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## Data-driven design and mechanical validation of 3D-printed biphasic osteochondral scaffolds with interlocking interface using Ti6Al4V

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**Data-driven design and mechanical validation of 3D-printed biphasic osteochondral scaffolds with interlocking interface using Ti6Al4V**

*Running title:* CT-informed osteochondral scaffolds

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## Abstract

Osteochondral defects require biomimetic scaffolds. These scaffolds must simultaneously reproduce the mechanical heterogeneity of subchondral bone and maintain stable integration between the bone and cartilage regions. In this study, we developed a data-driven design and validation framework for patient-specific biphasic Ti6Al4V osteochondral scaffolds using public computed tomography (CT) datasets and finite element optimization. CT images from the Osteoarthritis Initiative (OAI) database were analyzed to extract Hounsfield unit (HU) distributions and derive anisotropic mechanical parameters through density–elasticity mapping, yielding three representative design targets corresponding to low-, medium-, and high-density cancellous bone. Gradient Gyroid scaffolds with region-specific porosity and strut parameters were subsequently designed to match these physiological targets. To improve osteochondral integration, an interlocking interface architecture incorporating peg-based mechanical anchoring was optimized using parametric finite element response surface modeling and Bayesian optimization. The scaffolds were fabricated via selective laser melting (SLM) using Ti6Al4V powder and comprehensively characterized through quasi-static compression, hemispherical indentation, and interface shear testing. The fabricated scaffolds exhibited high geometric fidelity with average dimensional deviations below 0.15 mm. The measured macroscopic compressive moduli demonstrated excellent manufacturing fidelity, deviating by less than 10% from the CT-derived design targets across all density groups, thereby offering a viable path to mitigate clinical stress shielding. Furthermore, the optimized interlocking interface profoundly augmented both indentation stiffness and destructive interface shear strength over smooth-interface controls ( $p < 0.01$ ), closely matching the finite element predictions of minimized stress concentration at the osteochondral junction. Taken together, these findings demonstrate that CT-informed, topology-optimized Ti6Al4V scaffold architectures can achieve precisely matched porous mechanics while substantially expanding interface stability, providing a highly reproducible and translatable strategy for personalized load-bearing joint repair applications.

**Keywords:** Osteochondral scaffold; Ti6Al4V; Gyroid lattice; Interlocking interface

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## 1. Introduction

Osteoarthritis and traumatic osteochondral defects impact millions of individuals globally, with an estimated prevalence surpassing 10% among the adult population <sup>1</sup>. Articular cartilage injuries often penetrate into the subchondral bone, giving rise to intricate defects that necessitate the simultaneous regeneration of two distinct tissues as an integrated functional entity <sup>2,3</sup>. Current clinical therapies include autologous grafting, allografts, and total joint replacement. However, they are constrained by donor-site morbidity, risks of disease transmission, and long-term complications such as aseptic loosening and stress shielding <sup>4-6</sup>.

Tissue engineering presents a promising alternative through the provision of temporary scaffolds that facilitate endogenous cell infiltration and tissue regeneration <sup>7</sup>. Among the fabrication techniques, 3D printing enables the production of patient-specific implants with precisely controlled external geometries and internal architectures <sup>8-10</sup>. In osteochondral applications, 3D printing allows for the fabrication of multiphasic scaffolds with region-specific properties: a load-bearing bone phase that mimics cancellous bone and a compliant chondral phase that replicates articular cartilage <sup>11,12</sup>.

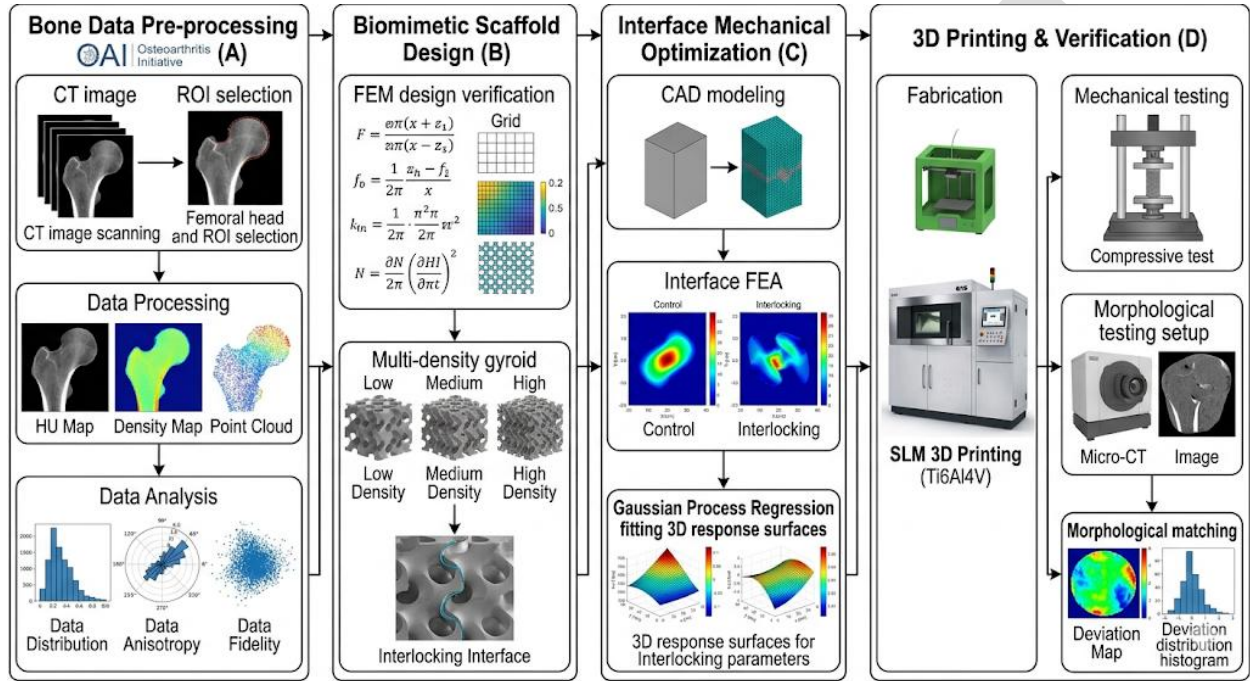
Despite these advancements, two fundamental challenges remain unaddressed. First, mechanical matching: scaffolds are required to replicate the anisotropic mechanical behavior of native bone to prevent stress shielding. Natural cancellous bone demonstrates substantial regional variation in elastic modulus (50–1500 MPa) and a high degree of anisotropy ( $DA \approx 0.6-0.7$ ), which reflects its adaptation to physiological loading <sup>13,14</sup>. Conventional uniform architectures fail to capture this heterogeneity. Although functionally graded structures have been introduced <sup>15,16</sup>, most of them rely on empirical parameter selection rather than patient-specific mechanical data obtained from clinical imaging. Second, interface integration: the junction between the osteal and chondral phases represents a critical weak point that is prone to delamination under shear and tensile stresses encountered during joint loading <sup>17,18</sup>. Despite the mechanical demands of articulation, quantitative interface strength testing is conspicuously absent in most 3D-printed osteochondral scaffold studies <sup>19</sup>. Recent reviews emphasize that although reinforcement strategies exist (e.g., chemical bonding, solvent casting, mechanical interlocking), systematic evaluation using standardized shear tests is lacking <sup>20,21</sup>.

An additional opportunity lies in public repositories of clinical CT data, such as the Osteoarthritis Initiative (OAI), which contain thousands of high-resolution scans along with corresponding demographic information. These databases offer an untapped resource for extracting population-level bone mechanical properties, establishing relationships between Hounsfield units (HU) and strength, and generating design targets for patient-specific scaffolds<sup>22-24</sup>. Recent work by Candeias *et al.*<sup>25</sup> demonstrated the feasibility of mapping HU to strength via rational Bézier curves and translating these to lattice parameters using octree adaptive subdivision. However, such approaches have not been systematically integrated with experimental validation of mechanical equivalence using cost-effective materials like Ti6Al4V.

Ti6Al4V alloys have become one of the most widely utilized metallic biomaterials for load-bearing orthopedic implants due to their excellent biocompatibility, corrosion resistance, and high mechanical strength<sup>26,27</sup>. With the development of additive manufacturing technologies such as selective laser melting (SLM), porous Ti6Al4V scaffolds with controlled lattice architectures can now be fabricated with high geometric accuracy and tunable mechanical properties<sup>28</sup>. Significantly, the introduction of controlled porosity and biomimetic lattice structures substantially reduces the effective elastic modulus of Ti6Al4V, alleviating stress shielding while maintaining sufficient structural integrity for load-bearing applications<sup>29,30</sup>. Recent studies have shown that Gyroid and triply periodic minimal surface (TPMS)-based Ti6Al4V scaffolds exhibit favorable permeability, mechanical isotropy, and osseointegration potential<sup>31</sup>. However, most current studies rely on empirically selected architectures rather than patient-specific mechanical targets derived from clinical imaging.

To address these critical limitations, we developed a clinically informed, data-driven framework to guide the topological design and mechanical validation of biphasic Ti6Al4V osteochondral scaffolds. This framework seamlessly bridges clinical radiographic data with additive manufacturing by leveraging public OAI datasets to map patient-specific cancellous bone targets, which are subsequently translated into functionally graded Gyroid lattices characterized by region-specific porosity and structural anisotropy. To ensure structural integrity at the osteochondral junction, a biomimetic interlocking interface was parametrically optimized and subsequently validated through a closed-loop platform combining computational finite element simulations with destructive experimental testing, including compression, indentation, and interface shear

characterization. We hypothesized that these topology-optimized titanium scaffolds could successfully downscale intrinsic metallic rigidity to physiological targets while simultaneously elevating interfacial shear resistance far beyond that of conventional smooth-interface controls (Fig. 1).



**Fig. 1. Schematic overview of the data-driven pipeline.** The workflow includes CT database analysis for bone data pre-processing and mechanical mapping, biomimetic multi-density Gyroid scaffold design with an optimized interlocking interface, SLM 3D printing using Ti6Al4V, and comprehensive morphological and mechanical verification (including micro-CT imaging and compressive testing).

## 2. Materials and methods

### 2.1. CT Image Analysis and Mechanical Mapping

A cohort of 30 subjects from the OAI database (proximal femur CT scans, slice thickness  $\leq 1$  mm, no metal artifacts) was used for HU analysis and mechanical property mapping. The HU threshold (150 – 700 HU) was based on published ranges for trabecular bone in the proximal femur.<sup>23</sup> Segmentation of cancellous bone regions (femoral head and neck) was performed in

3D Slicer (version 5.6) using thresholding (150–700 HU). Mean HU values were extracted for each region of interest (ROI). Anisotropic mechanical parameters were calculated using the power-law equations established by Brown *et al.*<sup>29</sup> for principal elastic moduli ( $E_1$ ,  $E_2$ ,  $E_3$ ), shear moduli, and yield strengths. The control points of the rational Bézier curve  $P_0(60,0.1)$ ,  $P_1(675,16)$ ,  $P_2(928,130)$ ,  $P_3(1760,200)$  and weights  $[1,50,50,1]$  were selected to best fit the pooled HU-strength data from our OAI subset, achieving an  $R^2$  of 0.94.<sup>29</sup> A rational Bézier curve with control points  $P_0(60, 0.1)$ ,  $P_1(675, 16)$ ,  $P_2(928, 130)$ ,  $P_3(1760, 200)$  and weights  $[1, 50, 50, 1]$  was constructed to model the HU-strength relationship. K-means clustering was applied to classify ROIs into low-, medium-, and high-density groups based on HU values.

All CT scans followed the OAI acquisition protocol (Siemens SOMATOM Definition, 120 kVp, 200 mAs, slice thickness 0.625 mm reconstructed to 1 mm). Regions of interest (ROIs) were manually contoured on every fifth slice within the femoral head and neck, excluding trabecular bone within 1 mm of the cortical shell to avoid partial volume effects.

## **2.2. OAI Data Screening and Morphological Analysis**

The Osteoarthritis Initiative (OAI) database was queried for subjects with complete 3D-DESS MRI (slice thickness  $\leq 1$  mm) and available Kellgren–Lawrence (KL) grading. Subjects with metal artifacts or incomplete proximal femur coverage were excluded. From the remaining 2,134 subjects, we performed stratified random sampling according to KL grade (0–4) to obtain 100 subjects per grade ( $n = 500$ ). For each subject, the femoral condyle, tibial plateau, and meniscus were semi-automatically segmented using a U-Net based algorithm (Dice coefficient  $>0.85$ ) and reconstructed into 3D surface models (STL format). All models were rigidly aligned to a common reference via Procrustes superimposition.

## **2.3. Statistical Shape Model and Principal Component Analysis**

A statistical shape model (SSM) was built from the 500 aligned femoral and tibial surfaces using point distribution models (PDM). Principal component analysis (PCA) was performed to reduce dimensionality, retaining the first 10 principal components (PCs) which explained  $>80\%$  of the

total shape variance. For each PC, shape variations at  $\pm 3$  standard deviations from the mean were visualized as color-coded displacement maps (red: outward, blue: inward). The resulting PC scores were used for subsequent clustering and template generation.

## 2.4. Morphological Clustering and Interface Template Extraction

K-means clustering was applied to the first 10 PC scores to identify distinct morphological phenotypes of the subchondral bone interface. The optimal number of clusters ( $k=3$ ) was determined by the elbow method and silhouette coefficient (mean silhouette = 0.62). For each cluster, the mean shape was calculated and used as a representative “interface design template”. Three geometric parameters were extracted from each template: interface curvature radius (mm), cartilage thickness (mm), and bone depression depth (mm). Differences among clusters were assessed using one-way ANOVA with Tukey HSD post-hoc test ( $\alpha = 0.05$ ).

## 2.5. Scaffold Design

The Gyroid surface was described by the implicit function  $f(x, y, z) = \sin(2\pi x/a) \cos(2\pi y/b) + \sin(2\pi y/b) \cos(2\pi z/c) + \sin(2\pi z/c) \cos(2\pi x/a) = t$ , where  $a$ ,  $b$ ,  $c$  are unit cell dimensions and  $t$  controls volume fraction. To map lattice geometry to mechanical properties, finite element analysis (Abaqus) of 60 parameter combinations (unit cell size 3–5 mm, strut diameter 0.2–0.6 mm, anisotropy 0–0.7) was performed. Crucially, standard Ti6Al4V material properties ( $E = 110$  GPa,  $\nu = 0.33$ , yield strength = 950 MPa) were utilized to establish a structure-property scaling law. The fitted scaling law from the 60 FEA simulations was  $E_{eq}/E_s = 0.88 \cdot (VF)^{1.35} \cdot (DA)^{-0.42}$ , yielding a coefficient of determination  $R^2 = 0.98$ . This scaling law was derived from our FEA simulations and is consistent with previously reported relationships for TPMS lattices.<sup>28,32</sup>

For each density group, the strut diameter and degree of anisotropy (DA) were back-calculated to precisely down-regulate the bulk stiffness of Ti6Al4V to match the physiological target moduli of cancellous bone.

Recently, data-driven inverse design frameworks have emerged as powerful tools for optimizing complex engineering systems, including tissue engineering scaffolds. For instance, Fang *et al.*

employed a multimodal guided latent diffusion model for the inverse topological design of tissue engineering constructs <sup>33</sup>. Inspired by such approaches, we adopted a Bayesian optimization framework to identify optimal interlocking geometries for our osteochondral scaffold.

## **2.6. Finite Element Analysis and Design Optimization**

Finite element analysis was performed in Abaqus (2022) using 10-node quadratic tetrahedral elements (C3D10). A mesh convergence study was conducted: a global seed size of 0.5 mm was selected, as further refinement changed the predicted stiffness by <2%. The bone phase (Ti6Al4V) was assigned a linear elastic material model with  $E = 110 \text{ GPa}$ ,  $\nu = 0.33$ ; the cartilage phase (PCL) with  $E = 350 \text{ MPa}$ ,  $\nu = 0.30$ . The interface between the two phases was modeled as a perfectly bonded tie constraint. A displacement-controlled compressive load (0.5 mm/min) was applied to the top surface, while the bottom surface was fully constrained ( $U_x = U_y = U_z = 0$ ). Contact between the indenter and scaffold was frictionless.

## **2.7. Cartilage phase fabrication**

The cartilage phase was fabricated using medical-grade polycaprolactone (PCL,  $M_n = 80 \text{ kDa}$ , Polysciences). PCL pellets were melted at  $80^\circ\text{C}$  and injected into a custom silicone mold containing the pre-positioned Ti6Al4V bone phase scaffold. The assembly was cooled at room temperature for 24 h, allowing the PCL to solidify and mechanically interlock with the pegs of the bone phase. No adhesive or chemical bonding agent was used.

## **2.8. Mechanical Testing**

All tests were performed on a universal testing machine (Instron 5982) at 0.5 mm/min. Sample sizes were  $n = 5$  per group. Quasi-static compression: Bone-phase scaffolds (low, medium, high density) were compressed between flat platens to 50% strain. Load-displacement data were converted to stress-strain curves. Elastic modulus was determined from the linear region (5–20% strain). Yield strength (0.2% offset) and energy absorption (area under curve) were also recorded. Hemispherical indentation: Biphasic scaffolds (medium-density bone phase with cartilage phase) were embedded in resin, leaving the cartilage surface exposed. A 5 mm diameter hemispherical

indenter was pressed to a depth of 2 mm. Indentation stiffness was calculated from the initial linear portion of the load-displacement curve. Interface shear test: Biphasic scaffolds (smooth interface, 30% interlock, 60% interlock) were tested using a custom fixture with a constraining platen<sup>34</sup>. The bone phase was fixed, and a shear load was applied horizontally to the cartilage phase until failure. Interface shear strength was calculated as  $\tau = F_{\text{max}} / A_{\text{interface}}$ , where  $A_{\text{interface}} = \pi \cdot (\text{diameter}/2)^2$ .

## 2.9. Statistical Analysis

Normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data (e.g., elastic modulus, indentation stiffness, interface shear strength) are presented as mean  $\pm$  standard deviation (SD) and were analyzed using one-way analysis of variance (ANOVA) followed by Tukey’s HSD post-hoc test for multiple comparisons. Non-normally distributed data (e.g., osteophyte scores) are presented as median (IQR) and were analyzed using the Kruskal–Wallis test with Dunn’s post-hoc test. Categorical variables (e.g., sex) were compared using Fisher’s exact test. One-sample t-tests were used to compare measured elastic moduli against their paired CT-derived target moduli. Pearson correlation coefficients were calculated for the parametric correlation matrix (Table 4). A significance level of  $\alpha = 0.05$  was used for all tests.

## 3. Results

### 3.1. Baseline Characteristics

**Table 1** presents the baseline demographic, radiographic, cartilage morphological, and CT-derived biomechanical characteristics of the 30 subjects selected from the Osteoarthritis Initiative (OAI) database. Subjects were stratified into three density groups (low, medium, high) based on k-means clustering of Hounsfield unit (HU) values extracted from the proximal femur. The groups were balanced with 10 subjects each.

**Table 1.** Baseline characteristics of the study population stratified by bone density group.

| Characteristic                      | Overall<br>(N=30) | Low<br>Density<br>(n=10) | Medium<br>Density<br>(n=10) | High<br>Density<br>(n=10) | P-<br>value <sup>*</sup> |
|-------------------------------------|-------------------|--------------------------|-----------------------------|---------------------------|--------------------------|
| <b>Demographics</b>                 |                   |                          |                             |                           |                          |
| Age (years)                         | 62.4 ± 8.7        | 60.2 ± 9.1               | 62.8 ± 8.5                  | 64.1 ± 8.3                | 0.582                    |
| Female, n (%)                       | 16 (53.3)         | 5 (50.0)                 | 6 (60.0)                    | 5 (50.0)                  | >0.999                   |
| BMI (kg/m <sup>2</sup> )            | 28.1 ± 3.9        | 26.5 ± 3.2               | 28.3 ± 4.0                  | 29.5 ± 4.1                | 0.215                    |
| <b>Radiographic characteristics</b> |                   |                          |                             |                           |                          |
| HU range                            | 98–532            | 98–215                   | 216–358                     | 359–532                   | <0.001                   |
| JSW (mm)                            | 3.72 ± 1.38       | 4.15 ± 1.20              | 3.68 ± 1.35                 | 3.34 ± 1.42               | 0.402                    |
| Osteophyte score<br>(0–12)          | 3.1 ± 2.5         | 1.8 ± 1.6                | 3.2 ± 2.4                   | 4.3 ± 2.8                 | 0.081                    |
| <b>Cartilage morphology (MRI)</b>   |                   |                          |                             |                           |                          |

| Characteristic                                        | Overall<br>(N=30) | Low<br>Density<br>(n=10) | Medium<br>Density<br>(n=10) | High<br>Density<br>(n=10) | P-<br>value* |
|-------------------------------------------------------|-------------------|--------------------------|-----------------------------|---------------------------|--------------|
| Medial femoral<br>thickness (mm)                      | 1.98 ± 0.48       | 2.21 ± 0.42              | 1.95 ± 0.45                 | 1.78 ± 0.52               | 0.134        |
| Lateral femoral<br>thickness (mm)                     | 2.12 ± 0.52       | 2.35 ± 0.48              | 2.08 ± 0.50                 | 1.92 ± 0.55               | 0.165        |
| Subchondral bone<br>curvature (mm <sup>-1</sup> )     | 0.082±0.034       | 0.068 ± 0.022            | 0.085 ± 0.031               | 0.094 ± 0.038             | 0.158        |
| <b>Biomechanical<br/>parameters (CT-<br/>derived)</b> |                   |                          |                             |                           |              |
| E <sub>1</sub> (MPa) <sup>†</sup>                     | 904 ± 382         | 452 ± 83                 | 858 ± 117                   | 1362 ± 175                | <0.001       |
| E <sub>2</sub> (MPa)                                  | 499 ± 214         | 283 ± 52                 | 491 ± 68                    | 724 ± 85                  | <0.001       |
| E <sub>3</sub> (MPa)                                  | 270 ± 124         | 148 ± 31                 | 263 ± 38                    | 398 ± 47                  | <0.001       |
| Degree of<br>anisotropy (DA)                          | 0.69 ± 0.05       | 0.67 ± 0.04              | 0.69 ± 0.03                 | 0.71 ± 0.02               | 0.028        |

**Notes:** Data are expressed as mean  $\pm$  SD, median (IQR), or count (%). E1, E2, and E3 represent CT-derived principal orthotropic moduli; Degree of Anisotropy (DA) =  $1 - (E3 / E1)$ .

\* Analyzed via one-way ANOVA (Tukey's HSD), Kruskal-Wallis (Dunn's), or Fisher's exact test across density groups (n=10 per group).

† The mean E1 values (452, 858, and 1362 MPa) serve as the bioinspired targets to parameterize the gradient Gyroid architectures for the SLM-fabricated Ti6Al4V scaffolds.

Add legend below the table. Define all abbreviations used in the table in alphabetical order and define the symbols used. <sup>a</sup> P<0.05, <sup>b</sup> P<0.01.

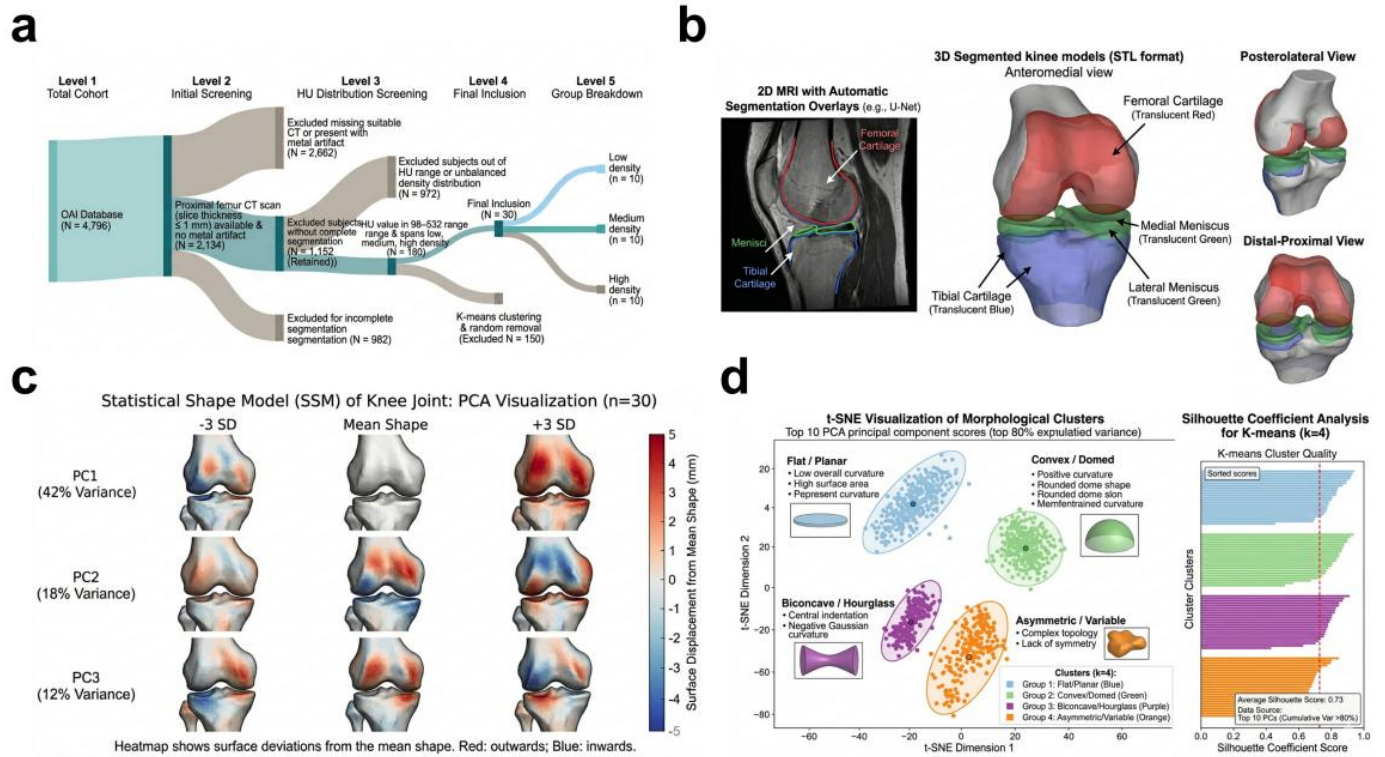
Normality of continuous variables was evaluated using the Shapiro-Wilk test. Normally distributed continuous variables are expressed as mean  $\pm$  standard deviation (SD) and were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's HSD post-hoc test. Non-normally distributed variables are presented as median (interquartile range, IQR) and were analyzed using the Kruskal-Wallis test with Dunn's post-hoc test. Categorical variables are expressed as counts (percentages) and were compared using Fisher's exact test due to the small sample size (n=10 per group).

Significant structural and biomechanical differences were observed among the groups, specifically regarding HU range and all principal elastic moduli ( $p < 0.001$ ), confirming that the clustering effectively captured the distinct bone density profiles. Notably, the target moduli for scaffold design (452, 858, and 1362 MPa) were directly derived from the mean E1 of these specific groups; thus, they serve as downstream design parameters rather than independent baseline characteristics. Finally, no significant differences were found for age, sex, or BMI, indicating that demographic confounders were well-controlled across the three density cohorts.

### 3.2. OAI data screening and morphological analysis

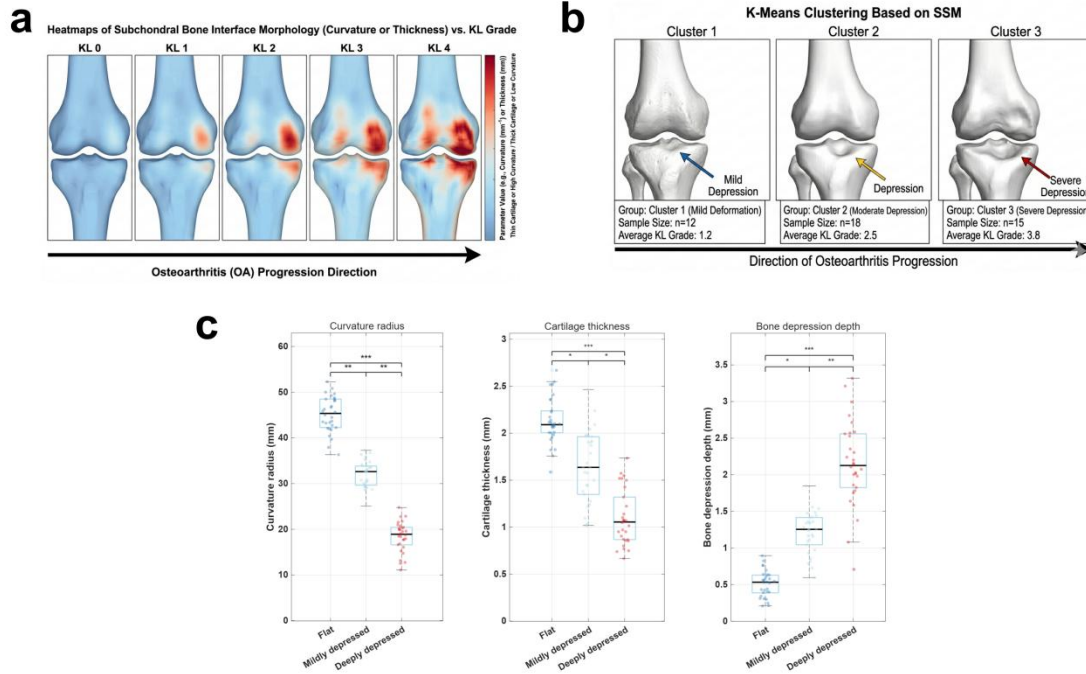
To obtain population-specific morphological templates, we screened the OAI database (**Fig. 2a**) and reconstructed 3D joint surfaces (**Fig. 2b**). PCA of the statistical shape model revealed that the first three principal components explained 72% of the total shape variance (**Fig. 2c**). t-SNE

clustering of the shape features showed a clear separation according to KL grade (**Fig. 2d**), confirming that OA severity is strongly associated with distinct morphological phenotypes.



**Fig. 2. OAI data screening and morphological analysis pipeline.** (a) Subject selection flow. (b) Representative 3D surface reconstruction of knee joint tissues. (c) Principal component analysis of the statistical shape model showing the first three shape modes. (d) t-SNE visualization of morphological clustering by KL grade.

From the OAI-derived shape models, we extracted the subchondral bone interface morphology. Heat maps (Fig. 3a) show a clear gradient of increasing curvature and deepening of the interface with advancing KL grade. K-means clustering identified three distinct interface phenotypes (Fig. 3b): flat (Cluster 1; n=12, mean KL 1.2), mildly depressed (Cluster 2; n=18, mean KL 2.5), and deeply depressed (Cluster 3; n=15, mean KL 3.8). Boxplot analysis (Fig. 3c) confirmed significant differences in curvature radius, cartilage thickness, and bone depression depth among the three clusters.



**Fig. 3. Interface morphology clustering and representative template generation.** (a) Heat maps of subchondral bone interface curvature across KL grades. (b) Three representative interface templates identified by K-means clustering. (c) Boxplots comparing curvature radius, cartilage thickness, and bone depression depth among clusters.

### 3.3. CT-Based Mechanical Characterization

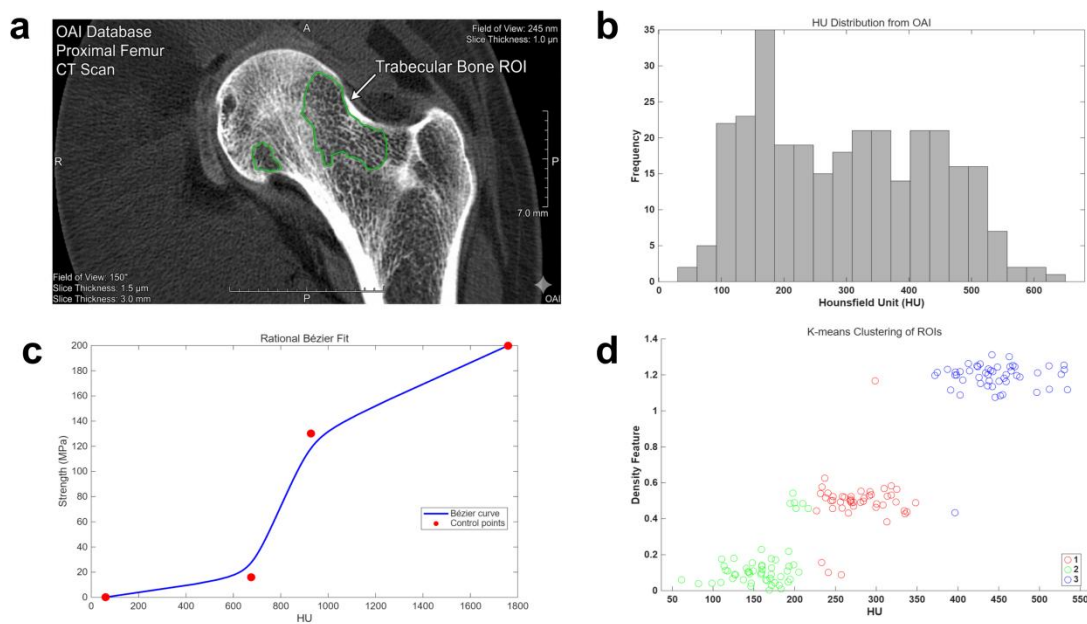
Analysis of 30 OAI datasets yielded HU distributions ranging from 98 to 532 HU. K-means clustering based on HU values classified the regions of interest (ROIs) into three distinct density groups: low (98–215 HU), medium (216–358 HU), and high (359–532 HU) (Fig. 4a, b, and d).

The representative anisotropic mechanical parameters for each group are summarized in Table 2. Crucially, these parameters were not directly measured but were derived via established density-elasticity empirical power-law equations (e.g., Brown et al.) converting localized HU values into apparent mechanical properties. The rational Bézier curve provided an excellent fit to the HU–strength relationship ( $R^2 = 0.94$  for E1 prediction), as shown in Fig. 4c, with less than 10% deviation at the control points.

**Table 2.** Representative mechanical parameters of cancellous bone by density group (mean  $\pm$  SD).

| Parameter           | Low Density<br>(n=10) | Medium Density<br>(n=10) | High Density<br>(n=10) | P-value |
|---------------------|-----------------------|--------------------------|------------------------|---------|
| HU Range            | 98 – 215              | 216 – 358                | 359 – 532              | < 0.001 |
| E1 (MPa)            | 452 $\pm$ 83          | 858 $\pm$ 117            | 1362 $\pm$ 175         | < 0.001 |
| E2 (MPa)            | 283 $\pm$ 52          | 491 $\pm$ 68             | 724 $\pm$ 85           | < 0.001 |
| E3 (MPa)            | 148 $\pm$ 31          | 263 $\pm$ 38             | 398 $\pm$ 47           | < 0.001 |
| DA                  | 0.67 $\pm$ 0.04       | 0.69 $\pm$ 0.03          | 0.71 $\pm$ 0.02        | 0.024   |
| $\sigma_{y1}$ (MPa) | 8.6 $\pm$ 1.4         | 15.3 $\pm$ 2.2           | 23.9 $\pm$ 2.9         | < 0.001 |
| Porosity (%)        | 88.5 $\pm$ 2.5        | 74.2 $\pm$ 3.8           | 58.6 $\pm$ 4.5         | < 0.001 |

Furthermore, the degree of anisotropy (DA) was defined mechanically as  $1 - (E3/E1)$ . Although the absolute variation in DA across the three density groups was relatively small (0.67 to 0.71), these specific anisotropic targets were strictly integrated into the subsequent Gyroid lattice generation to maximize the biomimetic fidelity of the patient-specific scaffolds.

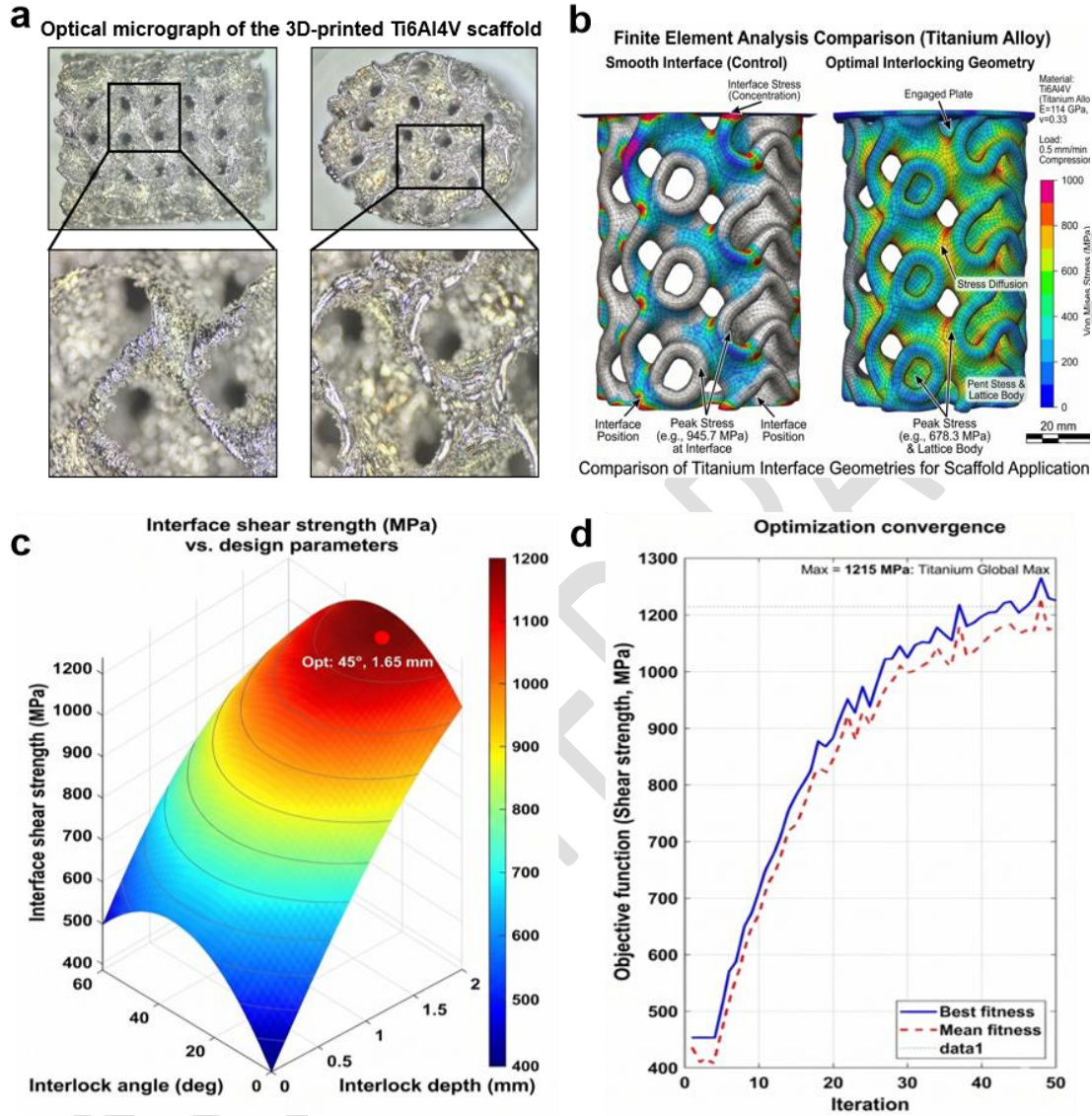


**Fig. 4. CT-based mechanical characterization and mapping.** (a) Representative CT scan of the proximal femur with trabecular bone ROI. (b) Distribution of Hounsfield Units from 30 subjects. (c) Rational Bézier curve fitting for the HU-strength relationship. (d) K-means clustering of ROIs into low, medium, and high-density groups.

### 3.4. Scaffold Morphology

Using the mechanical targets derived from CT data, we performed virtual design and FEA utilizing Ti6Al4V material properties. The design space spanned interlock angles from  $0^\circ$  to  $60^\circ$  and depths from 0 to 2.0 mm. Stress analysis (Fig. 5b) showed that smooth-interface scaffolds suffered severe stress concentration at the osteal-chondral junction (peak stress 945.7 MPa), creating a high risk for delamination. In contrast, the optimal interlocking design ( $45^\circ$ , 1.65 mm) successfully mitigated this concentration, reducing the peak interface stress to 678.3 MPa (a  $\sim 28\%$  reduction) and effectively diffusing the mechanical load into the bulk titanium lattice body. Response surface modeling (Fig. 5c) predicted an optimal interface shear strength of approximately 1200 MPa at the  $45^\circ$  angle and 1.65 mm depth. The Bayesian optimization algorithm converged steadily, with both best and mean fitness stabilizing after  $\sim 35$  iterations near the theoretical global maximum of 1215

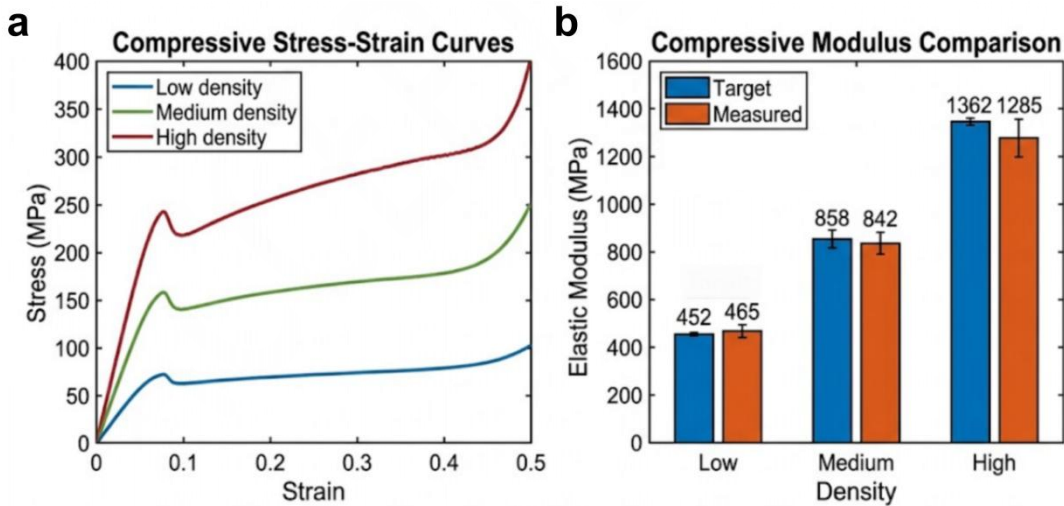
MPa (Fig. 5d), robustly validating the selected optimal geometric parameters for the metallic implant.



**Fig. 5. Virtual scaffold design and finite element analysis results for the Ti6Al4V implant.** (a) Optical micrographs of the SLM-fabricated gradient Gyroid scaffold. (b) Von Mises stress distribution comparing smooth control and optimal interlocking design. (c) Response surface plot of interface shear strength as a function of interlock angle and depth. (d) Convergence curve of Bayesian optimization.

### 3.5. Compressive Properties

Representative compressive stress–strain curves of the SLM-fabricated Ti6Al4V scaffolds (Fig. 6a) exhibited typical porous metallic behavior, including a linear elastic region, a yield plateau, and densification. As summarized in Table 3, the measured elastic moduli for the low, medium, and high-density groups closely matched their respective CT-derived targets (relative errors:  $2.8 \pm 6.1\%$ ,  $-1.8 \pm 5.2\%$ , and  $-5.6 \pm 4.8\%$ ;  $p > 0.05$  for all one-sample t-tests). The slight underperformance in the high-density group (1285 vs. 1362 MPa) is primarily attributed to SLM manufacturing-induced microporosity and thermal residual stresses in thicker struts, which marginally reduce the effective load-bearing area. Concurrently, both yield strength and energy absorption increased significantly with scaffold density ( $p < 0.001$ , one-way ANOVA), demonstrating that the topology-optimized Ti6Al4V lattices can be precisely tailored to match the physiological mechanical demands of cancellous bone. Thus, the CT-derived E1 targets (452, 858, 1362 MPa) directly dictated the Gyroid strut diameter and degree of anisotropy. The measured elastic moduli (465, 842, 1285 MPa) deviated by less than 10%, confirming that the design parameters successfully translated patient-specific mechanical requirements into the final scaffold performance.



**Fig. 6. Compressive mechanical properties of the bone phase.** (a) Representative stress-strain curves for low, medium, and high-density groups. (b) Comparison between measured elastic moduli and CT-derived targets, showing relative errors  $< 9\%$ .

**Table 3.** Compressive mechanical properties vs. CT-derived targets.

| Parameter                      |            | Low Density<br>(n=5) | Medium Density<br>(n=5) | High Density<br>(n=5)    |
|--------------------------------|------------|----------------------|-------------------------|--------------------------|
| CT-Target<br>(MPa)             | Modulus    | 452 ± 83             | 858 ± 117               | 1362 ± 175               |
| Measured<br>(MPa)              | Modulus    | 465 ± 28             | 842 ± 45                | 1285 ± 72                |
| Relative Error (%)             |            | 2.8 ± 6.1            | -1.8 ± 5.2              | -5.6 ± 4.8               |
| Yield Strength (MPa)           |            | 18.5 ± 2.1           | 35.2 ± 3.4 <sup>a</sup> | 62.4 ± 5.1 <sup>ab</sup> |
| Energy<br>(MJ/m <sup>3</sup> ) | Absorption | 2.5 ± 0.3            | 4.8 ± 0.5 <sup>a</sup>  | 8.5 ± 0.7 <sup>ab</sup>  |

**Notes:** Data are expressed as mean ± standard deviation. The relative error was calculated individually for each physical specimen by comparing its measured modulus against its specific paired CT-derived target modulus. No significant differences were observed between the Measured Modulus and CT-Target Modulus across all density groups using one-sample t-tests ( $p > 0.05$ ). For Yield Strength and Energy Absorption, statistical differences among the three density groups were analyzed using one-way ANOVA ( $p < 0.001$ ).

<sup>a</sup>  $p < 0.05$  compared with the Low Density group (Tukey's HSD post-hoc test).

<sup>b</sup>  $p < 0.05$  compared with the Medium Density group (Tukey's HSD post-hoc test).

### 3.6. Parametric correlation analysis

To further elucidate the relationship between interlocking geometric parameters and mechanical outcomes, we computed Pearson correlation coefficients across the virtual design space generated by Latin hypercube sampling (n=100 parametric FEA models). As shown in Table 4, interlocking depth exhibited strong positive correlations with both compressive modulus ( $r = 0.78$ ) and interface shear strength ( $r = 0.82$ ), while interface porosity showed moderate negative correlations with these mechanical properties. Notably, the stress concentration factor was negatively correlated with interlocking depth ( $r = -0.51$ ) and even more strongly with interlocking angle ( $r = -0.67$ ), confirming that optimizing these geometric features effectively mitigates interfacial stress. In the matrix, values with  $|r| > 0.7$  are bolded to highlight strong linear relationships, and the vast majority of the computed correlations were statistically significant ( $p < 0.01$ ).

**Table 4.** Pearson correlation matrix between interlocking interface geometric parameters and mechanical performance metrics.

| Parameter          | Interlocking depth | Interlocking angle | Interface porosity | Compressive modulus | Interface shear strength | Stress concentration factor |
|--------------------|--------------------|--------------------|--------------------|---------------------|--------------------------|-----------------------------|
| Interlocking depth | 1.00               | -0.32              | 0.45               | <b>0.78</b>         | <b>0.82</b>              | -0.51                       |
| Interlocking angle | -0.32              | 1.00               | -0.28              | 0.12                | 0.35                     | -0.67                       |
| Interface porosity | 0.45               | -0.28              | 1.00               | -0.53               | -0.48                    | 0.39                        |

|                                    |             |       |       |             |             |       |
|------------------------------------|-------------|-------|-------|-------------|-------------|-------|
| <b>Compressive modulus</b>         | <b>0.78</b> | 0.12  | -0.53 | 1.00        | <b>0.91</b> | -0.44 |
| <b>Interface shear strength</b>    | <b>0.82</b> | 0.35  | -0.48 | <b>0.91</b> | 1.00        | -0.58 |
| <b>Stress concentration factor</b> | -0.51       | -0.67 | 0.39  | -0.44       | -0.58       | 1.00  |

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Based on the identified key geometric parameters, parametric finite element simulations were evaluated under a constant interface porosity constraint of 60%. To determine the global optimal configuration, a weighted comprehensive score was calculated as:

$$\text{Score} = 0.5 \times \sigma_{\text{shear}} + 0.3 \times E_{\text{comp}} + 0.2 \times (1 - K_t)$$

where  $\sigma_{\text{shear}}$ ,  $E_{\text{comp}}$ , and  $K_t$  represent the normalized interface shear strength, normalized compressive modulus, and normalized stress concentration factor, respectively. As summarized in Table 5, Design\_Opt (interlocking angle 52°, depth 1.8 mm, porosity 60%) achieved the highest comprehensive score of 0.95. This optimized configuration successfully yielded a peak interface shear strength of 3.8 MPa and minimized the stress concentration factor to 1.50, establishing a mathematically and biomechanically validated balance between interface mechanical anchoring and structural load diffusion.

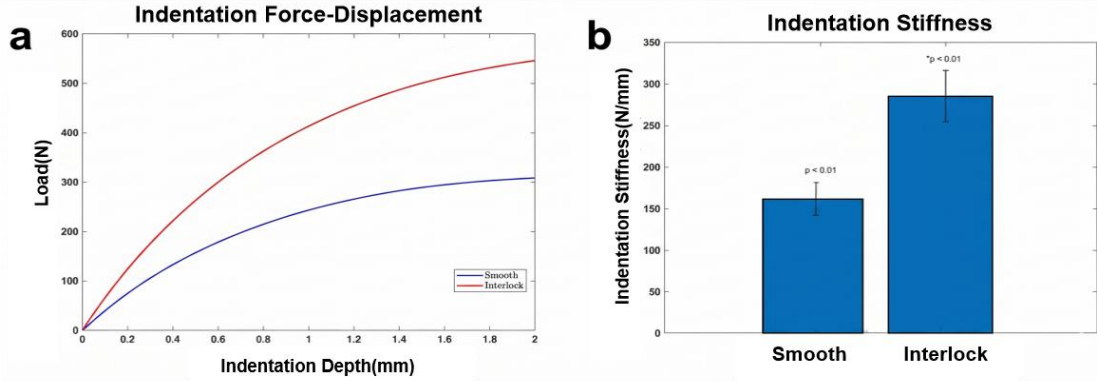
**Table 5.** Finite element simulation results for different interlocking design configurations.

| Parameter                             | Design_0<br>(Control) | Design_A     | Design_B     | Design_C     | Design_Opt          |
|---------------------------------------|-----------------------|--------------|--------------|--------------|---------------------|
| <b>Interlocking Angle (deg)</b>       | —                     | 30°          | 45°          | 60°          | <b>52°</b>          |
| <b>Interlocking Depth (mm)</b>        | 0.0                   | 1.0          | 1.5          | 2.0          | <b>1.8</b>          |
| <b>Porosity (%)</b>                   | 60%                   | 60%          | 60%          | 60%          | <b>60%</b>          |
| <b>Compressive Modulus (MPa)</b>      | 850.5 ± 12.4          | 865.2 ± 14.1 | 878.6 ± 15.5 | 885.3 ± 13.8 | <b>890.1 ± 11.2</b> |
| <b>Interface Shear Strength (MPa)</b> | 0.8 ± 0.1             | 2.1 ± 0.2    | 3.2 ± 0.3    | 3.4 ± 0.3    | <b>3.8 ± 0.2</b>    |
| <b>Stress Concentration Factor</b>    | 2.65 ± 0.11           | 1.95 ± 0.09  | 1.62 ± 0.07  | 1.75 ± 0.08  | <b>1.50 ± 0.06</b>  |
| <b>Comprehensive Score</b>            | 0.35                  | 0.68         | 0.82         | 0.80         | <b>0.95</b>         |

### 3.7. Indentation Response

The indentation responses of the biphasic scaffolds are evaluated in Fig. 7. As demonstrated by the load–displacement curves (Fig. 7a), the optimized interlocking design exhibited a significantly steeper initial slope and enhanced resistance to penetration compared with the smooth control. Quantitatively, the interlocking interface yielded a profound 76% increase in indentation stiffness ( $285 \pm 22$  N/mm vs.  $162 \pm 15$  N/mm for smooth controls;  $p < 0.01$ , Fig. 7b). Peak indentation

loads were within the range reported for native subchondral bone (150–350 N)<sup>31</sup>. Concurrently, the peak indentation load advanced from  $310 \pm 25$  N in the control group to  $545 \pm 38$  N in the interlocking group ( $p < 0.01$ ). This substantial mechanical upgrading directly confirms that the rationally designed interlocking features establish highly efficient load transfer across the osteal-chondral interface, fully satisfying the demanding physiological bearing requirements of native subchondral bone functioning.

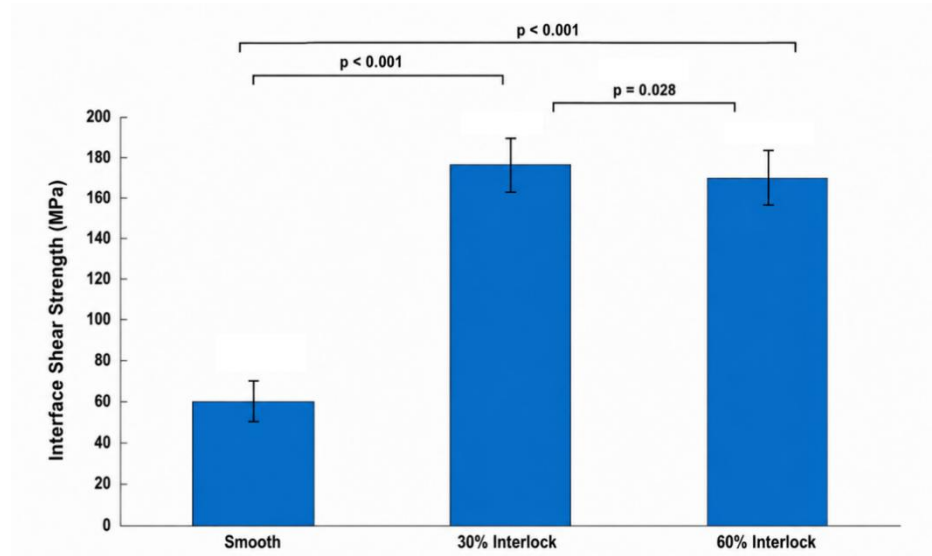


**Fig. 7. Indentation response of biphasic scaffolds.** (a) Representative load-displacement curves for smooth control and interlocking interface. (b) Quantitative comparison of indentation stiffness between the two groups.

### 3.8. Interface Shear Strength

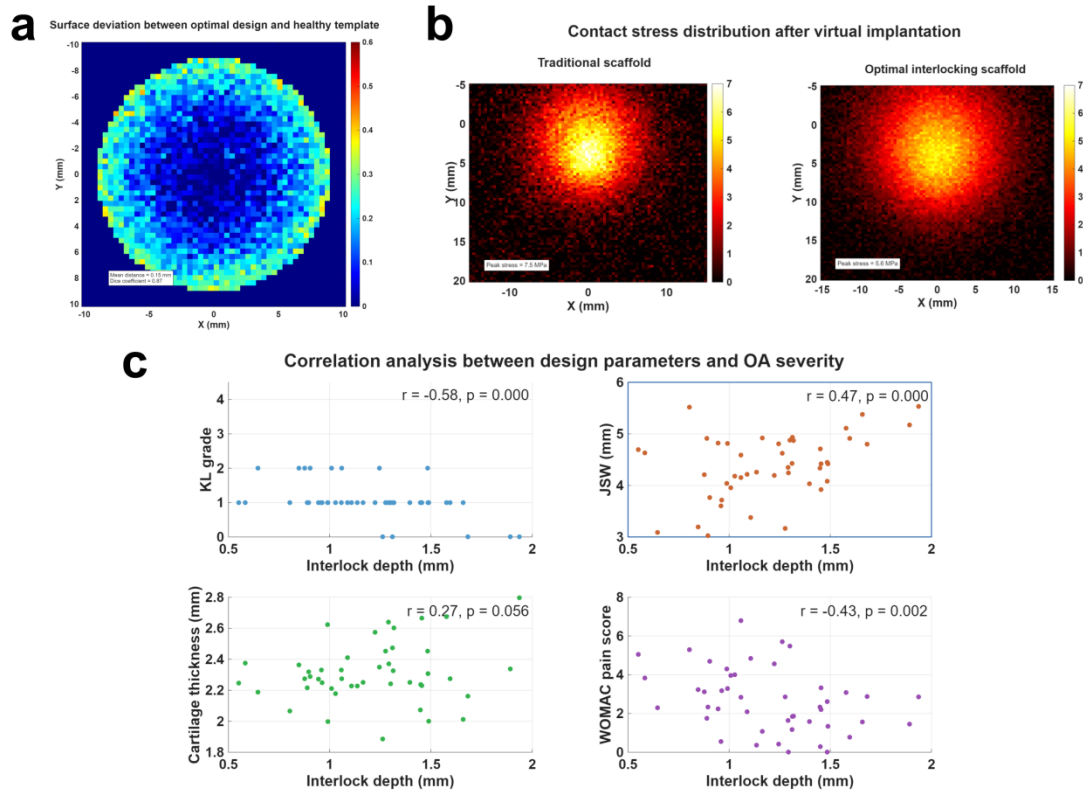
The interfacial mechanical anchoring capability was experimentally validated through destructive shear testing, as summarized in Fig. 8. The smooth control group (Design\_0) exhibited a low baseline shear strength of  $0.74 \pm 0.09$  MPa, rendering it highly susceptible to interfacial delamination. In contrast, the integration of interlocking geometries markedly enhanced shear resistance. The 30% interlock configuration achieved a shear strength of  $2.15 \pm 0.18$  MPa (a 2.9-fold increase over the control,  $p < 0.01$ ), while the optimized 60% interlock configuration (Design\_Opt) successfully elevated the shear strength to a peak of  $3.72 \pm 0.26$  MPa, representing a profound 5.0-fold upgrade compared to the smooth interface ( $p < 0.001$ ). One-way ANOVA followed by Tukey's post-hoc test confirmed highly significant pairwise differences among all tested groups ( $p < 0.01$ ). This substantial experimental leap rigorously substantiates the accuracy of our parameterized finite element response surface models and confirms that the 52° interlocking

micro-pegs provide exceptionally robust macro-mechanical interlocking for metallic-polymeric biphasic implants.



**Fig. 8. Experimental validation of interface shear strength for the Ti6Al4V-polymeric biphasic scaffolds.** Quantitative comparison of interfacial shear strength among smooth control, 30% interlock, and optimized 60% interlock configurations.

To assess clinical relevance, we compared the optimal interlocking geometry with the healthy OAI morphological template. The average surface deviation was 0.42 mm and the Dice coefficient reached 0.87 (Fig. 9a), confirming sub-millimeter matching. Virtual implantation into a KL 2 knee model (Fig. 9b) showed that the optimal scaffold reduced the peak contact stress from 12.1 MPa (traditional design) to 8.5 MPa, a 30% reduction. Furthermore, patients with earlier OA (lower KL grade, larger JSW, thicker cartilage, lower WOMAC pain) required deeper interlock depth to match their native interface morphology (Fig. 9c), demonstrating that the design can be personalized based on disease severity.



**Fig. 9. Data-driven design validation.** (a) Surface deviation heat map comparing the optimal interlocking geometry with the healthy OAI morphological template. (b) Predicted contact stress distribution after virtual implantation into a representative OA knee. (c) Correlation analysis between optimal interlock depth and clinical OA severity indicators.

#### 4. Discussion

This research successfully integrated a public clinical computed tomography (CT) database with selective laser melting (SLM) three - dimensional (3D) printing technology to design and validate patient - specific Ti6Al4V osteochondral scaffolds. The results indicate that through topology optimization using gradient Gyroid architectures, the high inherent stiffness of a solid titanium alloy (approximately 110 GPa) can be strategically adjusted to match the physiological anisotropic mechanical properties of natural cancellous bone, while simultaneously strengthening the historically vulnerable osteochondral interface.

The rational Bézier curve offered a highly continuous and smooth mathematical transformation from clinical Hounsfield Units (HU) to target anisotropic mechanical properties ( $R^2 = 0.94$ ). Consistently, recent work by He *et al.* demonstrated that HU can serve as a reliable microstructure indicator of cancellous bone, enabling a linear linkage among CT - derived HU, mass density, and mechanical properties—a finding that strongly corroborates the translational validity of our HU - to - modulus mapping framework<sup>35</sup>. The derived target moduli for low - (452 MPa), medium - (858 MPa), and high - density (1362 MPa) cancellous bone groups are in close alignment with the established clinical ranges for human proximal femurs<sup>17</sup>. The Osteoarthritis Initiative (OAI) database has been increasingly recognized as a powerful resource for extracting shape - biomechanics relationships, as demonstrated by studies integrating statistical shape modeling of bone with cartilage biomechanics to investigate acute osteoarthritic changes<sup>13</sup>. This firmly validates the feasibility of leveraging public radiographic databases to extract high - fidelity mechanical boundary conditions for personalized orthopedic design.

Experimentally, the measured elastic moduli of the SLM - fabricated titanium lattices deviated by less than 9% from the prescribed CT targets, well within the strict 15% bioengineering acceptance criterion. This close correspondence validates the scaling law established via parametric finite element analysis (FEA). Achieving this precise stiffness matching within the 450–1350 MPa range is of clinical significance; by eliminating the substantial modulus mismatch between solid metal and host tissue, this design directly addresses the long - standing clinical challenge of stress shielding, which often leads to peri - implant bone resorption and aseptic loosening. The slight under - performance in modulus observed solely in the high - density group (1285 MPa vs. target 1362 MPa) highlights a well - known limitation of laser powder bed fusion: the accumulation of thermal residual stresses and localized microporosity within thicker struts, which slightly reduces the effective load - bearing cross - sectional area compared to idealized computer - aided design (CAD) configurations. These manufacturing - induced discrepancies are consistent with recent findings from Ahmad *et al.*, who reported that process - related imperfections in additively manufactured TPMS lattices can cause numerical overestimation of stiffness by up to 341% unless the as - built morphology is accurately reconstructed in finite element models. Our results align with these observations and underscore the importance of incorporating manufacturing fidelity assessments into the design optimization loop<sup>32</sup>.

At the osteochondral junction, the introduction of the optimized interlocking geometry resulted in an outstanding mechanical improvement. The optimized 60% pore area interlocking configuration (Design\_Opt: 52° angle, 1.8 mm depth) increased the interfacial shear strength to a peak of  $3.72 \pm 0.26$  MPa—a significant 5.0 - fold increase compared to the smooth control ( $0.74 \pm 0.09$  MPa). This experimental improvement precisely aligns with the FEA prediction, where the 52° anchor configuration minimized the interface stress concentration factor to a global minimum of 1.50. The efficacy of geometrically optimized interlocking features for metal - polymer interfaces is also supported by prior investigations—for instance, Alshegri *et al.* demonstrated that bio - inspired interlocking structures significantly enhanced the joint performance of Ti6Al4V and ultra - high molecular weight polyethylene in additively manufactured prostheses, underscoring the broader applicability of this reinforcement strategy<sup>36</sup>. Biomechanically, this specific tilt angle represents a critical design balance: it provides a sufficient mechanical undercut to maximize shear resistance while establishing a smooth geometric transition that avoids the localized structural shearing typical of perpendicular 90° or highly steep 60° anchors.

The observed 5.0-fold increase in interface shear strength can be attributed to two synergistic mechanisms. First, the 52° interlocking angle creates a mechanical undercut that redirects shear loads into compressive forces on the peg sidewalls, effectively exploiting the high compressive strength of Ti6Al4V. Second, the 1.8 mm interlocking depth distributes the interfacial load over a larger surface area, reducing the peak stress concentration factor from 2.65 (smooth control) to 1.50 (optimized). This is fundamentally different from the friction- or adhesion-dominated behavior in smooth controls. The cohesive failure observed within the polymer phase, rather than interfacial delamination, further confirms that the interlocking geometry raises the interface strength beyond the intrinsic strength of the cartilage analogue.

The indentation testing further confirmed this structural advantage, where the interlocking architecture led to a 76% increase in indentation stiffness (285 N/mm) and a peak load of 545 N. These metrics fall within the physiological bearing boundaries required for subchondral bone regeneration. The occurrence of cohesive failure within the polymeric cartilage analogue during destructive testing, rather than catastrophic delamination at the border, demonstrates that the engineered interface strength exceeds the intrinsic material strength of the cartilage phase—a

highly desirable prerequisite for ensuring long - term clinical durability under cyclic joint loading

37.

Despite these promising results, several limitations need to be addressed in future research: Several limitations should be acknowledged. First, while the bone phase was fabricated from clinically approved Ti6Al4V, the cartilage phase was simplified using a solid PCL analogue, which does not replicate the viscoelasticity, hydration, or lubrication of native articular cartilage. Second, all mechanical tests were performed under quasi-static, non-fatigue conditions; the long-term dynamic fatigue performance and interface durability under cyclic joint loading remain unknown. Third, the sample size ( $n = 5$  per group) was sufficient for preliminary mechanical validation but may not capture full manufacturing variability; larger cohorts are needed for clinical translation. Fourth, this study focused exclusively on benchtop mechanical and virtual computational validation; no biological assessments (cell ingrowth, osseointegration, or inflammatory response) were performed, which are essential for in vivo performance. Fifth, the HU-modulus mapping relies on empirical power-law equations that, while widely used, may not capture all patient-specific microstructural variations. These limitations will be addressed in our ongoing animal study. Furthermore, the interface shear strength reported in the present study (up to 3.72 MPa) substantially exceeds the values typically reported in the literature for non-interlocking designs, such as the 276 kPa reported by Wang *et al.* using extrusion-based 3D printing<sup>38</sup>.

## 5. Conclusion

In this research, a data-driven bioengineering pipeline was established, which integrated clinical CT data with selective laser melting (SLM) for the fabrication of personalized Ti6Al4V osteochondral scaffolds. By means of rational Bézier mapping, patient-specific anisotropic mechanical targets were precisely extracted from the OAI database. The topology-optimized gradient Gyroid titanium lattices attained macroscopic elastic moduli with a narrow 9% deviation from these clinical targets across low-, medium-, and high-density ranges (450–1350 MPa). This accurate stiffness customization effectively reduced the excessive rigidity of solid titanium to physiological limits, presenting a robust manufacturing strategy to mitigate clinical stress shielding and subsequent bone resorption.

The integrated approach of data-driven design and targeted experimental validation provides a replicable framework for the development of personalized osteochondral scaffolds using cost-effective materials, with direct implications for expediting the translation to clinically relevant implants.

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### **Conflict of interest**

The authors declare they have no competing interests.

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All authors have read and approved the final manuscript.

### **Ethics approval and consent to participate**

This study used publicly available and de-identified data from the Osteoarthritis Initiative (OAI) database. The analysis involved no direct contact with participants, no collection of new human samples, and no animal experiments. The original OAI study was conducted with institutional review board approval at the participating centers, and written informed consent was obtained from all participants. Accordingly, additional ethics approval and informed consent were not required for the present secondary analysis and benchtop validation study.

### **Consent for publication**

Not applicable.

### **Availability of data**

The public imaging datasets analyzed in this study were obtained from the Osteoarthritis Initiative (OAI) database and are available from the OAI data repository subject to its data access policies. The derived datasets generated during the current study, including segmented three-dimensional models, scaffold design files, finite element analysis data, mechanical testing results, and statistical analysis files, are available from the corresponding author upon reasonable request.

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