



HAL
open science

HOMOGENIZATION AND μ CT ANALYSIS FOR THE TRABECULAR BONE REMODELLING

Claudia Chan Yone, Jean-Louis Milan, Jean-Marie Rossi, Jean-François Witz,
Mathias Brieu, Patrick Chabrand

► **To cite this version:**

Claudia Chan Yone, Jean-Louis Milan, Jean-Marie Rossi, Jean-François Witz, Mathias Brieu, et al..
HOMOGENIZATION AND μ CT ANALYSIS FOR THE TRABECULAR BONE REMODELLING.
Journal of Biomechanics, 2012, 45, pp.S532. 10.1016/S0021-9290(12)70533-X . hal-03550976

HAL Id: hal-03550976

<https://hal.science/hal-03550976v1>

Submitted on 14 Feb 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0
International License

Homogenization and μ CT analysis for the trabecular bone remodeling

Claudia Chan Yone, Jean-Louis Milan, Jean-Marie Rossi, Jean-François Witz,
Mathias Brieu, Patrick Chabrand

February 23, 2012

1 Introduction

1 Osteoporosis is a bone disease characterized by low bone mass but also a degradation of can-
2 cellous bone micro-architecture. Bone weakness can generate fracture, that is why tools have
3 been developed to assess probability of fracture. The clinical device DEXA, is a quantitative
4 measure of bone mineral density (result is a T-score), while FRAX® (1) is a questionnaire based
5 on statistical analysis including criteria like age, bone mass index and lifestyle. Although those
6 informations are essential in fracture assessment, one in two person undeclared osteoporotic
7 according to WHO definition (T-score < -2.5) will have a fracture (2; 3; 4; 5). That is why
8 bone quantity, or statistical analysis are insufficient to predict bone weakness, but bone quality
9 i.e bone micro-structure should be considered.

10 Many numerical models have been developed in purpose to predict bone alteration and so
11 fracture assessment. Bone alteration is due to an imbalance in the bone remodeling process :
12 quantity of new deposited tissue is smaller than the removal old matrix tissue. Furthermore,
13 bone is well known to adapt its morphology to the mechanical environment. From those obser-
14 vations many researchers developed numerical models based on biological and/or mechanical
15 criteria (6; 7; 8; 9; 10; 11; 12; 13). Among those theoretical approaches, some authors worked
16 on real cancellous bone micro-architecture alteration (14; 15; 16; 17; 18). They have simulated

17 trabecular plate perforation, decrease of bone volume fraction and loss of mechanical properties
18 which can lead to bone fracture. Those approaches are interesting because they used real human
19 bone, and predicted realistic altered cancellous micro-structure due to aging or disease.
20 Those models used micro-finite element analysis (μ FEA) based on 3-D reconstruction from
21 micro-computed tomography acquisition (μ CT). Voxels are directly convert in finite elements,
22 as a consequence models are composed of several millions of elements (until 20 millions). The
23 quantity of degree of freedom is not compatible with an iterative process in order to consider
24 biological or mechanical stimuli changes. That is why alteration was randomly distributed over
25 trabeculae and consider not any mechanical criteria. However mechanical environment play a
26 crucial role in activation (19) and localization of bone remodeling : indeed damage and cracks
27 are generally used as precursors of bone remodeling (20; 21; 22; 23).
28 In this study we will present a method to build μ FE model from μ CT acquisition reducing
29 degree of freedom in order to simulate bone degradation with an iterative process, so that to
30 integrate mechanical stimuli variations (bed-ridden case), or biological modifications (medical
31 treatment). We will study what is the influence of reducing model complexity in term of me-
32 chanical global and local behaviour. Furthermore we will investigate if material heterogenities,
33 like hypermineralized bone, influence repartition of areas which are over or under-constrained
34 among the structure. Indeed, hypermineralized bone is a privileged place of cracks accumula-
35 tion (24), and can play an important role in ordre to identify remodeling sites.

36

37 **2 Materials and methods**

38 **Trabecular bone sample and μ CT imaging**

39 Studied bone is a human femoral head collected behind a femoral neck fracture. The willing
40 donor, was a woman aged of 87 years old, her bone mass index was 19.8 (limit underweight
41 ≤ 18.5) and was prone to bone weakness because she fractured her shoulder in the past.
42 A cubic specimen was harvested (10x10x10mm) from femoral head and prepared removing
43 marrow with a water bath (37°C) containing a stirring rod. Remaining marrow was extracted
44 with compressed air. Sample was scanned by a μ CT system (model Skyscan 1172) at 20 μ m

45 resolution. Cross-section images were stored in 16-bit format (format tif) with 1000x1000
 46 pixels in size. Phantoms of cortical and trabecular bone were placed under the sample with
 47 respectively a density of hydroxyapatite of 1750 and 800mg/cm³, *i.e* a physical density of 2.17
 48 and 1.53g/cm³. These latters gave us a grayscale reference to identify material component and
 49 so mechanical properties. Some morphologic datas were computed directly after acquisition by
 50 the software SKYSCAN CTANalyser (table 1).

BV/TV (%)	BS/BV (mm⁻¹)	SMI	Tb,Th (mm)	Tb,N (mm⁻¹)	Tb,Sp (mm)	DA
29.87	10.18	0.69	0.343	0.869	0.769	0.677

*BV/TV : Bone Volume/ Total Volume; BS/BV : Bone Surface/Bone Volume; SMI : Structure Model Index
 Tb,Th : Trabeculae Thickness; Tb,N : Trabeculae Number; Tb,Sp : Trabeculae Space; DA : Degree of Anisotropy*

Table 1: Morphometric parameters computed after μ CT acquisition

51 **Homogenization/Coarsening method**

52 For the numerical study a central cubical sub-volume equivalent to 4x4x4mm (200x200x200
 53 voxels) was extracted. A coarsening method (25; 26) was applied on the whole volume contain-
 54 ing both marrow and bone tissue elements : figure 1 describe the principle in two dimensions
 55 : initial voxels of 20x20 μ m² were grouped to new voxels of 40x40 μ m² until 100x100x100 μ m².
 56 Initial micro-structure is showed in 3 dimensions without marrow voxels in figure 2(a), and
 57 figure 2(c) to figure 2(f) illustrate different case of coarsened voxel. This method allows to
 58 simulate degradation of system acquisition, but also to reduce numbers of voxels contained in
 59 studied volume.

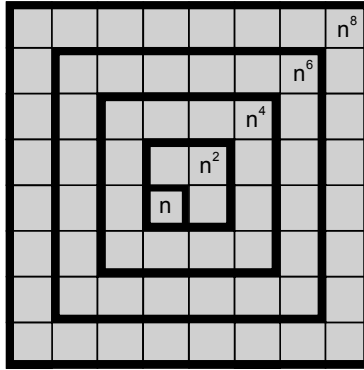


Figure 1: Principle of coarsening in two dimensions : n^m contain $m \times m$ voxels of $20\mu\text{m}$

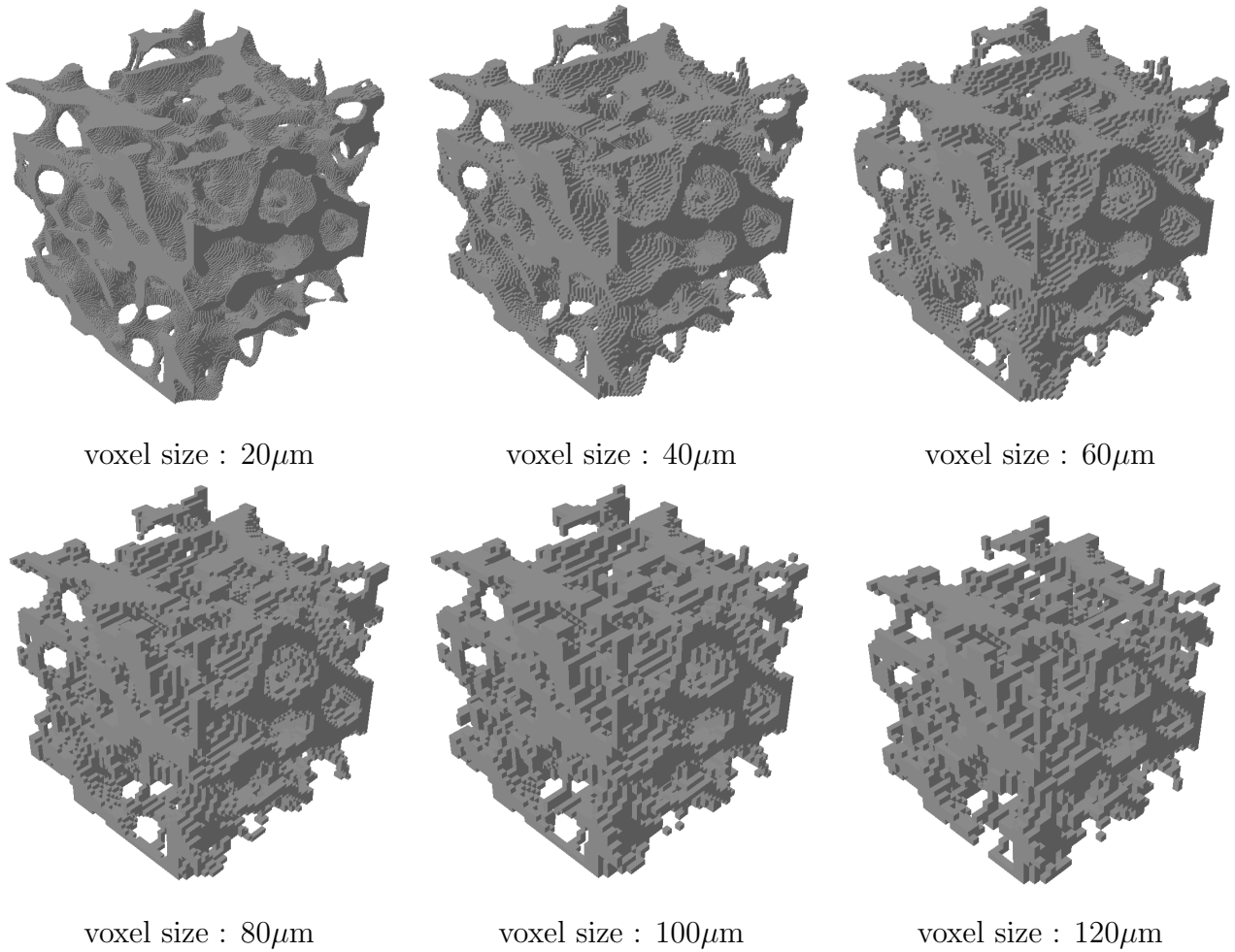


Figure 2: Coarsened models of cancellous bone for different voxel size (sample of $4\text{mm} \times 4\text{mm} \times 4\text{mm}$)

60 **Thresholding and mass computation**

61 Repartition of gray-value of whole volume was plotted (figure 3). Two significant peaks were
 62 identified : the highest correspond to the background gray-value (remaining marrow and arte-
 63 facts), although the smallest correspond to the bone tissue gray-value. Thresholding between
 64 background and bone tissue was determined as the middle point between these two peaks. As
 65 the black dash-line is cortical phantom gray-value, this graph puts forward the hypermineral-
 66 ized bone : around 70% of bone elements are hypermineralized.

67 Initial bone mass noted M_0 was computed supposing that element bone mass was linearly
 68 correlated to the gray-value element. For coarsened geometry, mass was computed from mass
 69 density and also, cortical and trabecular phantom gray-value : each bone mass element was
 70 computed and added to get total bone mass. Thresholding was made as sample bone mass was
 71 in best agreement with M_0 , so as $\frac{|M-M_0|}{M_0} \leq 0.1\%$.

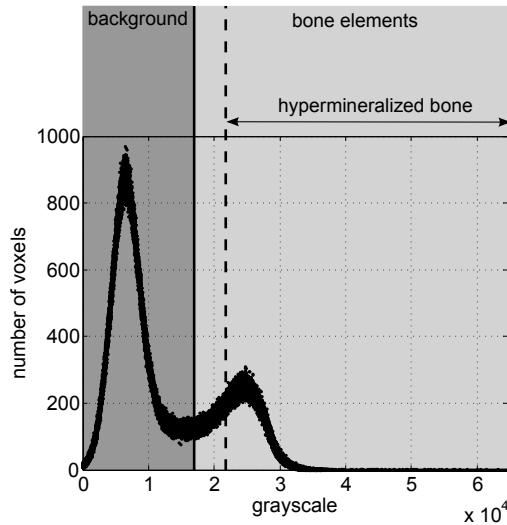


Figure 3: Grayscale of whole reference volume (without coarsening), black solid line is thresholding void/bone and black dotted line is thresholding bone/hypermineralized bone

72 **Material heterogeneous method**

73 Finite element model were generated directly from converting voxels to equally sized eight-
 74 node brick elements. All elements are considered elastic linear isotropic. Poisson's ratio was

75 set to 0.3 and Young Modulus value was calculated with the formula (25) :

$$E_{element} = E_{max}(GV_{element})^{\gamma} \quad (1)$$

76 where $GV_{element}$ is the normalized gray-value of the element, γ a constant set to 1.5, and E_{max}
 77 is the maximal elastic modulus according to maximal gray-value considered and is determined
 78 with the equation 2:

$$E_{max} = exp\left(\log(E_{cort}) - \gamma \log\left(\frac{GV_{cort}}{GV_{max}}\right)\right) \quad (2)$$

79 where E_{cort} is cortical bone elastic modulus defined by nano-indentation and set to 19GPa
 80 (27; 28), GV_{cort} is cortical phantom gray-value, and GV_{max} is maximum gray-value of coarsened
 81 volume. E_{cort} was considered as treshold between mineralized and hypermineralized bone be-
 82 cause at microscopic scale cancellous and cortical bone elastic modulus are similar (27).
 83 More than 99.9% of bone elements have a Young modulus between 13 and 40GPa, with a
 84 maximum at 23GPa (figure 4).

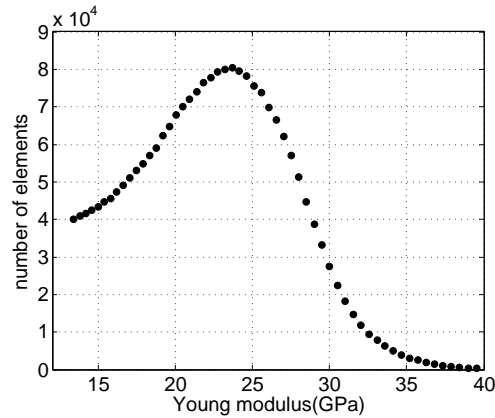


Figure 4: Young modulus distribution taking account of hypermineralized bone for initial voxel size (without coarsening)

85 Binarization method

86 As previous method, finite element model were generated directly from converting voxels to

87 equally sized eight-node brick elements. All elements are considered elastic linear isotropic with
88 a Poisson's ratio was set to 0.3 and Young Modulus set to 19GPa.

89 **Computation and post-processing**

90 Marrow and isolated elements were removed from the finite element analysis. Three static
91 compression tests were simulated with an uniaxial displacement so that global mean strain was
92 equal to -0.3%. Loading was imposed on one face of the sample, on the opposite face displace-
93 ment along the loading was constrained, furthermore one node was encastred (to avoid part
94 sliding). Reaction force was computed to determine apparent Young modulus of the structure
95 and also strain energy density (directly computed with post-processing Abaqus software).

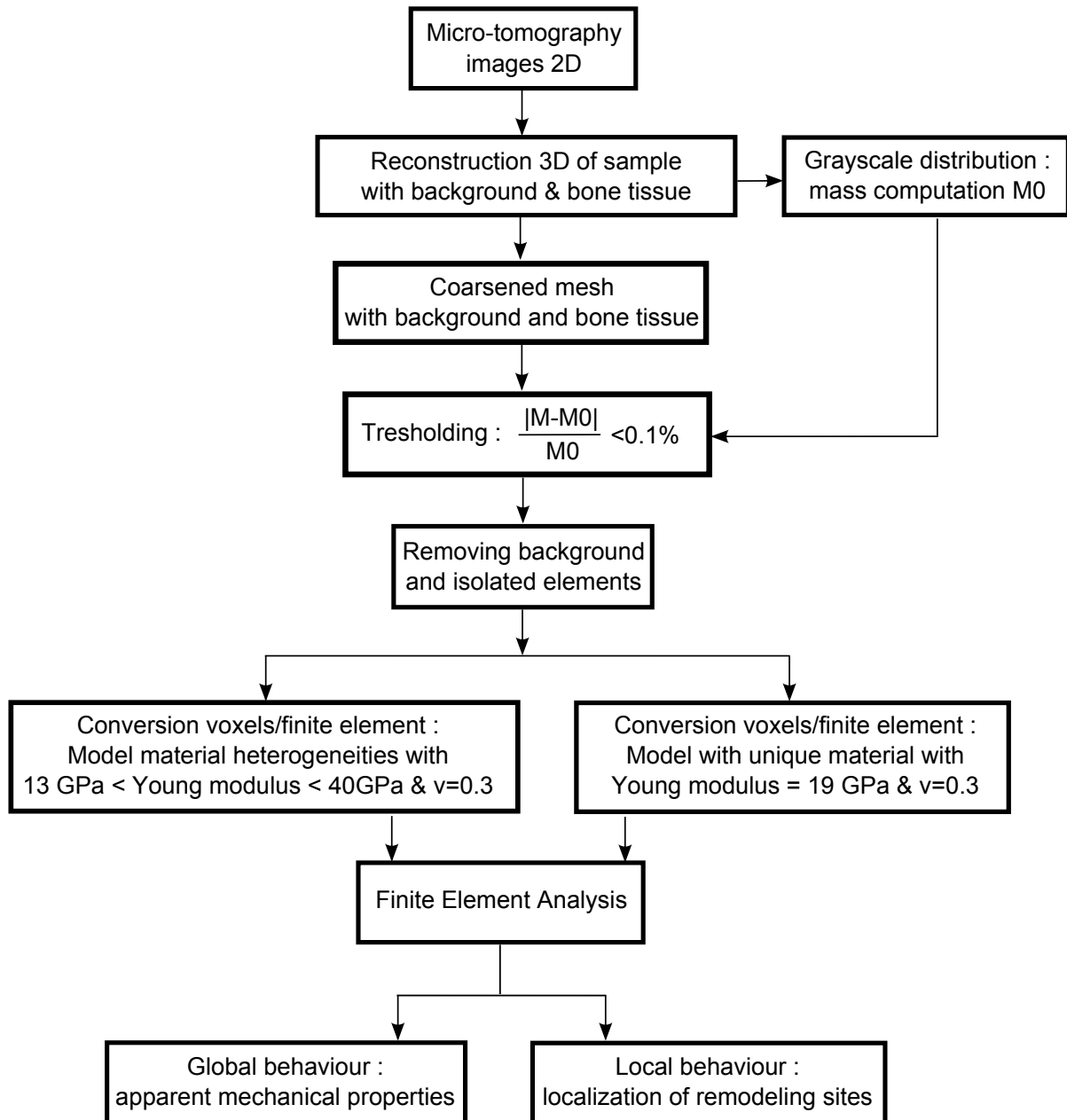


Figure 5: Schematization of method : from micro-tomography acquisition to post-processing of FEA

3 Results

Influence of homogenization

As far as global mechanical behaviour is concerned, apparent Young modulus was computed in 3 principal directions \vec{x} , \vec{y} and \vec{z} which correspond to normal sample faces, for different coarsen voxel size. Apparent Young modulus were sorted as $E_3 > E_2 > E_1$, with $E_3 = E_z$, $E_2 = E_x$ and $E_y = E_1$.

Results are plotted in figure 6(a) : for voxel size smaller than $80\mu\text{m}$ relative apparent Young modulus error is less than 10% compared to the original micro-structure. Relative mean strain energy density error varies from 2.8% to 29.2% respectively for voxel size of $40\mu\text{m}$ and $100\mu\text{m}$ (figure 6(b)). Relative error increases significantly from $80\mu\text{m}$ voxel size.

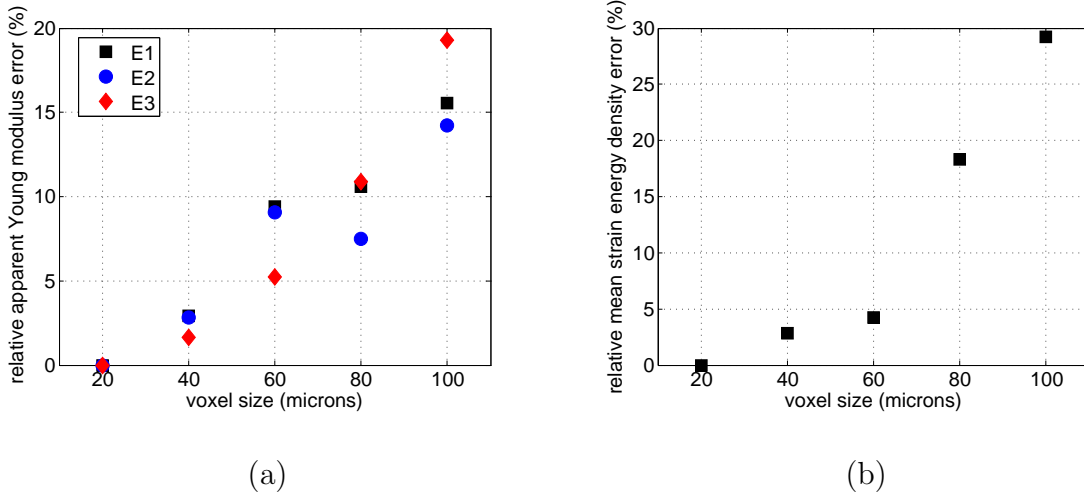


Figure 6: Relative apparent Young modulus error (a) and relative mean strain energy error (b) computed for coarsened model

As far as local mechanical behaviour is concerned, we compared distribution of strain energy density between initial and coarsen model. Bone tissue where strain exceeds $3000\mu\epsilon$, which can correspond from a biological point of view to remodeling sites, were identified. Indeed, when strain stimulus is over $3000\mu\epsilon$ new bone tissue is apposed (29), that is why we focused on hyper-stimulated bone, where strain energy density is over w_{max} defined by :

$$w_{max} = \frac{1}{2} E_{bone} \epsilon_{max}^2 \quad \text{with} \quad E_{bone} = 19GPa, \quad \text{and} \quad \epsilon_{max} = 3000\mu\epsilon \quad (3)$$

111 To validate that coarsening method do not degrade localization and volume of remodeling
 112 sites, mean distance between remodeling sites was calculated in coarsen model and compared
 113 with initial model. Smaller is this value, better is the accuracy of coarsen model. Moreover
 114 volume remodeling sites, that is to say bone tissue where strain density exceed $3000\mu\varepsilon$ were
 115 compared. As a results, remodeling sites are located in the same place on both coarsen and
 116 initial model (figure 7 (a) and (b)). For coarsen voxel of $60\mu\text{m}$, mean distance between
 117 remodeling sites is around two voxels, and relative resorbable volume error is low (table 3).

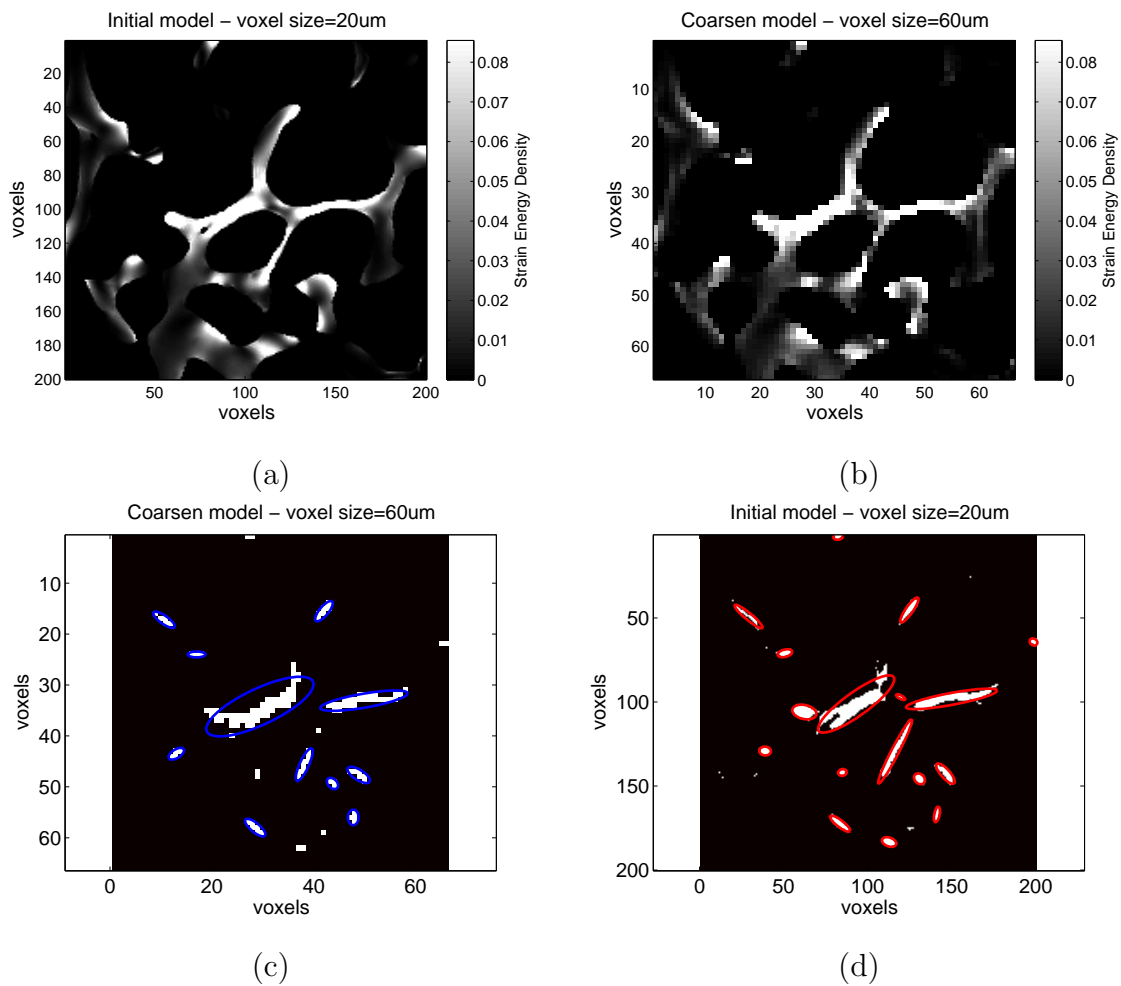


Figure 7: Comparison of strain energy distribution on initial (a) and coarsen model (b) - Localization of remodeling sites on initial (c) and coarsen model (d)

voxel size (μm)	number of elements	CPU time (sec)
20	2344910	35927
40	295180	634
60	85336	129
80	36924	44
100	18927	23

Table 2: Number of bone element in finite element analysis and computation time

voxel size (μm)	maximal Von	relative error mean		distance remodeling		relative resorbable volume
	Mises stress (MPa)	strain energy density (%)	error sites (μm)	(%)	(%)	
20	488.8	0	-	-	-	
40	298.5	2.8	29	0.1		
60	185.1	4.2	62	1.4		
80	184.3	18.3	199	22.1		
100	162.7	29.2	153	27.4		

Table 3: Maximal von mises stress and strain energy density for different degree of coarsening

118 **Influence of binarization**

119 Binarized model, generally used in literature, was computed in order to compare influence
 120 of material heterogeneities on mechanical behaviour. Mean relative error on apparent Young
 121 modulus due to difference of mineralization is 7.5%, which is in agreement with literature (30).
 122 Furthermore relative mean strain energy density error is less than 10 % (table 4).

	Heterogeneous model	Binarized model
E1 (MPa)	1223	1138
E2 (MPa)	1374	1286
E3 (MPa)	1852	1682
Mean strain energy density (MPa/mm ⁻³)	0.0284	0.0257

Table 4: Apparent young modulus and mean strain energy density on heterogeneous and binarized model

123 Maximum Von mises stress are not exactly similar : 489MPa and 548MPa respectively for
 124 heterogeneous and binarized model. Nevertheless this maximum is reached at the same loca-
 125 tion, which means that structure effect is predominant over material heterogeneities.

126

127 From a biological point of view, although number of remodeling sites are same in het-
 128 erogeneous and binarized model, difference of volume of remodeling sites reaches 19%. So with
 129 heterogeneous model remodeling sites are more expanded, which is correlated to material hetero-
 130 geneities distribution (figure 8). Material heterogeneities do not influence the global mechanical
 131 behaviour, nevertheless its influence volume of remodeling sites.

132 **Influence of thresholding**

133 After μ CT acquisition, thresholding was made to distinguish background to bone tissue. This
 134 step is essential for the rest of the numerical study. Indeed a threshold variation result in
 135 variation in bone volume fraction and maximal stiffness (31).

136 Threshold value was chosen as the middle point between the two significant peaks on grayscale

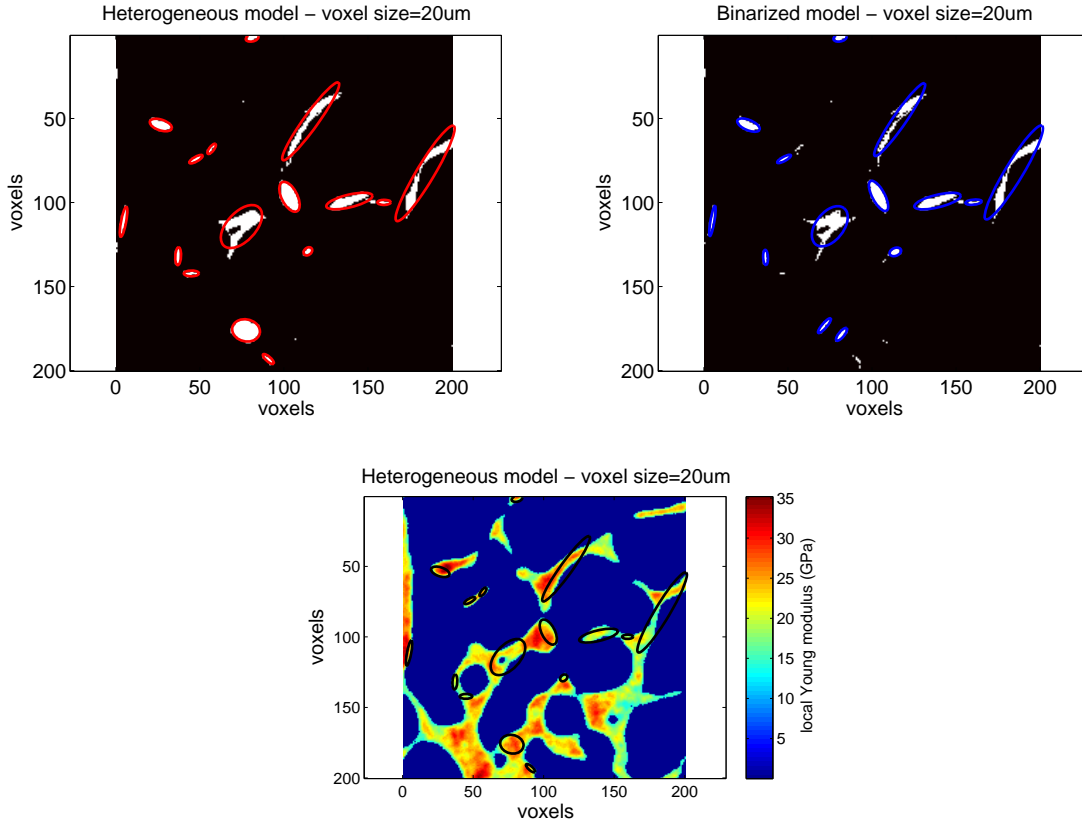


Figure 8: Localization of remodeling sites on heterogeneous and binarized model : sites are located on same place, but more expanded in heterogeneous case which correspond to hyper-mineralized bone tissue (Young modulus $\approx 19\text{GPa}$)

137 distribution (figure 3), nevertheless a variation of 5% in tresholding was possible and results in a
 138 variation of 5% on bone volume fraction. Higher is coarsen voxel size, higher is the difference in
 139 bone volume fraction because voxel volume increases while coarsening (table 5). Moreover
 140 many tresholding were made on coarsen models, and a linear relationship was established
 141 between apparent Young modulus versus gray-value tresholding (figure 9). Decreasing gray-
 142 value treshold consiste in considering thicker trabeculaes and so micro-structure becomes stiffer.

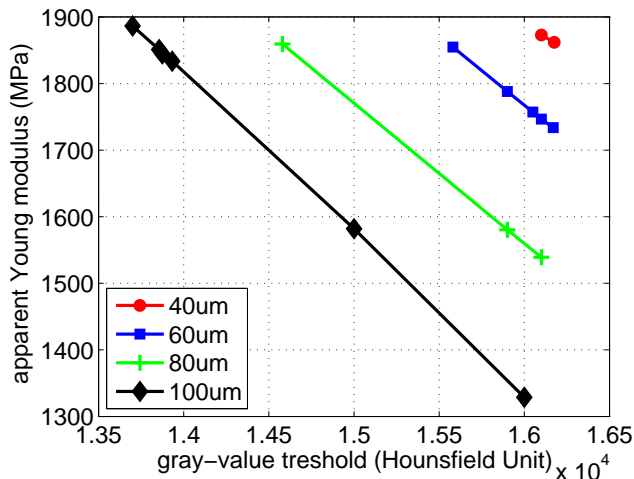


Figure 9: Linear relationship between apparent Young modulus (E_3) and gray-value threshold

voxel size (μm)	Difference in bone volume fraction (%)	Difference in apparent Young modulus (%)
20	3.5	X
40	3.5	6.3
60	4.1	8.6
80	10.3	8.2
100	13.7	9

Table 5: Difference in bone volume fraction and apparent Young modulus for a variation of 5% in thresholding

143 4 Discussion

144 Mechanical cancellous bone properties is a decisive parameter in bone fracture. Numerical
 145 simulations allow to quantify elastic bone properties during disease or aging (16; 18; 14). Nev-
 146 ertheless those methods use millions of elements and models are not suitable for simulation of
 147 iterative process like bone remodeling. So mechanical consideration, like stress concentration,
 148 or local mechanical stimulus (inside tissue bone) are not available due to computational cost.
 149 In this paper we studied the influence of coarsening voxel size in term of global mechanical
 150 behaviour, but also in term of local mechanical behaviour. From micro-tomography acqui-

151 tion, we have numerically built new voxels whose gray-value correspond to an average of initial
152 gray-values. This methods allows to increase numerically voxel size, which decrease number of
153 considered elements and degree of freedom for the finite element analysis.

154 Coarsening voxel size from $20\mu\text{m}$ (μCT resolution) to $60\mu\text{m}$, leads to reduce number of elements
155 from 2 millions to 90000 (for a bone sample of $4\times 4\times 4$ mm). Furthermore, apparent Young mod-
156 ulus varies from 5%, and computation time which initially goes on 10 hours is reduced to 2
157 minutes. From a biomechanical point a view, if we are interested in bone remodeling we should
158 compare the agreement of remodeling sites between coarsen and initial model. If we focus on
159 sites where strain exceeds $3000\mu\epsilon$, which correspond to the treshold of activation of new bone
160 tissue deposit, we have seen that over-constrained areas in coarsen and initial model one voxel
161 size away, for a coarsen voxel of $60\mu\text{m}$. This difference of localization is negligible at osteoclast
162 scale because during remodeling process, several osteoclasts, which measure until $100\mu\text{m}$ of
163 diameter, come on trabeculae surface and dig a channel on hundred micrometers on trabeculae
164 bone surface. So a variation of $60\mu\text{m}$ on remodeling site localization is insignificant.

165 Compared to binarization method which is largely used in the literature, it was put forward that
166 in a hypermineralized bone tissue, volume of bone where strain energy density is over $3000\mu\epsilon$ is
167 under estimated at 19% in a binarized model. Nevertheless binarization give an accurate global
168 mechanical behaviour until coarsen voxel of $60\mu\text{m}$. Cancellous bone mechanical properties are
169 more dictated by the micro-structure than local material heterogeneities.

170 Coarsening method is a relevant method to get mechanical cancellous bone properties, nev-
171 ertheless, as trabeculae are relatively thin, voxel size is limited in order to keep connectivity
172 and realistic bone morphology. Indeed a trabeculae should be composed of 4 or 5 voxels to be
173 relevant in term of mechanical behaviour (32). A numerical study with a voxel size upper than
174 $80\mu\text{m}$ is not conceivable in order to simulate realistic case.

175

176 As a conclusion, it is now possible to compute cancellous bone mechanical properties of re-
177 alistic sample ($8\times 8\times 8\text{mm}$) with directly coarsened voxel while reducing the computational cost.
178 However, a remodeling process can be planned in order to simulate a physiological case : bone
179 alertation due to a low-loading case (bed-ridden case, microgravity), or bone adaptation due
180 to an overloading case (sport). Lastly, as hypermineralized bone is a privileged place of cracks

¹⁸¹ concentration, this data can be used as initiator sites of bone remodeling.

References

- [1] <http://www.shef.ac.uk/FRAX/>, “Frax® : Who fracture risk assessment tool,”
- [2] J. Pasco, E. Seeman, M. Henry, E. Merriman, G. Nicholson, and M. Kotowicz, “The population burden of fractures originates in women with osteopenia, not osteoporosis,” *Osteoporosis International*, vol. 17, pp. 1404–1409, 2006. 10.1007/s00198-006-0135-9.
- [3] E. S. Siris, P. D. Miller, E. Barrett-Connor, K. G. Faulkner, L. E. Wehren, T. A. Abbott, M. L. Berger, A. C. Santora, and L. M. Sherwood, “Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women,” *JAMA: The Journal of the American Medical Association*, vol. 286, no. 22, pp. 2815–2822, 2001.
- [4] P. D. Miller, E. S. Siris, E. Barrett-Connor, K. G. Faulkner, L. E. Wehren, T. A. Abbott, Y.-T. Chen, M. L. Berger, A. C. Santora, and L. M. Sherwood, “Prediction of fracture risk in postmenopausal white women with peripheral bone densitometry: Evidence from the national osteoporosis risk assessment,” *Journal of Bone and Mineral Research*, vol. 17, no. 12, pp. 2222–2230, 2002.
- [5] S. C. E. Schuit, M. van der Klift, A. E. A. M. Weel, C. E. D. H. de Laet, H. Burger, E. Seeman, A. Hofman, A. G. Uitterlinden, J. P. T. M. van Leeuwen, and H. A. P. Pols, “Fracture incidence and association with bone mineral density in elderly men and women: the rotterdam study,” *Bone*, vol. 34, no. 1, pp. 195 – 202, 2004.
- [6] C. H. Turner, V. Anne, and R. M. V. Pidaparti, “A uniform strain criterion for trabecular bone adaptation: Do continuum-level strain gradients drive adaptation?,” *Journal of Biomechanics*, vol. 30, pp. 555–563, June 1997.
- [7] M. Bagge, “A model of bone adaptation as an optimization process,” *Journal of Biomechanics*, vol. 33, pp. 1349–1357, Nov. 2000.
- [8] R. Huiskes, R. Ruimerman, G. H. Van Lenthe, and J. D. Janssen, “Effects of mechanical forces on maintenance and adaptation of form in trabecular bone,” *Nature*, vol. 405, pp. 704–706, June 2000.

- [9] T. Adachi, K.-I. Tsubota, Y. Tomita, and S. J. Hollister, “Trabecular surface remodeling simulation for cancellous bone using microstructural voxel finite element models,” *Journal of Biomechanical Engineering*, vol. 123, pp. 403–409, Oct. 2001.
- [10] C. J. Hernandez, G. S. Beaupré, and D. R. Carter, “A theoretical analysis of the changes in basic multicellular unit activity at menopause,” *Bone*, vol. 32, pp. 357–363, Apr. 2003.
- [11] R. Huiskes, H. Weinans, H. Grootenboer, M. Dalstra, B. Fudala, and T. Slooff, “Adaptive bone-remodeling theory applied to prosthetic-design analysis,” *Journal of Biomechanics*, vol. 20, no. 11-12, pp. 1135–1150, 1987.
- [12] J. Martínez-Reina, J. M. García-Aznar, J. Domínguez, and M. Doblaré, “A bone remodelling model including the directional activity of bmus,” *Biomechanics and Modeling in Mechanobiology*, vol. 8, pp. 111–127, Mar. 2008.
- [13] B. Mulvihill and P. Prendergast, “Mechanobiological regulation of the remodelling cycle in trabecular bone and possible biomechanical pathways for osteoporosis,” *Clinical Biomechanics*, vol. 25, no. 5, pp. 491 – 498, 2010.
- [14] X. S. Liu, A. H. Huang, X. H. Zhang, P. Sajda, B. Ji, and X. E. Guo, “Dynamic simulation of three dimensional architectural and mechanical alterations in human trabecular bone during menopause,” *Bone*, vol. 43, pp. 292–301, Aug. 2008. PMID: 18550463.
- [15] R. Müller and P. Rügsegger, “Analysis of mechanical properties of cancellous bone under conditions of simulated bone atrophy,” *Journal of Biomechanics*, vol. 29, pp. 1053–1060, Aug. 1996.
- [16] R. Müller, “Long-term prediction of three-dimensional bone architecture in simulations of pre-, peri- and post-menopausal microstructural bone remodeling,” *Osteoporosis International*, vol. 16, pp. S25–S35, Aug. 2004.
- [17] J. C. Van Der Linden, J. A. N. Verhaar, and H. Weinans, “A three-dimensional simulation of age-related remodeling in trabecular bone,” *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research*, vol. 16, pp. 688–696, Apr. 2001. PMID: 11315996.

- [18] J. C. Van Der Linden, J. A. N. Verhaar, H. A. P. Pols, and H. Weinans, “A simulation model at trabecular level to predict effects of antiresorptive treatment after menopause,” *Calcified Tissue International*, vol. 73, pp. 537–544, Dec. 2003.
- [19] J. Klein-Nulend, A. Van Der Plas, C. Semeins, N. Ajubi, J. Frangos, P. Nijweide, and E. Burger, “Sensitivity of osteocytes to biomechanical stress in vitro,” *FASEB J.*, vol. 9, no. 5, pp. 441–445, 1995.
- [20] D. B. Burr, R. Martin, M. B. Schaffler, and E. L. Radin, “Bone remodeling in response to in vivo fatigue microdamage,” *Journal of Biomechanics*, vol. 18, no. 3, pp. 189–200, 1985.
- [21] L. McNamara and P. J. Prendergast, “Bone remodelling algorithms incorporating both strain and microdamage stimuli,” *Journal of Biomechanics*, vol. 40, no. 6, pp. 1381–1391, 2007.
- [22] S. Ramtani and M. Zidi, “A theoretical model of the effect of continuum damage on a bone adaptation model,” *Journal of Biomechanics*, vol. 34, pp. 471–479, Apr. 2001.
- [23] M. Doblaré and J. García, “Anisotropic bone remodelling model based on a continuum damage-repair theory,” *Journal of Biomechanics*, vol. 35, pp. 1–17, Jan. 2002.
- [24] E. G. Vajda and R. D. Bloebaum, “Age-related hypermineralization in the female proximal human femur,” *The Anatomical Record*, vol. 255, pp. 202–211, June 1999.
- [25] J. Homminga, R. Huiskes, B. Van Rietbergen, P. Rügsegger, and H. Weinans, “Introduction and evaluation of a gray-value voxel conversion technique,” *Journal of Biomechanics*, vol. 34, no. 4, pp. 513–517, 2001.
- [26] D. Ulrich, B. Van Rietbergen, H. Weinans, and P. Rügsegger, “Finite element analysis of trabecular bone structure: a comparison of image-based meshing techniques,” *Journal of Biomechanics*, vol. 31, no. 12, pp. 1187 – 1192, 1998.
- [27] C. H. Turner, J. Rho, Y. Takano, T. Y. Tsui, and G. M. Pharr, “The elastic properties of trabecular and cortical bone tissues are similar: results from two microscopic measurement techniques,” *Journal of Biomechanics*, vol. 32, no. 4, pp. 437 – 441, 1999.

- [28] T. Hoc, L. Henry, M. Verdier, D. Aubry, L. Sedel, and A. Meunier, “Effect of microstructure on the mechanical properties of haversian cortical bone,” *Bone*, vol. 38, no. 4, pp. 466–474, 2006.
- [29] H. M. Frost, “On our age-related bone loss: Insights from a new paradigm,” *Journal of Bone and Mineral Research*, vol. 12, no. 10, pp. 1539–1546, 1997.
- [30] R. M. Zebaze, A. C. Jones, M. G. Pandy, M. A. Knackstedt, and E. Seeman, “Differences in the degree of bone tissue mineralization account for little of the differences in tissue elastic properties,” *Bone*, vol. 48, pp. 1246–1251, June 2011.
- [31] T. Hara, E. Tanck, J. Homminga, and R. Huiskes, “The influence of microcomputed tomography threshold variations on the assessment of structural and mechanical trabecular bone properties,” *Bone*, vol. 31, pp. 107–109, July 2002.
- [32] G. T. Charras and R. E. Guldborg, “Improving the local solution accuracy of large-scale digital image-based finite element analyses,” *Journal of Biomechanics*, vol. 33, pp. 255–259, Feb. 2000.