	0.04%	0.04%	0.09%	0.09%