Translating the lacuno-canalicular network into multi-scale bone scaffold design: a bio-inspired approach integrating nano-imaging, modeling, and advanced fabrication

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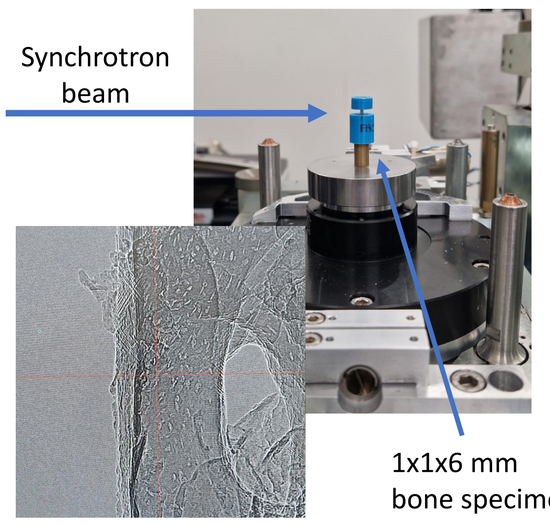
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Introduction and Aim

The exceptional properties of human bone arise from its multi-scale hierarchical organization. At the meso-scale, trabecular architecture optimizes mechanical response. At the micro- and nano-scale, the Lacuno-Canalicular Network (LCN) provides additional porosity, housing osteocytes in lacunae and enabling cell–cell interactions through canaliculi. Although the LCN is recognized as critical for bone homeostasis and mechanosensing, its inclusion in Bone Tissue Engineering (BTE) approaches remains underexplored. Current bio-inspired bone scaffolds tend to reproduce trabecular porosity; the addition of an LCN-like network may increase scaffold efficacy across scales. This study aims to translate nano-scale imaging of the human LCN into design principles for BTE scaffolds. The morphometry of the LCN is reconstructed in 3D and described through selected parameters, focusing on lacunar shape, canalicular complexity, and network interconnectivity. Design principles are derived from this analysis and translated into a bio-inspired representation of the LCN, to be integrated into realistic trabecular geometries, resulting in a fabricable, biocompatible scaffold. The integration of high-resolution imaging, computational modeling, and advanced fabrication aims to define a novel multi-scale bio-inspired approach for BTE scaffold design.

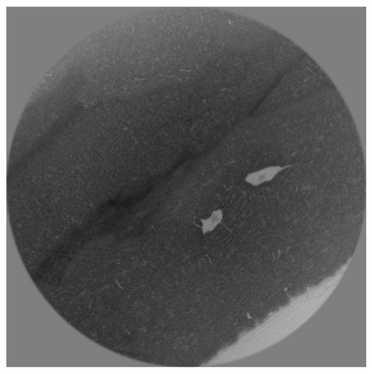
Nano-scale imaging and 3D reconstruction

Nano-holotomographies (voxel size = 50 nm) of human femoral trabecular bone are acquired at ESRF Synchrotron (ID16b) in Grenoble, France [ClinicalTrials.gov ID: NCT04787679]



Set-up of the specimen and positioning system's preview

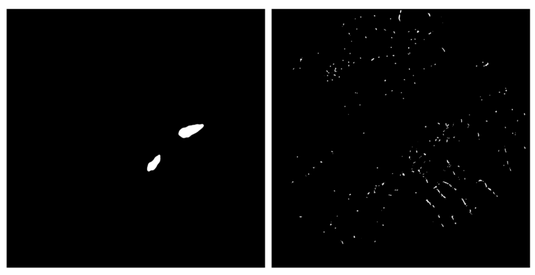
ESRF's reconstruction algorithm



Example of reconstructed slice

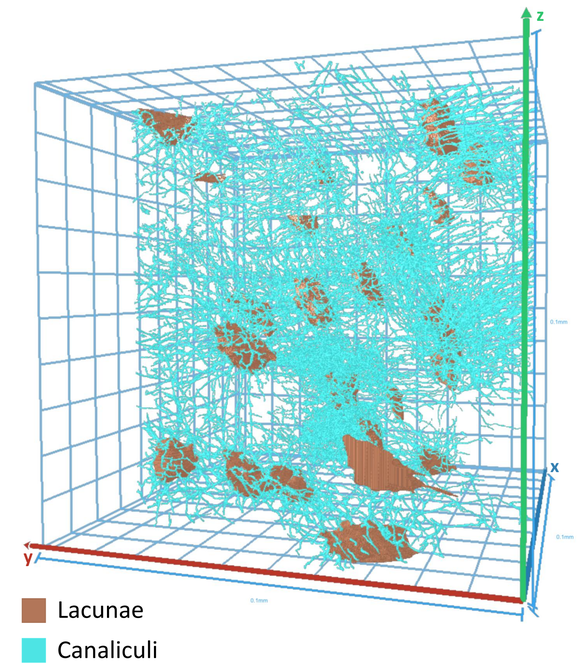
Stacks of grayscale pictures are obtained. Brighter areas correspond to porosities. FOV: 100 μm^3

A literature-inspired, custom segmentation algorithm is developed to recognize the LCN. Lacunae are segmented through Otsu-based hysteresis thresholding and connected-components analysis. Vesselness filtering combined with percentile thresholding and weighted growing ensure canaliculi detection.



Example of segmented lacunae and canaliculi

Once input parameters are set, a full specimen can be segmented without supervision within 9 hours on 256 Gb RAM.



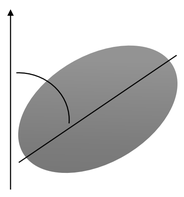
3D visualization of segmented LCN

Characterization of LCN morphology and interconnectivity

Lacunae are labelled and fully visible ones are analyzed:

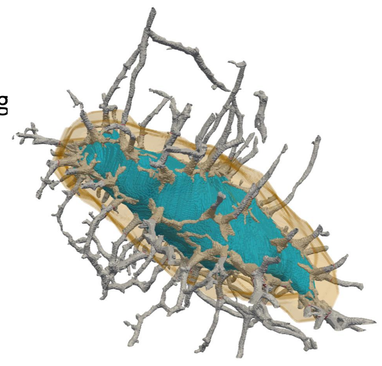


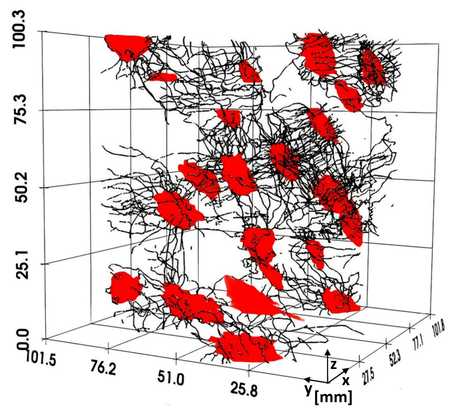
- Volume
- Surface
- Axes length
- Shape (stretch, oblateness, sphericity)
- Orientation with respect to femur's loading direction



Lacunae can be approximated with ellipsoids with major, intermediate and minor axis of, respectively: ≈ 35 µm, ≈ 19 µm, ≈ 9 µm. The average orientation angle is 57° ± 18°.

The number of canaliculi emerging from the lacunar surface was computed at 1 µm distance, showing typically ~30–120 connections per lacuna, with high inter-lacunar variability.



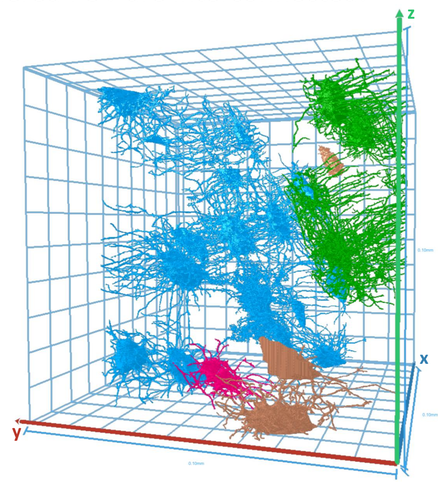


Canaliculi are skeletonized to extract:

- Tortuosity: ≈ 1.42
- Branches orientation: ≈ 58° ± 1.3° with respect to femur's loading direction, with 49% ± 3% of branches showing an angle > 60°
- Branching pattern: branchpoints of degree = 3; ≈ 5 x 10^{-4} branchpoints/μm^3

At the considered scale and FOV, the registered LCN porosity is around 1%, of which about 0.6% is due to lacunae and 0.3% is due to canaliculi.

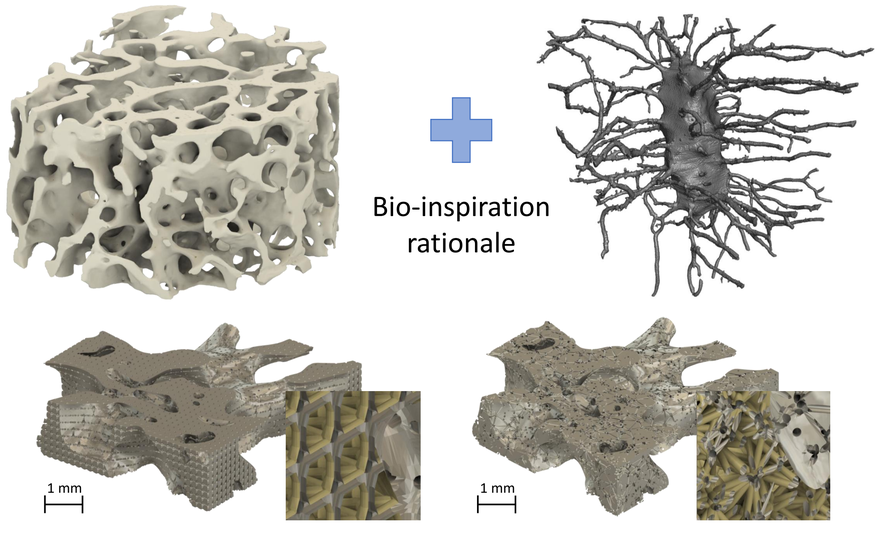
On average, 50% of the lacunae visible in the considered FOV are interconnected.



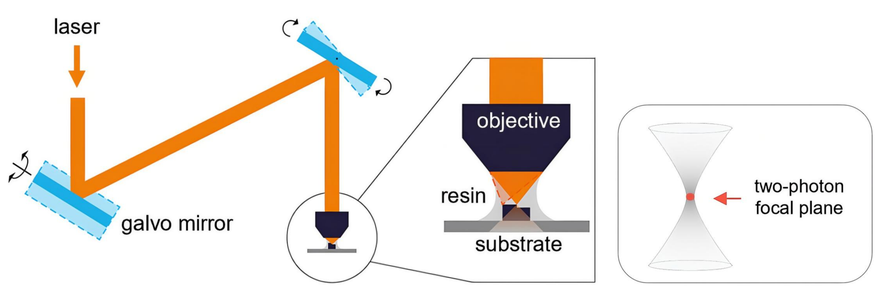
Example of connected-components analysis on LCN

Multi-scale design and 2PP fabrication

Bone scaffold designs are developed by integration of realistic trabecular architecture (derived from synchrotron µ-CT scans with micrometric resolution) with bio-inspired LCN-like micro-porosities



Two first designs with mathematical organization of LCN-like micro-structures (on the left: lattice-based; on the right: Delaunay-based)



Multi-scale scaffolds are successfully fabricated via Two-Photon Polymerization (2PP), a high-resolution 3D printing technology, showing:

- Fabricability across scales (micrometric LCN-like features in a millimeter-scaled construct)
- Use of a biocompatible photosensitive resin, indicated for 3D cell culture studies
- Satisfactory printing fidelity, as assessed by subsequent synchrotron scans

Next steps

- Further development of scaffold designs with increasingly realistic LCN-like networks
- Mechanical validation (numerical and experimental)
- In-vitro assessment of multi-scale effects on osteogenesis

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