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From Geometry to Function: Programmable Mechanical Response in 3D-Printed Adipose-Inspired Soft Metamaterials

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ABSTRACT

Replicating the nonlinear, strain-dependent mechanics of soft biological tissues remains a central challenge in scaffold engineering, implantable devices and tissue-mimicking phantom development. Current approaches lack a systematic, experimentally validated framework that quantitatively links unit cell characteristics to macroscopic mechanical response across clinically relevant stiffness ranges. Here, we introduce a geometry-driven design strategy for 3D-printed adipose-inspired soft metamaterials, systematically varying unit cell diameter, shell thickness, orientation angle, and base material across multiple architectures. Compression experiments reveal that shell thickness governs initial stiffness and buckling onset, cell diameter controls the extent of the progressive instability plateau, and orientation angle switches the deformation mode from instability-driven buckling to progressive compaction. Finite element simulations capture these mechanisms quantitatively, while a multivariate regression model predicts effective modulus, buckling stress, and energy absorption ($R^2_{\text{adj}} > 0.86$). The resulting design space spans elastic moduli from units to hundreds of kPa, covering the mechanical ranges of multiple soft biological tissues, demonstrating that a single geometric framework can be systematically tuned to target diverse soft-tissue mechanical environments. This integrated experimental–computational–statistical platform establishes a mechanistic and geometry-driven design foundation that can inform the rational development of programmable soft metamaterials for regenerative scaffolds, tissue-mimicking phantoms, and soft implantable devices.

1 | Introduction

Nature provides a wealth of porous structures with extraordinary performance and versatility, from bone and coral to honeycombs, wood, shells, and sponges [1]. These natural designs have inspired various fields to create bioinspired porous materials for transformative applications, from civil infrastructure [2] to biomedical innovations [3, 4]. Some of these materials, with programmable architectures, are classified as metamaterials—materials whose properties arise primarily from geometry rather

than composition—which are redefining how we design multifunctional cellular and adaptive architectures, such as lattice and shell-based metamaterials [5–9], foam-like metamaterials [10], auxetic metamaterials [11–13], origami [14–16] and kirigami metamaterials [17]. By tuning the internal architecture of their repeating unit, these systems can exhibit mechanical behaviors far beyond those of bulk materials, including programmable stiffness, controlled buckling, and customized energy absorption [18–23]. One of their defining features is the ability to decouple stiffness from density, a breakthrough that enables

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the creation of materials capable of imitating the mechanical and functional behaviors of soft tissues with unprecedented accuracy [24–26]. Understanding how the unit cell geometry governs macroscopic behavior is therefore fundamental to the rational design and function of metamaterials, especially for those applications where mechanical compatibility and biological functionality must coexist [27, 28].

Emerging as a transformative area in biomedical engineering, metamaterials for tissue replacement and regeneration hold exceptional potential [29, 30]. They can be specifically engineered to exhibit unique properties that do not occur in natural materials [31–33], leveraging metamaterial architectures to tailor the mechanical and biological performance of soft-tissue scaffolds. Moreover, in regenerative medicine, scaffolds are designed not merely as passive supports but as bioactive frameworks that emulate the extracellular matrix (ECM) and recreate the correct mechanical stimulus for direct tissue formation [28, 34, 35].

When referring to soft tissue regeneration, pores in the range of 500–1000 μm have been shown to favor cellular differentiation [36]; however, increasing pore size unavoidably reduces stiffness, thus needing to find a compromise between biological and mechanical performance. Literature provides many examples for adipose tissue scaffold design [37–39], with applications commonly applied to breast tissue reconstruction. For example, Luo et al. [40] developed alginate–polydopamine (Alg–PDA) scaffolds with stiffness comparable to mammary tissue, promoting mammary cell proliferation and tumor regression in vivo, while Tytgat et al. [36] printed GelMA and GelMA/CarMA hydrogels seeded with adipose-derived stem cells, achieving compressive moduli of units of kPa—close to native breast tissue—and sustained biocompatibility over 21 days. Zhou et al. [39] correlated the mechanical behavior of polyurethane lattices of varying architectures with finite-element predictions and in vivo adipogenesis, showing that softer scaffolds enhanced vascularization, reduced fibrosis, and improved tissue viability.

Within this context, engineering controlled architectures via unit cell-based metamaterials, while enabling the modulation of local and global mechanical stimuli to which the surrounding environment (e.g., living cells) can respond, represents a rapidly growing research frontier also for soft tissue applications [28]. As an example, Zhao et al. developed a family of bio-inspired cubic elastic metamaterials based on lipidic cubic phases, demonstrating through parametric numerical simulations that while the primitive architecture exhibits significant anisotropy, the diamond configuration can achieve complete elastic isotropy independently of the constituent material properties [41]. Nevertheless, while biocompatible implementation remains the ultimate translational goal, establishing a robust structure–mechanics framework first requires systematic characterization of architectural effects in isolation from biological variables — a prerequisite that motivates the use of well-characterized photopolymer blends in the present study, as well as PolyJet multi-material technology, to uniquely enable independent and reproducible tuning of constituent stiffness across nearly two orders of magnitude [42].

Recent advances in Additive Manufacturing (AM) have extended the design space of metamaterials, encompassing the limitations

of conventional approaches that typically provide a more limited control over internal interconnected morphologies, toward increasingly complex, function-driven architectures [34]. Indeed, the application of high-resolution 3D printing enables the realization of metamaterials with programmable mechanical responses beyond pure stiffness tuning [5, 11, 27]. For example, Rahmani et al. demonstrate that 3D/4D-printed PA12 composites with honeycomb, honeycomb-circle hybrid, and auxetic geometries can achieve shape-memory recovery, force-regulated response, and high energy absorption under compression [43]. However, manufacturing effects inevitably complicate the mechanical response of architected materials: AM introduces limitations related to minimum feature size, surface roughness, and process-induced anisotropy that alter stiffness, strength, and reproducibility [44, 45]. Compared with idealized CAD models, printed geometries consistently yield lower moduli and modified deformation patterns, as CAD-based simulations systematically overestimate stiffness by neglecting geometric irregularities and bulk-material inhomogeneities introduced during printing, washing, and post-curing [45].

Despite these advances, a critical gap remains: no study has simultaneously quantified the contributions of unit cell geometry, assembly orientation, and base material stiffness to the full nonlinear compressive response of soft metamaterials — from initial stiffness through instability onset to energy absorption — within a single, experimentally validated and statistically appropriate framework. Existing FEM approaches capture local deformation mechanisms [11, 46], but rely on idealized geometries and cannot efficiently explore large parametric spaces under realistic manufacturing variability. Data-driven methods, while powerful, demand large datasets and sacrifice physical interpretability [47–49], both of which are critical limitations in biomedical design contexts where experimental data are inherently scarce.

While experimental–computational–statistical pipelines have been applied to lattice metamaterials, existing works typically treat geometric and material parameters independently, reporting their effects in isolation rather than mapping their joint and ranked contributions to the full nonlinear compressive response within a single validated framework. Moreover, regression models employed in prior studies are rarely accompanied by cross-validated predictive accuracy metrics or manufacturing-aware uncertainty quantification, limiting their practical utility as design tools.

Here, we close this gap by introducing an integrated experimental–computational–statistical framework with Monte Carlo bootstrap validation for the programmable design of adipose-inspired soft metamaterials. Unlike previous works that address geometry and material effects independently, our approach simultaneously maps and quantifies how unit cell diameter, shell thickness, orientation angle, and base material jointly govern mechanical programmability. The experimental approach uses a controlled one-factor-at-a-time strategy to isolate primary geometric effects, while the adopted multivariate regression enables the simultaneous quantification of the contributions of all investigated descriptors. Complementing rather than replacing FEM, the approach provides interpretable sensitivity metrics, confidence intervals, and validated trends that explicitly account for manufacturing-

induced variability. This enables the construction of reliable parametric maps within the investigated design space, offering a practical and computationally efficient design tool that spans the stiffness regimes of multiple soft biological tissues within a single geometric framework and directly links each geometric and material descriptor to its quantitative contribution to macroscopic response — a feature particularly critical in biomedical design contexts. By establishing mechanical compatibility with multiple soft tissue benchmarks, this framework provides the quantitative design foundation required prior to biocompatible material translation and functional biological validation.

2 | Results and Discussion

2.1 | Design and Fabrication of Adipose-Inspired Metamaterials

Figure 1 illustrates the overall design strategy of the proposed adipose-inspired metamaterials and their fabrication through a J850 Digital Anatomy PolyJet printer (Stratasys) [50, 51]. The architectures are inspired by the mesoscale morphology of natural adipose tissue, in which roughly spherical fat lobules are separated by thin connective septa that guide deformation under physiological loading [52–54]. From a histological point of view, lobules are primary structural units of adipose tissue, which represent 3D clusters of adipocytes, while septa are thin fibrous partitions composed mainly of collagenous connective tissue that provide structural support, constrain lobular deformation, and act as load-bearing pathways, governing stress transmission, buckling, and compaction mechanisms within the tissue [55, 56].

The bioinspiration adopted here operates at the mesoscale architectural level: the spherical shell unit cell appears as the simplest topologically faithful abstraction of the lobular morphology, capturing the defining feature of closed, approximately spherical cells bounded by thin, compliant walls, without claiming to reproduce tissue microstructural heterogeneity or the full complexity of adipocyte packing, while enabling systematic parametric variation and fabrication reproducibility. For these reasons, we mimicked the fibrous supporting structure of the septa, basing the architectures on spherical unit cells whose geometry could systematically vary through three morphological descriptors: diameter (D), shell thickness (t), and orientation angle of the 3D assembly (α) (Figure 1). By combining these parameters, a variety of distinct configurations were generated to explore controlled deformation modes, including septal bending, buckling, and post-buckling compaction, and thus able to suppress buckling when a monotonic response is required (e.g., for load-bearing scaffolds) or to preserve it when programmable compliance is desired (e.g., for energy-absorbing or mechanically graded devices).

Each unit cell was repeated in a periodic $5 \times 5 \times 5$ array to form mesoscale specimens with homogeneous structural behavior, providing a consistent basis for both experimental testing and numerical modeling (Supporting Information Section A and Figure S1), in agreement with other literature works [8, 25, 57–59].

Three photopolymer blends, namely MAT-1, MAT-2, and MAT-3 (from the softest to the stiffest, see the [Experimental Section](#)

and the Supporting Information Section B), were designed and employed to create metamaterials able to cover a wide range of mechanical properties.

Post-processing included removal of support material via chemical-assisted cleaning, followed by inspection of shell integrity and dimensional verification to ensure fabrication fidelity, first with direct inspection through optical microscopy, followed by micro Computerized Tomography (μ -CT), resulting in a variation from its respective theoretical model of, on average, 0.1 mm (Supporting Information). The edges of the printed samples were the regions most affected by the 3D printing process (Figure S12). However, the impact of these boundary inaccuracies on the overall compressive response is expected to be limited, and boundary effects are progressively attenuated toward the specimen core.

Among the possible geometric configurations, and with reference to the macroscopic organization of the adipose tissue, we chose as reference configuration the structure characterized by $\alpha = 0^\circ$ (namely, α_1), $D = 3.0$ mm (namely D_2), $t = 0.3$ mm (namely t_3). From this set, we obtained seven additional configurations by varying one parameter at a time, as reported in Figure 2 and Table S2. These eight configurations were fabricated and tested for each material blend (MAT-1 to MAT-3) through uniaxial compression tests, a well-established mechanical test for the evaluation of the mechanical properties of metamaterials [60, 61].

2.2 | Metamaterials Response under Compression

All investigated configurations exhibited the characteristic three-regime compressive response of cellular metamaterials: an initial linear elastic phase governed by shell bending, followed by an instability-driven plateau associated with local buckling and unit cell rotation, and a final densification regime marked by rapid stress recovery upon inter-cell contact [8, 45]. The extent and prominence of each regime varied systematically with unit cell geometry and material composition, enabling a controlled comparison across configurations. Figure 3 presents representative stress–strain curves for selected configurations (reported as median responses, with first and third quartile bounds), highlighting the influence of individual geometric parameters on the compressive response. The reference configuration (MAT-3, α_1) is compared, for the same material composition, with architectures obtained by decreasing the unit cell diameter (MAT-3, D_1), increasing the cell assembly angle (MAT-3, α_4), and reducing the septal thickness (MAT-3, t_2).

Qualitative differences are first evident from the deformation paths shown in Figure 3B. In particular, variations in a single geometric parameter lead to pronounced changes in the onset and evolution of buckling. Notably, reducing the unit cell diameter suppresses the development of global buckling, resulting in a more homogeneous deformation mode and a smoother, monotonic stress–strain response (Figure 3D). This behavior suggests a transition from instability-driven deformation to a regime dominated by distributed shell bending and progressive compaction [45, 59, 62]. By increasing the assembly angle from 0° to 45° (from α_1 to α_4), the instability-driven response observed in the reference configuration is progressively suppressed. At

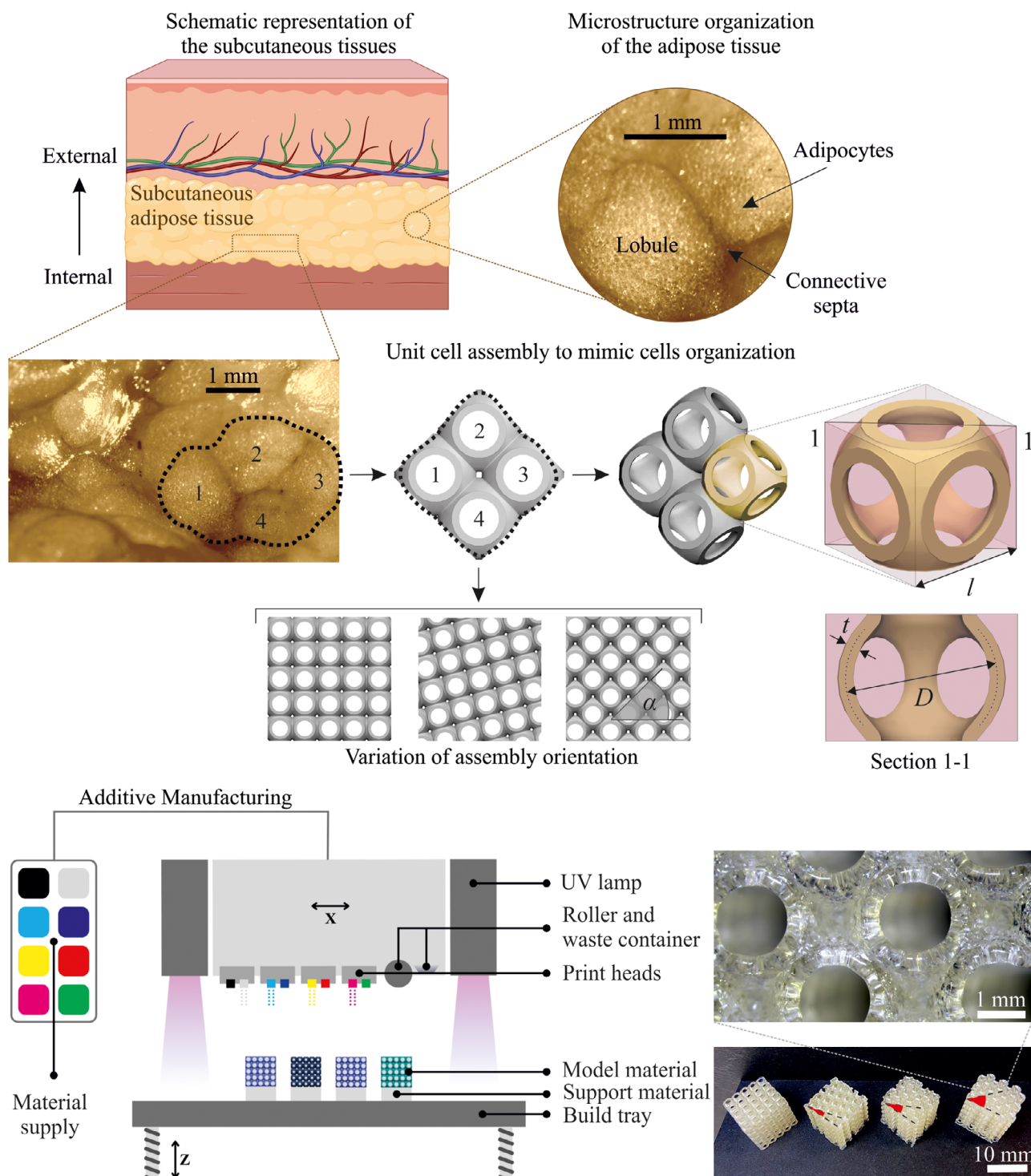


FIGURE 1 | Bio-inspired design of the unit-cell: from microstructural organization of the subcutaneous adipose tissue to unit cell geometries and 3D printing. In the cross-sectional view of the unit cell, the geometrical parameters D (diameter) and t (thickness) are identified. Finally, the PolyJet 3D-printing process is summarized, where multiple print heads dispense photopolymer resins to enable multi-material and multi-color fabrication. Optical images of the adipose tissue were realized with an Olympus SZ61-TR stereomicroscope equipped with an EP50 digital camera; 30 $\times$ magnification; scale bar as reported.

higher orientation angles, adjacent unit cells undergo mutual interlocking during compression, compacting into the voids created between neighboring cells in the layers above and below (Figure 3B MAT-3, α_4). This geometric rearrangement enables more efficient accommodation of deformation distribu-

tion through inter-cell compaction rather than lateral expansion. As a result, the metamaterial does not exhibit the characteristic behavior observed at α_1 , and the compressive response remains dominated by progressive densification rather than global buckling.

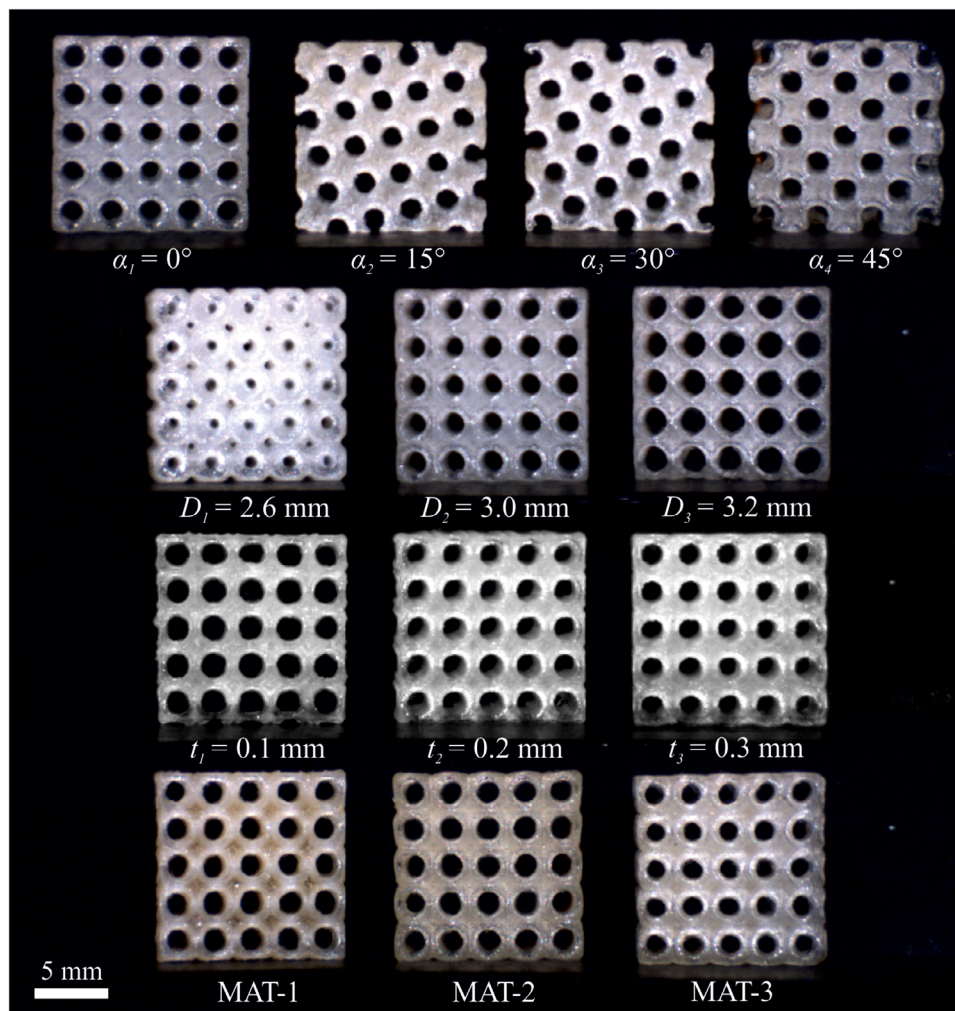


FIGURE 2 | Resulting metamaterials from 3D printing. Starting from the reference configuration (α_i , D_2 , t_3), seven other configurations were obtained by varying one parameter at a time, specifically: D (from D_1 to D_3), t (from t_1 to t_3), α (from α_1 to α_4), for each material blend (MAT-1 to MAT-3).

On the contrary, a reduction in septal thickness further enhances buckling-dominated behavior, leading to earlier instability and a pronounced softening response prior to densification. Overall, these results highlight that buckling can be selectively activated or suppressed through targeted modulation of unit cell parameters, depending on the application. Other works focused on buckling development and evolution, as, for instance, in 3D auxetic metamaterials, the buckling of thin ligaments surrounding spherical voids was able to induce an inward contraction, resulting in a negative Poisson's ratio [11]. Similarly, Walker et al. observed that pore shape influences the global buckling onset and evolution, which can move from an *orthogonal alternating deformation pattern* (spherical pores) to a simple right-shifted collapse (cubic pores) [45]. In our case, the adopted shape of the unit cell is kept constant, while geometrical parameters influence the septa slenderness and thus the buckling propagation. In other cases, buckling has been addressed as a design target, as in Mohammadi et al., where they evaluated which geometric parameters place the buckling transition point exactly at a user-specified displacement in flexible beam-based metamaterials under tensile loading [63]. This was achieved by computational inverse design to prescribe a desired buckling onset in tensile flexible structures.

Other instability-driven strategies were proposed, where graded soft/stiff unit cells are intentionally introduced to control the sequence of local densification and post-buckling deformation, thus providing vibration isolation performance at low-frequency ranges [64]. Moreover, Zolfagharian et al. exploited controlled arm bending and snap-through instability in auxetic and zero-Poisson-ratio cylindrical springs to generate a quasi-zero stiffness (QZS) region, enabling vibration isolation through a high-static, low-dynamic stiffness response [65]. In their system, buckling is intentionally induced at the structural level to produce the negative-stiffness transition needed for the QZS plateau, but uncontrolled buckling in thinner plates was identified and eliminated by increasing plate thickness. Similarly, in our adipose-inspired metamaterials, reducing t produces early-onset, low-amplitude buckling that may be undesirable for load-bearing applications, while thicker shells (e.g., t_3) at aligned orientations ($\alpha_1 = 0^\circ$) yield a controlled instability plateau that can be leveraged for energy absorption or mechanical programmability.

To quantify differences among the analyzed geometries, four mechanical parameters were extracted from each stress-strain curve (Figure 3C): the initial elastic modulus E_{lin} , the buckling

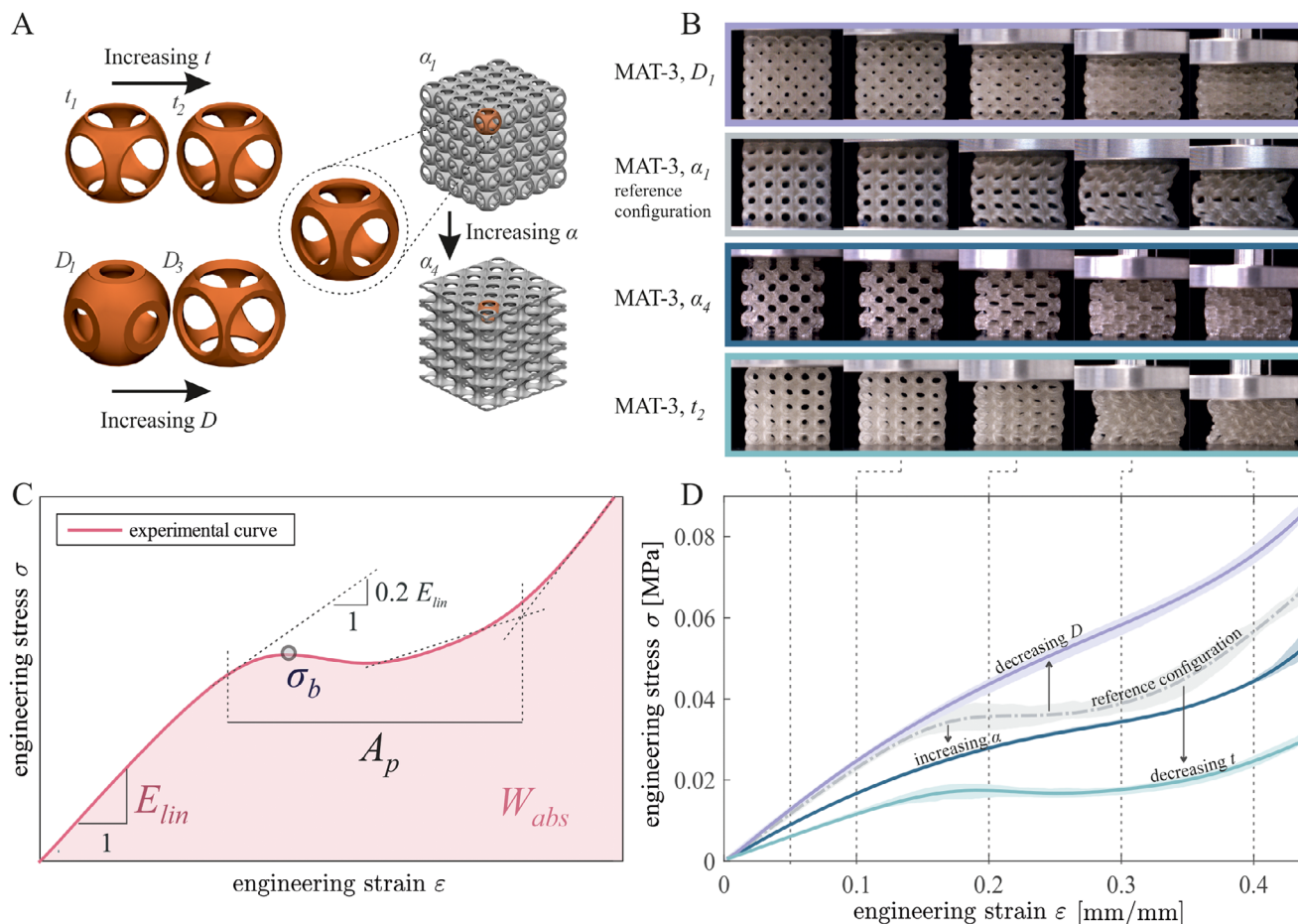


FIGURE 3 | Metamaterials deformation in compression and representative stress-strain curves. (A) Schematic illustration of the unit cell design strategy, showing how selected geometrical parameters are systematically varied to generate eight distinct metamaterial architectures. (B) Evolution of the compressive deformation at different strains (from 0.05 to 0.4), with reference to different geometrical parameters (same material). Depending on the unit cell properties and assembly, the resulting metamaterial exhibits either buckling or cell interlocking. (C) An example of stress-strain curve, with the identification of mechanical quantities that were extracted for comparisons among metamaterials. (D) Stress-strain curves with first and third quartile bounds, to show inter and intra-sample variability, with reference to the case studies reported in (B).

stress σ_b , the total absorbed energy W_{abs} and the progressive instability plateau amplitude A_p [5, 8].

The initial linear slope (E_{lin}) was used to define the effective elastic modulus, capturing the stiffness of the metamaterial in the small-strain regime dominated by shell bending. The onset of instability was identified through the buckling stress σ_b (or, in case of no maximum, the stress associated to a deviation of 20% from the initial stiffness), while A_p , was quantified to assess the deformation window governed by instability-driven mechanisms. Finally, the energy absorbed during the loading phase, W_{abs} , was calculated as the area under the stress-strain curve, providing an integrated measure of the capacity of each architecture to dissipate mechanical energy.

In general, these quantities appear comparable to those reported by Vafaefar et al., where the authors analyzed the compressive behavior of three distinct biomimetic lattice architectures (i.e., the periodic gyroid, the stochastic spinodoid, and the Voronoi-like dual-lattice) [5]. In this case, samples were realized with a single flexible elastomeric resin (Elastic Resin 50A, modelled as a Neo-Hookean hyperelastic material) through stereolithography,

a material that has similar stiffness, strain at break and strength to our MAT-3. Indeed, the global mechanical responses appear comparable, as well as the energy absorbed W_{abs} , between 0.01 MPa and 0.042 MPa for all the geometries with similar volume fractions as in this work. If we look at the efficiency (computed as Vafaefar et al., equal to W_{abs}/σ_b), we can observe on average higher values with respect to these authors, with a maximum value of 72% for MAT-1, t_1 configuration. Similar results for the Specific Energy Absorption (SEA, Tables 1–3) for metamaterials made by soft material (i.e., silicon) have also been reported by Bodaghi et al., where they demonstrated that bioinspired auxetic structures can reduce peak stresses in prosthetic interfaces by up to 80%, highlighting the role of geometry in enhancing biomechanical compatibility [66].

Notably, our experimental results reveal that energy absorption does not scale linearly with the stiffness of the base material. Even when the bulk modulus is reduced by a factor of 25 (from MAT-3 to MAT-1), the structures retain up to one-third of the SEA of their stiffest counterparts (Figure S7). This highlights the dominant role of geometry in governing energy dissipation mechanisms.

TABLE 1 | Mechanical characteristics of specimens fabricated with MAT-1 as a function of the geometric configuration. Median values with the interquartile range (25th–75th percentiles) are reported. The Specific Energy Absorption (SEA) has been computed as W_{abs}/ρ , (ρ is the material density, [Supporting Information](#)), and the efficiency was defined as W_{abs}/σ_b [5].

No.	Configurations	E_{lin} [MPa]	σ_b [MPa]	A_p [-]	W_{abs} [MPa]	SEA [J/kg]	Efficiency [%]
1	MAT-1, α_1	0.050 (0.045–0.050)	0.006 (0.006–0.008)	0.206 (0.190–0.207)	0.004 (0.003–0.004)	2.148	58.4%
2	MAT-1, α_2	0.036 (0.036–0.039)	0.006 (0.006–0.007)	0.245 (0.205–0.255)	0.003 (0.003–0.003)	1.610	45.1%
3	MAT-1, α_3	0.028 (0.028–0.031)	0.006 (0.005–0.006)	0.239 (0.232–0.267)	0.002 (0.002–0.003)	1.352	43.3%
4	MAT-1, α_4	0.019 (0.019–0.019)	0.004 (0.004–0.004)	0.237 (0.236–0.249)	0.002 (0.001–0.002)	0.938	41.0%
5	MAT-1, D_1	0.091 (0.073–0.099)	0.023 (0.020–0.024)	0.000 (0.000–0.000)	0.010 (0.008–0.011)	5.554	42.0%
6	MAT-1, D_3	0.028 (0.027–0.031)	0.003 (0.003–0.003)	0.243 (0.242–0.271)	0.002 (0.002–0.002)	0.913	49.9%
7	MAT-1, t_1	0.008 (0.007–0.010)	0.001 (0.001–0.001)	0.233 (0.230–0.260)	0.001 (0.001–0.001)	0.514	72.0%
8	MAT-1, t_2	0.025 (0.024–0.026)	0.003 (0.003–0.004)	0.260 (0.233–0.266)	0.002 (0.001–0.002)	0.918	52.1%

TABLE 2 | Mechanical characteristics of specimens fabricated with MAT-2 as a function of the geometric configuration. Median values with the interquartile range (25th–75th percentiles) are reported. SEA has been computed for the median value as W_{abs}/ρ , where ρ is the material density (reported in the [Supporting Information](#)), and the efficiency was defined as W_{abs}/σ_b [5].

No.	Configurations	E_{lin} [MPa]	σ_b [MPa]	A_p [-]	W_{abs} [MPa]	SEA [J/kg]	Efficiency [%]
9	MAT-2, α_1	0.142 (0.136–0.144)	0.025 (0.023–0.028)	0.209 (0.196–0.209)	0.010 (0.009–0.011)	7.570	40.3%
10	MAT-2, α_2	0.133 (0.130–0.135)	0.017 (0.014–0.018)	0.215 (0.207–0.234)	0.009 (0.008–0.009)	6.526	49.2%
11	MAT-2, α_3	0.105 (0.105–0.110)	0.018 (0.017–0.020)	0.256 (0.255–0.271)	0.008 (0.008–0.008)	6.014	43.0%
12	MAT-2, α_4	0.097 (0.094–0.099)	0.016 (0.015–0.016)	0.251 (0.250–0.258)	0.007 (0.007–0.007)	5.317	43.2%
13	MAT-2, D_1	0.210 (0.168–0.224)	0.065 (0.039–0.068)	0.000 (0.000–0.183)	0.023 (0.016–0.026)	17.363	34.6%
14	MAT-2, D_3	0.098 (0.087–0.098)	0.006 (0.005–0.008)	0.292 (0.184–0.293)	0.004 (0.003–0.005)	3.021	62.3%
15	MAT-2, t_1	0.019 (0.019–0.021)	0.002 (0.001–0.002)	0.252 (0.215–0.273)	0.001 (0.001–0.001)	0.879	65.6%
16	MAT-2, t_2	0.074 (0.069–0.077)	0.009 (0.008–0.011)	0.221 (0.220–0.229)	0.005 (0.004–0.005)	3.477	50.1%

2.3 | Influence of Geometrical Parameters on the Compressive Mechanical Response

The experimental results reveal a clear dependence of the mechanical response on the geometrical parameters of the unit cell (Figure 4). Variations in cell spatial orientation, spherical shell diameter, and shell thickness lead to significant changes in stiffness, the onset (or suppression) of local instability phenomena, and the densification behavior. The extracted mechanical quantities are reported in Tables 1–3 for the three material blends (median values and IQR).

2.3.1 | Effect of Cell Orientation

Across all material formulations (MAT-1–MAT-3), increasing the unit cell orientation angle drives a systematic transition from a buckling-dominated response to a largely monotonic compressive behavior (Figure 4A,D,G). Configurations with aligned cells ($\alpha = 0^\circ$) exhibit local instabilities which result in a plateau phase (A_p between 0.200–0.210 mm/mm, see Tables 1–3), whereas inclined architectures ($\alpha \geq 30^\circ$) progressively suppress buckling, leading to an almost monotonic stress–strain response governed

by inter-cell compaction. This transition is accompanied by a reduction in σ_b (66% for MAT-1, 64% for MAT-2, 89% for MAT-3) and in the initial stiffness (38% for MAT-1, 68% for MAT-2, 77% for MAT-3) with respect to the reference configuration, indicating that orientation affects both instability mechanisms and the metamaterial initial elastic response. In particular, it appears that the decrease in the elastic modulus E_{lin} is more pronounced in softer materials (MAT-1) rather than stiffer ones (MAT-3).

We may also state that by changing the orientation of the cells, the compressive component acting along the cell walls is reduced, thereby decreasing the effect of buckling.

Absorbed energy W_{abs} reduces with increasing α (50% for MAT-1, 70% for MAT-2, 80% for MAT-3), consistently with previous observations.

Overall, cell orientation emerges as an effective design parameter for modulating instability and post-buckling behavior, while also influencing the initial elastic response and maintaining the stresses within a limited range of variation (Figure 4A,D,G), as further confirmed by W_{abs} (Tables 1–3).

TABLE 3 | Mechanical characteristics of specimens fabricated with MAT-3 as a function of the geometric configuration. Median values with the interquartile range (25th–75th percentiles) are reported. SEA has been computed for the median value as W_{abs}/ρ , where ρ is the material density (reported in the [Supporting Information](#)), and the efficiency was defined as W_{abs}/σ_b [5].

No.	Configurations	E_{lin} [MPa]	σ_b [MPa]	A_p [-]	W_{abs} [MPa]	SEA [J/kg]	Efficiency [%]
17	MAT-3, α_1	0.229 (0.226–0.239)	0.037 (0.032–0.039)	0.21 (0.188–0.219)	0.015 (0.014–0.016)	12.831	41.0%
18	MAT-3, α_2	0.243 (0.220–0.247)	0.042 (0.039–0.044)	0.210 (0.186–0.212)	0.017 (0.015–0.018)	14.606	40.9%
19	MAT-3, α_3	0.196 (0.181–0.198)	0.040 (0.038–0.041)	0.243 (0.21–0.243)	0.015 (0.015–0.015)	12.734	37.3%
20	MAT-3, α_4	0.176 (0.168–0.178)	0.033 (0.031–0.033)	0.276 (0.263–0.287)	0.012 (0.012–0.012)	10.302	36.3%
21	MAT-3, D_1	0.264 (0.243–0.264)	0.055 (0.050–0.057)	0.281 (0.278–0.287)	0.020 (0.019–0.020)	16.818	35.7%
22	MAT-3, D_3	0.198 (0.190–0.221)	0.019 (0.016–0.021)	0.234 (0.232–0.252)	0.009 (0.008–0.010)	7.584	47.8%
23	MAT-3, t_1	0.034 (0.032–0.036)	0.003 (0.003–0.003)	0.256 (0.238–0.265)	0.002 (0.001–0.002)	1.308	52.4%
24	MAT-3, t_2	0.121 (0.119–0.121)	0.017 (0.016–0.019)	0.229 (0.219–0.270)	0.007 (0.007–0.007)	6.012	40.3%

2.3.2 | Effect of Unit Cell Diameter

Variations in spherical shell diameter exert a strong and systematic influence on the mechanical response of the metamaterials, primarily by governing the onset and development of instability (Figure 4B,E,H). Across all materials, decreasing the diameter increases both peak stress and stiffness, whereas larger diameters promote the development of an extended progressive instability plateau. This effect is most pronounced in MAT-1 and MAT-2, where the smallest diameter configuration D_1 completely suppresses buckling (Figure 4B,E), resulting in a monotonically increasing stress–strain response and substantially higher stresses at equivalent strains (e.g., σ_b was 3.8 and 2.6 times greater, respectively, with respect to the reference configurations identified by D_2). When local instabilities are present, A_p consistently increases with diameter (from zero to 0.243 for MAT-1, from zero to 0.292 for MAT-2), reflecting enhanced structural compliance and delayed densification, while stays almost constant (around 0.240) for MAT-3. Notably, E_{lin} increases when the diameter decreases, indicating that this geometric parameter enables effective tuning of instability and densification mechanisms, while also altering the initial stiffness, especially for the softest material (Tables 1–3). In this case, with respect to the reference case (MAT-1, α_1 , $E_{lin} = 0.05$ MPa), the parameter decreases to nearly half its reference value when the diameter is increased, while it increases to almost twice the reference value when the diameter is reduced. When moving from MAT-1 to MAT-3 this effect mitigates and, with respect to the reference case (0.229 MPa), both increasing and decreasing the diameter result in variations of comparable magnitude (approximately $\pm 15\%$), leading to values of 0.198 MPa and 0.264 MPa, respectively.

2.3.3 | Effect of Shell Thickness

As evident from the data in Tables 1–3, decreasing the thickness from t_3 to t_1 leads to a reduction in the initial stiffness (84–86%) and in σ_b (83% to almost 100% from MAT-1 to MAT-3), consequently affecting the absorbed energy W_{abs} (a decrease to approximately one tenth from the reference configuration). Across all material compositions, shell thickness emerges as the dominant geometric parameter governing the compressive

mechanical response (Figure 4C,F,I). Conversely, thinner shells consistently buckle at lower stress levels and exhibit a broader progressive instability plateau, reflecting increased structural compliance and delayed densification. This trend is particularly pronounced in MAT-2 and MAT-3, whereas in MAT-1 the effect, although present, is comparatively less marked. Notably, the interquartile ranges remain narrow across thickness variations, especially for MAT-2 (Figure 4F and Table 2), indicating limited sample-to-sample variability and good reproducibility of the mechanical response. From a structural mechanics perspective, this dominance is consistent with the cubic contribution of thickness to bending stiffness, which governs both the pre-buckling response and the critical instability load across all three material compositions tested — a relationship further confirmed quantitatively by the statistical analysis in Section 2.5. Moreover, if analyzing the variation of E_{lin} relative to the bulk modulus of the material, we can observe an almost linear dependence on the ratio t/l , where l is the unit cell length (see Figure S6). This relationship is also confirmed by Zhao et al., who analyzed a family of bio-inspired cubic elastic metamaterials, based on lipidic cubic phases from a numerical point of view, with similarities to our adopted configuration [41]. They also demonstrated the structures' ability to achieve complete elastic isotropy independently of the constituent material properties, even if the primitive architecture exhibits significant anisotropy.

2.4 | Computational Modeling

To examine the deformation behavior under compressive loading, we performed finite element method (FEM) simulations on the same structures that were tested experimentally.

As a first numerical assessment, a specimen-scale finite element model was developed to reproduce the experimentally tested metamaterial architecture and to establish a consistent framework for comparison between simulations and experiments. The simulations explicitly accounted for large deformations, contact and self-contact between septa, and frictional interactions arising from the elastomeric nature of the printed material. Given the buckling-dominated response observed experimentally, an initial linear buckling analysis was performed to identify the dominant

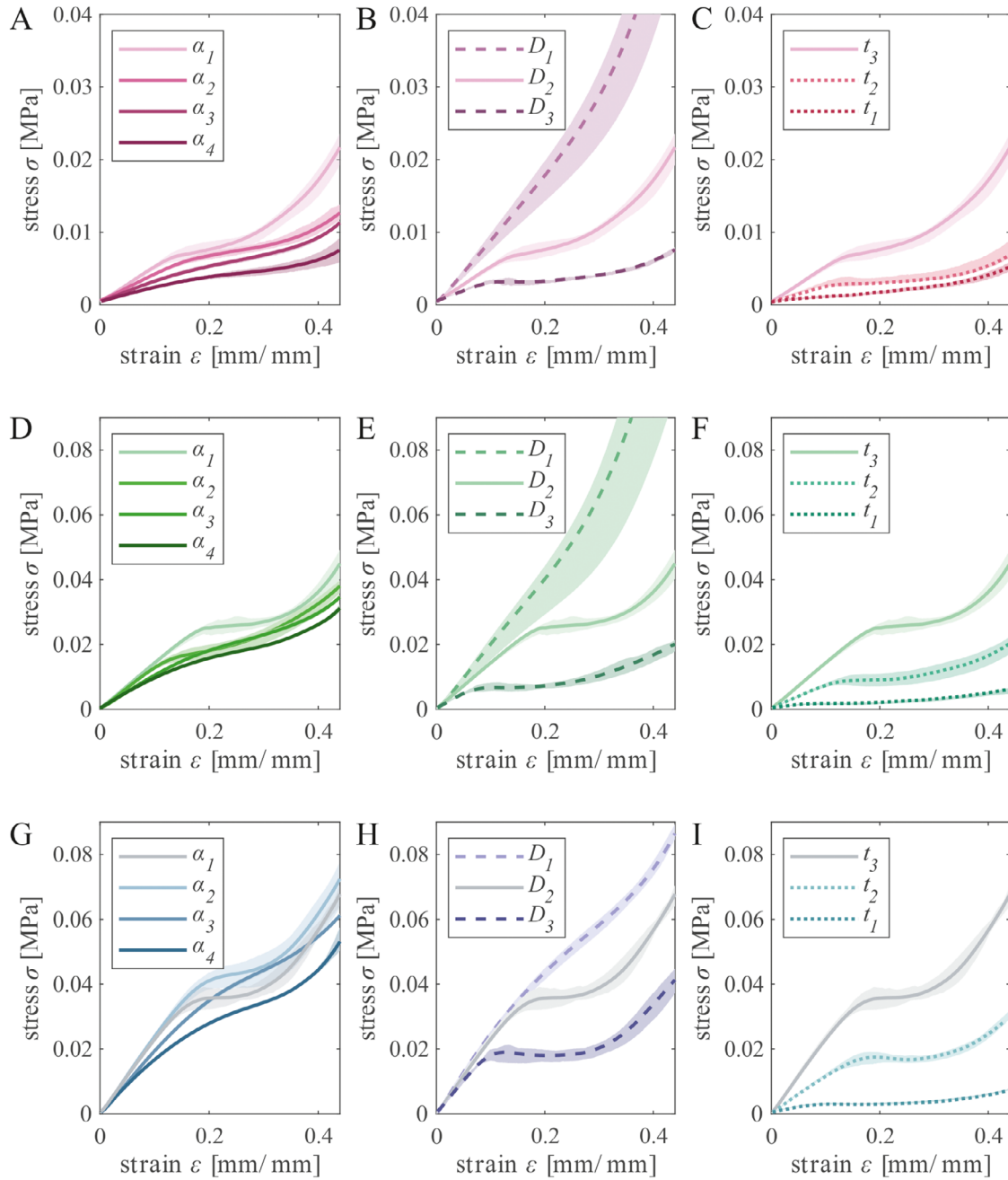


FIGURE 4 | Stress-strain curves comparisons for all the materials by varying α , D and t . Mean curves are reported for each configuration, with bounds representing the interquartile range (25th–75th percentiles). (A) to (C) stress-strain curves for MAT-1. Note that the y-axis has a different limit with respect to the other materials, due to its softer behavior. (D) to (F) stress-strain curves for MAT-2. (G) to (I) stress-strain curves for MAT-3.

instability mode, which was subsequently introduced as a geometric imperfection to trigger realistic post-buckling behavior. This approach enabled the numerical model to capture the onset and evolution of instability observed during compression. Post-buckling deformation was first investigated using both implicit and explicit solution strategies, allowing the identification of a quasi-static explicit formulation that provided results comparable to the more computationally demanding Riks method (Figure S10 in Supporting Information F).

A direct qualitative and quantitative comparison is reported in Figure 5. Figure 5A–D shows the consistency between the

resulting computational behavior and the experimental one. Again, local buckling occurred in those geometries characterized by low angles (α_i in Figure 5A) or smaller septa thickness (t_i in Figure 5D), whereas cell densification or interlocking dominated the mechanical response for greater angles (α_4 in Figure 5B) and smaller diameters (D_i in Figure 5C). In addition, FEM allowed the evaluation of local strains (reported as logarithmic strain, LE_{min}), a quantity that was not possible to measure experimentally.

Specimen-scale models reproduce the tested architectures and loading conditions, enabling direct comparison with measured stress–strain responses (Figure 5E–L). The simulations capture

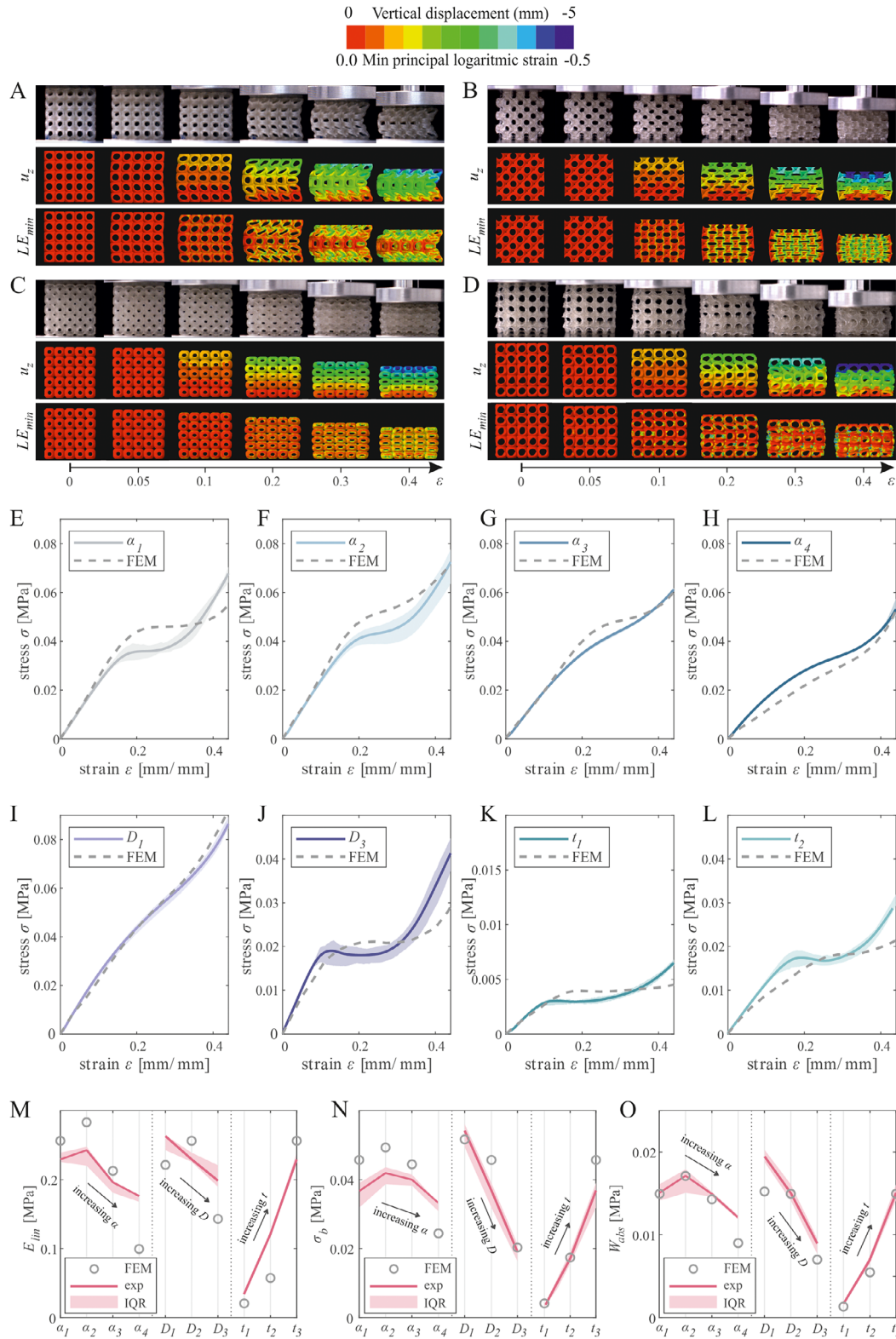


FIGURE 5 | Finite Element model results and comparison with experimental observations. (A) Displacement (u_z) and logarithmic strain (LE , minimum principal), as engineering strain increases from 0% to 40% for the metamaterial reference configuration (MAT-3, α_1) reported as computational results with corresponding experimental frame. Same variables obtained for MAT-3 (B) α_2 , (C) D_1 and (D) t_1 . Experimental stress-strain curve (median curve and IQR) comparisons between experiments and computational outputs referring to E) the reference case (MAT-3 α_1), (F) MAT-3 α_2 , (G) MAT-3 α_3 , (H) MAT-3 α_4 , (I) MAT-3 D_1 , (J) MAT-3 D_3 , (K) MAT-3 t_1 , (L) MAT-3 t_2 . Effective mechanical quantities extracted from experimental tests (referring to the median curve and IQR) and computational results, with reference to the eight geometrical configurations, such as M) effective elastic modulus E_{lin} , (N) buckling stress σ_b , and (O) absorbed energy W_{abs} in compression.

the transition from buckling-dominated to monotonic compression observed experimentally, confirming how variations in shell thickness, cell diameter, and orientation alter septal bending, buckling activation, and load redistribution. In particular, FE results confirm that increasing t stabilizes the structure by delaying instability, while a larger D promotes earlier buckling and an extended instability plateau due to reduced relative density. Inclined cell assemblies are shown to favor progressive compaction through inter-cell contact rather than lateral bulging, consistent with the suppression of macroscopic instability observed in experiments. Mechanical quantities such as E_{lin} , σ_b , and W_{abs} are also extracted from the stress-strain curves obtained computationally, and results are compared with experiments (Figure 5M–O). Numerical results (grey dots in the graphs) show a good qualitative and quantitative agreement with the experimental values, revealing the same trend as in the analyzed case. Differences from the experimental results can be attributed to deviations from the ideal geometry of the FE models with respect to the 3D-printed structures. This is a well-known phenomenon, extensively discussed in Walker et al. [45], where they show evidence that these discrepancies arise from process-related effects which alter the architecture thickness, shape, pore size, and location. These geometric deviations, which also depend on the technology (e.g., SLA printing, or PolyJet), lead to a mechanical response that differs from that predicted by the ideal model: stiffness and strength may generally be reduced, densification may arise earlier, and the collapse sequence can appear more irregular. The authors suggested adopting a μ CT-based model, which captures the real geometry, and could reproduce the experimental behavior more accurately than the CAD-FEM model [45]. Our computational models explicitly accounted for macroscopic observed discrepancies, including the suppression of sub-resolution cavities (with dimensions smaller than one-tenth of the reference unit cell diameter), the incorporation of defects identified by optical microscopy, and the calibration of constitutive parameters used to describe the printed material blends (Figures S8 and S9, Table S3). This modeling strategy enabled an accurate reproduction of the metamaterial response, particularly in the linear and buckling regimes, where the model clearly identifies the presence or absence of the instability path. Notably, the associated strain ranges correspond to the deformation levels most relevant for prospective adipose tissue scaffolds, where mechanical stability and controlled compliance are required under low-to-moderate loading conditions. Nevertheless, it should be noted that the mechanical characterization of soft specimens fabricated via advanced 3D printing technologies inherently introduces limitations in the predictive accuracy of FEM. In particular, the densification regime at higher strain levels was occasionally underestimated by the simulations, as evident in Figure 5E and Figure 5J–L. This discrepancy underscores the critical importance of incorporating realistic geometrical features and accounting for alterations introduced during fabrication, including both systematic effects inherent to the printing process and operator-dependent factors such as post-processing and cleaning procedures [45]. This aspect has been investigated through micro-CT acquisitions, followed by a geometric deviation analysis (Figure S12 and Table S6).

Even if results show deviations of 0.1 ± 0.05 mm on average, higher values can be found concentrated at peripheral unit cells, especially for the thinnest configuration. Nevertheless, these

localized inaccuracies are not expected to significantly alter the overall force–displacement response, since they represent a minor fraction of the total cross-section, and the compressive response is predominantly governed by the geometrically more homogeneous inner region.

Acknowledging the geometric discrepancies inherent to the use of idealized CAD models in place of as-printed geometries, FEM nonetheless represents an efficient tool for expanding the design space, evaluating deformation mechanisms that are not directly accessible experimentally (including buckling pathways, local stress and strain distributions), and finally increasing the number of investigated configurations while reducing experimental costs. At the same time, the reliance on simplifying assumptions—such as idealized boundary conditions and constitutive descriptions—inevitably affects predictive accuracy, motivating the integration of complementary parametric and data-driven models to support the metamaterial design and performance prediction. To this end, a multivariate regression framework is introduced in the following section, extending predictive capability across the full design space and quantifying the relative contribution of each geometric and material descriptor to the macroscopic mechanical response.

2.5 | Multivariate Regression Analysis

To quantitatively assess the relative influence of geometric and material parameters on the mechanical response (namely E_{lin} , σ_b , W_{abs} and A_p), a multivariate regression framework was applied to the experimental dataset. Statistical indicators, including p -values, and confidence bounds, enabled direct ranking of parameter sensitivity and supported the mechanistic interpretations derived from experimental and finite element analyses.

Statistical analysis confirms and quantifies the hierarchy observed experimentally: shell thickness and base material stiffness emerge as the dominant predictors across all mechanical outputs ($p < 10^{-6}$), as reported in Table 4. For the initial elastic modulus (E_{lin}), shell thickness t ($p = 1.51 \times 10^{-7}$) and base material stiffness E_s ($p = 1.52 \times 10^{-8}$) are highly significant in affecting the linear regime of the metamaterial. Indeed, they are the dominant positive predictors, showing that increased septal thickness and stiffer constituent materials substantially enhance linear stiffness. On the contrary, the unit cell diameter ($p = 0.025$) and unit cell orientation angle ($p = 0.034$) have weaker negative effects, reflecting the slight reduction in stiffness associated with larger cells and more inclined architectures. This indicates that early load-bearing properties are primarily influenced by the load-carrying capacity of the septa and the intrinsic material properties, whereas overall cell geometry and orientation play a secondary role. Figure 6 shows the performance of the multivariate regression in terms of metamaterial property prediction with respect to the experimentally obtained values. In particular, Figure 6A directly compares the predicted results of E_{lin} (vertical axis) with the expected ones (horizontal axis). The quality of the model is expressed by the $R^2_{adj} = 0.875$, which highlights the good performance of the adopted method. Model robustness is evaluated through Monte Carlo resampling, yielding consistently high coefficients of determination across iterations and narrow

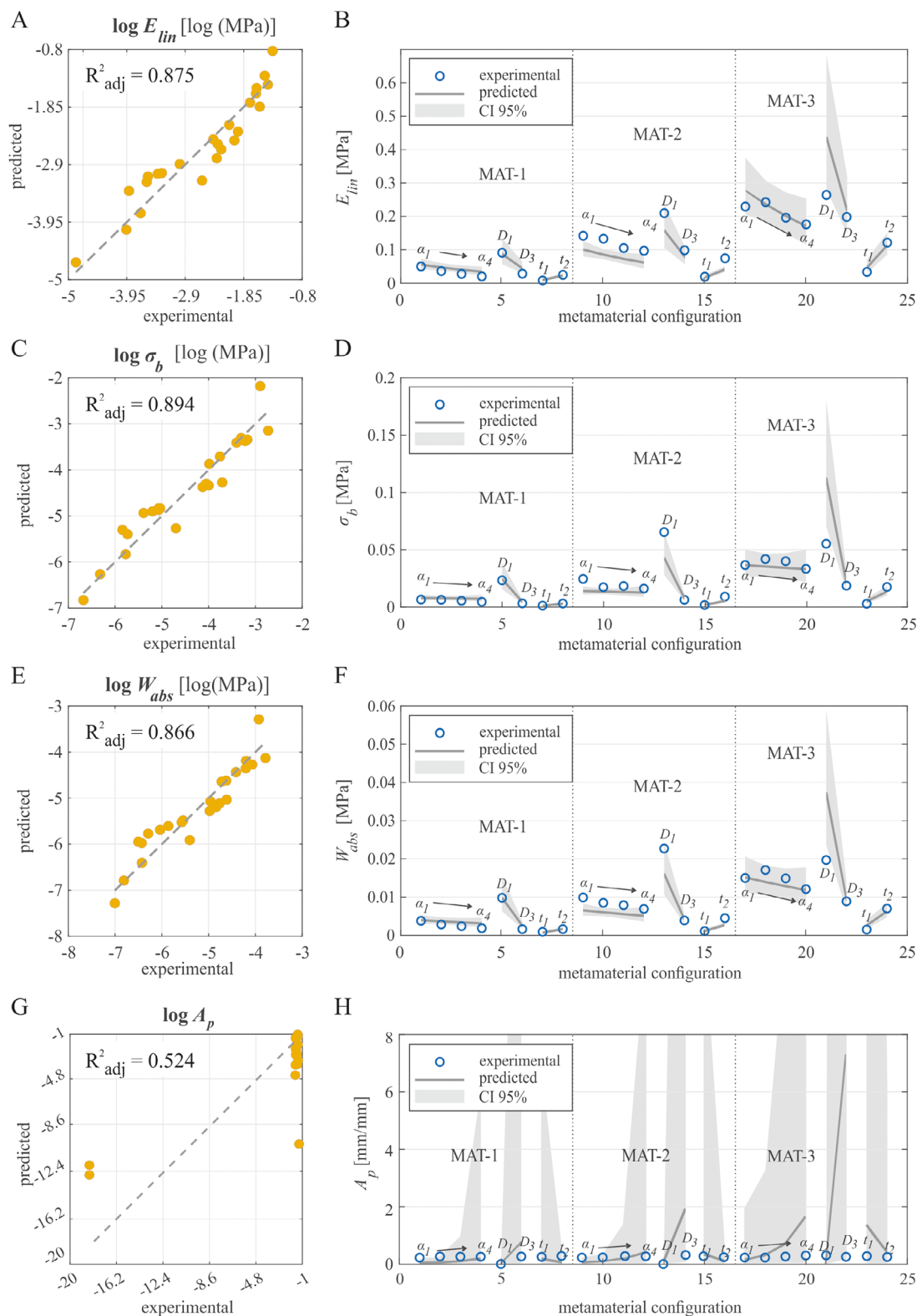


FIGURE 6 | Experimental–predicted comparison and statistical validation of the multivariate regression model. (A) Experimental vs. predicted values (log–log scale) of the initial elastic modulus (E_{lin}). (B) Model-predicted E_{lin} as a function of the geometric configuration (sample numbers reported in Tables 1–3), including Monte Carlo–derived confidence intervals (CI) at 95%; experimental median values are reported as discrete markers. (C) Experimental vs. predicted values (log–log scale) of the buckling stress (σ_b). (D) Model-predicted σ_b across the different geometric configurations (same sample numbers as before) with associated CI and experimental median values. (E) Experimental vs. predicted values (log–log scale) of the absorbed energy during loading (W_{abs}). (F) Model-predicted W_{abs} across the investigated configurations with CI and experimental median values. (G) Experimental vs. predicted values (log–log scale) of the progressive instability plateau amplitude during loading (A_p). (H) Model-predicted A_p across the investigated configurations with CI and experimental median values.

TABLE 4 | Results of the multivariate linear regression performed on the log-transformed mechanical responses. For each mechanical variable and each predictor (normalized), the estimated regression coefficient (β_i), standard error (SE), and p -value are reported. Coefficient significance indicates the effect of the corresponding predictor on the relative variation of the mechanical response.

Mechanical quantity	Predictor	Estimate (β_i)	SE	p -value
E_{lin}	—	−2.586	0.071	5.06E-19
	$\bar{D}$	−0.180	0.074	0.025
	$\bar{t}$	0.637	0.079	1.51E-07
	$\bar{E}_s$	0.680	0.073	1.52E-08
	$\bar{\alpha}$	−0.181	0.079	0.034
σ_b	—	−4.468	0.075	4.55E-23
	$\bar{D}$	−0.449	0.078	1.48E-05
	$\bar{t}$	0.708	0.083	6.67E-08
	$\bar{E}_s$	0.644	0.077	7.90E-08
	$\bar{\alpha}$	−0.037	0.084	0.662
W_{abs}	—	−5.250	0.073	1.33E-24
	$\bar{D}$	−0.360	0.076	1.42E-04
	$\bar{t}$	0.625	0.081	2.95E-07
	$\bar{E}_s$	0.563	0.075	4.01E-07
	$\bar{\alpha}$	−0.091	0.081	0.276
A_p	—	−2.845	0.676	4.73E-04
	$\bar{D}$	3.286	0.701	1.60E-04
	$\bar{t}$	−0.864	0.750	0.264
	$\bar{E}_s$	0.958	0.690	0.181
	$\bar{\alpha}$	0.972	0.752	0.212

confidence intervals for the most influential predictors (Table S4). Moreover, Leave-One-Out Cross-Validation (LOOCV) was also performed to provide an estimate of the predictive accuracy of the adopted model, given the moderate dataset. In this framework, each observation was iteratively excluded from the dataset, the model was re-fitted on the remaining data, and the excluded point was predicted. The resulting R^2_{CV} values, together with R^2_{adj} , are reported in Table S5. The value of R^2_{CV} close to R^2_{adj} indicates limited overfitting and good generalization capability. Specific comparisons between the experimental results and the model prediction are shown in Figure 6B. In this graph, sample numbers refer to the 24 different combinations tested, where 1 to 8 states for MAT-1, 9 to 16 for MAT-2, 17 to 24 for MAT-3 (see numbers from Tables 1–3). The values obtained through the multivariate regression are in very good agreement with those extracted from the experimental curve (blue dots represent the median results on three samples each, three loading curves along the two symmetric directions), with the majority lying within the associated confidence intervals and following the same trend.

Moreover, this graph clearly denotes the same relative behavior among different materials, where peaks and valleys are quantitatively repeated from the softest to the stiffer material.

Buckling stress (σ_b) exhibits a similar trend (Figure 6D) with $R^2_{adj} = 0.894$ (Figure 6C) and a close R^2_{CV} (Table S5), where the dominant variation in stress can be attributed to diameter

and thickness of the shell, as well as the material stiffness. This is confirmed by the significance associated with the predictors (Table 4), since thickness ($p < 7 \times 10^{-8}$) and material stiffness ($p < 8 \times 10^{-8}$) strongly increase these stresses, whereas diameter ($p < 1.5 \times 10^{-5}$) has a negative contribution and reduces them. Orientation angle was not significant ($p = 0.662$), indicating that the reached stresses are less sensitive to cell tilt. However, α remains one of those parameters that can tune the deformation process from instability modes to cells interlocking. Energy absorption (W_{abs}) follows the same hierarchy: t ($p = 2.95 \times 10^{-7}$) and E_s ($p = 4.01 \times 10^{-7}$) positively contribute in increasing the quantity of energy the metamaterial can store during the loading phase, while D ($p = 1.42 \times 10^{-4}$) reduces it; again, α appears to not affect the energy absorption ($p = 0.276$).

Finally, the multivariate regression analysis for the plateau amplitude A_p , in contrast to the other mechanical outputs, exhibits reduced predictive capability, as shown by the coefficient of determination $R^2_{adj} = 0.524$ (Figure 6G), with R^2_{CV} significantly different (0.136, Table S5). This substantial gap between the two metrics also indicates overfitting issues, confirming the non-suitability of this model to describe and predict the evolution of A_p , which also reflexes a limitation of the modest number of data points adopted in this study. Among the considered predictors, only the cell diameter (D) shows a statistically significant contribution ($p < 0.05$, Table 4), whereas shell thickness (t), solid

elastic modulus (E_s), and orientation angle (α) are not statistically significant.

The relatively poor model performance suggests that the plateau amplitude is weakly correlated with the selected geometrical and material descriptors and may be influenced by additional factors not captured within the present parameterization, such as local instabilities, geometric imperfections, or microstructural heterogeneity. Overall, despite the limited interpretation observed for A_p , for the other three quantities, the model provides a quantitative framework to guide the design of soft tissue-inspired metamaterials, as it robustly captures the primary mechanical descriptors governing stiffness, instability onset, and densification, which define their functional behavior.

Moreover, the power of the geometry-driven parametric model was confirmed via Monte Carlo–derived confidence intervals, as well as tested with LOOCV, to address the lack of independent validation and the relatively small dataset ($n = 24$). These insights highlight that both structural design and material selection can be strategically tuned to control not only linear stiffness but also post-buckling and energy absorption characteristics. From a practical standpoint, this confirmed that septal thickness and base material stiffness serve as the primary levers to enhance load-bearing and stress-mitigation capability, while orientation angle and cell diameter can be exploited to modulate instability behavior without significantly affecting the linear regime. In conclusion, even if the experimental campaign was structured using a controlled one-factor-at-a-time strategy to isolate primary geometric effects, the adopted multivariate regression enables the simultaneous quantification of the contributions of all investigated descriptors. Nevertheless, higher-order nonlinear interactions between parameters are not explicitly modeled and may represent an important direction for future work.

3 | Conclusion

The present study introduces a geometry-driven framework for the design of soft metamaterials capable of targeting the nonlinear and strain-dependent mechanical response ranges of biological tissues through systematic geometric tuning. In contrast to conventional scaffold design strategies, which often rely on empirical tuning or limited parametric exploration, this work establishes a quantitative and geometry-driven relationship between unit cell geometry and macroscopic mechanical response. This represents a significant advancement toward rational and programmable design of tissue-mimicking architectures.

Previous studies have demonstrated the potential of architected materials to tailor mechanical properties through geometric design. For instance, Ma et al. showed that TPMS-based scaffolds can achieve enhanced stiffness, strength, and energy absorption through remeshing strategies that introduce controlled anisotropy [67]. While their work highlights the importance of geometric refinement, it primarily focuses on load-bearing bone-mimicking structures operating in the MPa range. In contrast, the present study targets the kPa regime relevant to soft tissues, extending the concept of geometry-driven design to highly compliant materials and capturing complex deformation mechanisms such as buckling and post-buckling compaction.

Complementary approaches have addressed transport-related limitations in porous scaffolds. Tan et al. proposed membrane-based architectures to improve permeability and mitigate clogging, achieving extremely high porosity (about 97%) and enhanced mass transport [68]. However, these designs prioritize fluid dynamics over mechanical tunability. The current work, instead, focuses on mechanical programmability while maintaining structural coherence, demonstrating that a wide range of stiffness values can be achieved within a single geometric framework without resorting to multi-material systems or complex multi-domain architectures.

Moreover, the mechanical response of 3D-printed adipose-inspired soft metamaterials — spanning initial stiffness, instability onset, plateau behavior, and energy absorption — can be effectively programmed through systematic modulation of unit cell geometry and base material properties. Among all geometric descriptors, shell thickness offers the widest tunability range — from initial stiffness to energy absorption — making it the primary design lever for targeting specific soft-tissue mechanical environments, while cell diameter controlled the extent of the progressive instability plateau and orientation angle enabled switching between instability-driven and compaction-dominated deformation modes. Finite element simulations provided mechanical insight into local deformation pathways, accurately capturing buckling modes, strain concentrations, and densification evolution, and micro-CT imaging quantified the variations of the printed metamaterials with respect to the ideal ones, providing additional information for interpreting the computational results. Geometric deviations were found to concentrate predominantly at peripheral unit cells, where boundary effects associated with the additive manufacturing process are most pronounced. Finally, the multivariate regression framework — tested through Monte Carlo bootstrap resampling and LOOCV — delivered interpretable and validated predictions of three out to four key mechanical quantities ($R^2_{\text{adj}} > 0.86$) from a moderate dataset of 24 configurations. Together, these three complementary tools establish a coherent and practical framework for geometry-driven metamaterial design that explicitly accounts for manufacturing-induced variability.

Overall, the investigated metamaterial architectures span a broad mechanical spectrum, achieved through the combined modulation of unit cell geometry and base material properties (elastic modulus referring to the linear regime ranking from units to hundreds of kPa, Figure 7). This wide design frame enables the exploration of stresses and stiffness regimes extending well beyond a single target tissue, effectively covering the mechanical ranges associated with multiple soft biological tissues, spanning from foot adipose tissue (final elastic modulus between 10–75 kPa) [52], breast adipose and glandular tissue (0.5–50 kPa) [69], but could be further extended to other soft tissues as prostate (10–20 kPa) [70] or liver (66–386 kPa) [71]. Importantly, within this spectrum, the physiological stress levels characteristic of these tissues are fully encompassed, demonstrating that adipose-inspired cellular architectures — tunable through only four descriptors — can serve as versatile platforms for regenerative scaffolds, tissue-mimicking phantoms, and shock-absorbing layers in implantable devices. Notably, our results demonstrate that energy absorption is not only governed by the stiffness of the base material, as also revealed by the regression model. Despite a strong reduction

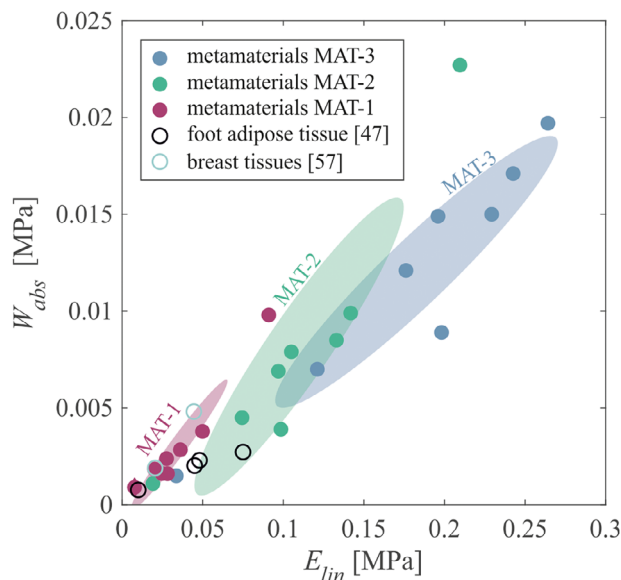


FIGURE 7 | Mechanical design space of the investigated metamaterial configurations in terms of initial elastic modulus (E_{lin}) and absorbed energy (W_{abs}), compared with experimentally measured values for human foot adipose tissue (black dots) [52] and breast tissue (light blue empty dots) [69]. The overlap between metamaterial clusters and tissue data points indicates that geometry–material tuning within the proposed framework can access the mechanical ranges relevant to soft tissue scaffold and implantable device applications, providing a quantitative mechanical basis for future biocompatible implementations. The ellipses are computed from the samples bivariate covariance matrix and enclose the central 50% of the data, corresponding to a χ^2 confidence level with 2 degrees of freedom at probability $p = 0.50$.

in the bulk modulus of the analyzed structures, they retain up to one-third of the SEA of their stiffest counterparts. This finding underscores the dominant role of geometry in controlling energy dissipation and is particularly relevant for soft tissue engineering, where mechanical compliance must be preserved to match native tissue properties. The ability to maintain significant energy absorption capacity in highly compliant structures enables the design of scaffolds that are both mechanically compatible and functionally protective, thus highlighting the potential for the design of future mechanically efficient, highly compliant biomaterials.

Despite the advances, some assumptions and limitations should be acknowledged. First of all, in addition to uniaxial tension/compression characterization of the bulk materials, additional tests could be performed for a better description of the adopted materials. Moreover, the focus on compressive loading conditions for the metamaterials may not fully capture the complex multiaxial stress states experienced in physiological environments. Additional mechanical tests, such as shear tests, should be explored in an early future. Another point refers to the adopted materials: the photopolymer blends employed in this study — while offering exceptional controllability and reproducibility for systematic mechanical characterization — are not biocompatible in their current form and are not intended for direct implantation. Their use is justified as a mechanistic step: establishing the geometry–mechanics relationships in a well-controlled material

system is a necessary prerequisite before translating the design framework to biocompatible substrates. Thus, the in vivo validation and biological assessment remain essential steps towards translational applications. In addition, the proposed geometry-driven framework was developed through a one-parameter-at-a-time variation strategy around a reference configuration. While this approach enabled a systematic isolation of the effect of each geometric descriptor on the mechanical response, it does not fully account for possible nonlinear coupling effects and higher-order interactions among geometrical parameters. Future studies based on larger datasets and multidimensional design-space exploration strategies will therefore be necessary to improve the predictive generalizability of the framework and to capture more complex architected metamaterial behaviors. Finally, whereas the proposed framework spans a wide range of stiffness values, further investigation is required to assess its applicability to dynamic loading scenarios and fatigue behavior.

Thus, several directions remain open for future investigations, to overcome current limitations. Extending the experimental characterization, moving from idealized loading conditions to cyclic, multiaxial, and dynamic loading regimes will be essential to fully capture the viscoelastic and fatigue behavior relevant for in vivo environments. Incorporating μ CT-based geometries into the FEM framework will further close the gap between idealized models and real printed structures, particularly in the densification regime. Furthermore, a quantitative morphometric comparison between the unit cell geometry and image-based reconstruction of the adipose tissue microstructure would strengthen the biological grounding of the design framework and is identified as a priority direction for future investigation, as well as translating the proposed design framework to biocompatible and bioresorbable material systems — such as silicon-based elastomers (including Ecoflex, already employed in additive-manufactured soft robotic components) [72], hydrogels, or biodegradable polyurethanes — represents the natural next step toward functional scaffold implementation. The integration of the validated statistical model with inverse design algorithms will enable direct targeting of tissue-specific mechanical signatures, opening new opportunities for patient-specific and application-driven metamaterial design in regenerative medicine and beyond.

4 | Experimental Section

4.1 | Design of Adipose-Inspired Metamaterial Architectures

Inspired by the mesoscale morphological organization of adipose tissue and building on previous literature [41, 46, 55], adipose-tissue-inspired metamaterial geometries were designed through parametric variation of three morphological descriptors of the spherical unit cell: diameter (D), shell thickness (t), and orientation angle (α). The spherical shell topology was selected as the minimal geometric unit that preserves the dominant structural motif of adipose tissue — the closed lobular architecture bounded by thin septa — while remaining amenable to systematic parametric variation and high-fidelity PolyJet fabrication. A first reference configuration was created, namely $D = 3$ mm; $t = 0.3$ mm; $\alpha = 0^\circ$. These parameters were then systematically combined to generate seven additional distinct configurations

($D = 2.6 \text{ mm} - 3 \text{ mm} - 3.2 \text{ mm}$; $t = 0.1 \text{ mm} - 0.2 \text{ mm} - 0.3 \text{ mm}$; $\alpha = 0^\circ - 15^\circ - 30^\circ - 45^\circ$), enabling controlled tuning of deformation modes associated with buckling, septal bending, and post-buckling compaction. Each architecture was constructed by periodic repetition of the unit cell, yielding $5 \times 5 \times 5$ ($l = 2.5 \text{ mm}$, $L = 5l = 12.5 \text{ mm}$) arrays for both numerical modelling and mechanical testing to ensure homogeneous mesoscale behavior (Figure S1). All geometries were exported as STL files for subsequent fabrication.

4.2 | Design and Preparation of the Soft Material Blends

All specimens were printed using the J850 Digital Anatomy printer (Stratasys, Eden Prairie, MN, USA). Materials preparation was performed using the Digital Anatomy Creator tool, available on the GrabCAD Print Pro software, with the creation of specific digital materials. We employed four materials from the PolyJet and Digital Anatomy families (Stratasys) in specimen fabrication: Agilus30Clear (elastomeric photopolymer designed to simulate flexible, rubber-like materials, Shore A 30–40), TissueMatrix (the softest commercially available material, exhibiting a gel-like, viscous behavior with Shore 00), BoneMatrix (photopolymer composed of a mixture of polymers and ceramic particles), and GelMatrix (soft material with Shore A 00–30).

Specimens were produced using various combinations of these four materials to achieve different mechanical properties and stiffness levels. The following material blends were employed, namely MAT-1 (50% Agilus30, 50% TissueMatrix), MAT-2 (70% Agilus30, 15% GelMatrix, 15% BoneMatrix), MAT-3 (85% Agilus30, 15% BoneMatrix). Details of the compositions are reported in the [Supporting Information](#).

4.3 | Mechanical Characterization of Material Blends

For the mechanical characterization of the designed materials, cubic and dog-bone samples were fabricated using PolyJet 3D printing technology (deposition of photopolymer micro-droplets onto a build platform with simultaneous UV curing). The samples were then mechanically tested using an MTS Insight Electromechanical-10 kN Standard Length system (MTS Systems Corporation, Eden Prairie, MN, USA) at Tækniðsetur ehf IceTec (Reykjavík, Iceland), performing both tensile and compression tests, as standard procedures to characterize the materials response [5, 22, 43, 45, 73]. The specimen geometries were designed according to ASTM D695 (cylindrical samples: 12.7 mm diameter, 25.4 mm height) and ASTM D638 (dog-bone samples: 115 mm overall length, 25 mm gauge length, 6 mm width, and 3 mm thickness) standards. Compression tests were performed with strain values between 0 and 0.6, while tensile tests were performed with increasing deformation until failure. Three (MAT-1) and five (MAT-2,3) specimens were tested in both tension and compression. In the strain range of 0.02–0.06, the interpolant elastic moduli resulted in: $E_{sl} = 0.2 \text{ MPa}$ (MAT-1), $E_{s2} = 2.1 \text{ MPa}$ (MAT-2), $E_{s3} = 5.3 \text{ MPa}$ (MAT-3) (Figures S2–S5 and Table S1).

4.4 | Constitutive Modelling

To account for non-linear behavior at large strains within the numerical simulations, MAT-3 was modelled using a two-term Ogden hyperelastic law, with quasi-incompressible behavior (initial Poisson's ratio of 0.45):

$$W(\mathbf{C}) = \sum_{p=1}^2 \frac{2\mu_p}{\alpha_p^2} \left(\lambda_1^{\alpha_p} + \lambda_2^{\alpha_p} + \lambda_3^{\alpha_p} - 3 \right) + \sum_{p=1}^2 \frac{1}{D_p} (J - 1)^{2p}$$

Unlike the other hyperelastic models, the Ogden formulation is able to include strain-stiffening effects up to high stretch ratios (>20% strain), which are characteristic of the PolyJet materials used in this study. The first material calibration yielded to an initial set of model parameters by inverse analysis of both compression and tensile tests (Figure S8). Then, as a common procedure when moving from material to structural level, the set of parameters was recalibrated in order to replicate the experimental compression response of the reference configuration (α_1 , D_2 , t_3) specifically targeting the linear elastic regime of that metamaterial in compression, thus taking into account local inhomogeneities and discrepancies from the real geometries (Figure S9) [5, 74, 75]. The final set of constitutive parameters was: $\mu_1 = 0.226 \text{ MPa}$, $\mu_2 = 0.362 \text{ MPa}$, $\alpha_1 = -3.205$, $\alpha_2 = -3.209$, $D_1 = 0.137 \text{ MPa}^{-1}$ and $D_2 = 6.13\text{E-}05 \text{ MPa}^{-1}$. All the other FE analyses of the other configurations were obtained through the adoption of these constitutive coefficients.

4.5 | Manufacturing of Metamaterial Constructs via PolyJet 3D Printing

Specimens were fabricated using PolyJet 3D printing technology, with all the material blends previously tested (details in Figure S1). All samples were printed with standard Digital Anatomy support material, removed using manufacturer-recommended waterjet and chemical-assisted post-processing. Each configuration was printed in triplicate, resulting in a total of 72 specimens. Quality-control procedures included inspection of shell integrity, dimensional measurements of D and t ($\pm 0.05 \text{ mm}$ tolerance) through optical microscopy (Olympus SZ61-TR stereomicroscope equipped with an EP50 digital camera; 30 $\times$ magnification), and verification of complete support removal to prevent post-curing stiffening artifacts.

4.6 | Micro-Computed Tomography and Geometric Deviation Analysis

Eight printed metamaterial specimens (one per configuration) were scanned via X-ray micro-computed tomography (micro-CT) using an RX-Solutions system (RX-Solutions, Chavanod, France), with no additional beam filtration. Projections were acquired in cone-beam geometry (source-to-object distance: 101.6 mm; source-to-detector distance: 543.1 mm) over a total of 1,504 angular positions, with an integration time of 250 ms per frame on a $1,944 \times 2,456$ pixel flat-panel detector. 3D volumes were reconstructed via filtered backprojection, yielding volumetric datasets of $1,897 \times 2,189 \times 1,897$ voxels at an isotropic voxel size of $23.2 \mu\text{m}$. Specimen volumes were reconstructed from the

micro-CT scans using Materialise Mimics 24.0 (Materialise NV, Leuven, Belgium) and subsequently imported into Geomagic Design X (3D Systems, Rock Hill, SC, USA) for surface-based rigid registration to the corresponding nominal CAD geometries and geometric deviations computation. For each configuration, the median, first quartile (Q1), third quartile (Q3) and Root Mean Square (RMS) of the deviation distribution were extracted as summary statistics and are reported in the [Supporting Information](#) together with color-coded deviation maps (Figure S12 and Table S6).

4.7 | Mechanical Testing of Metamaterial Scaffolds

Mechanical characterization was performed on the Mach-1 v500css, Biomomentum Inc., Canada, 250 N load cell. Uniaxial compression was selected as the primary loading mode consistent with the intended application environment and the compression-dominated deformation mechanism of the shell-based unit cell architecture. Tests were carried out by imposing strain up to 0.45, with a strain rate $\dot{\epsilon} = 0.005 \text{ s}^{-1}$. Each sample was tested with three loading-unloading cycles, with a 1-min recovery period between cycles, both along x and y axes (z -axis identified as the 3D printing direction) to assess in-plane isotropy of the printed structures. Since no significant differences in the maximum force were observed among the three loading cycles, the force (F)–displacement (ΔL) pairs from all cycles were exported. For each metamaterial configuration, loading curves from three samples, three cycles, and two testing directions (x and y) were pooled, yielding 18 curves per configuration; the associated median curve was then computed and used for subsequent mechanical parameter extraction.

4.8 | Data Preprocessing and Mechanical Parameter Extraction

Raw outputs were imported into MATLAB R2024b. Data cleaning removed duplicated points, negative or non-physical positions, and all unloading segments. Engineering stress and strain were computed as $\sigma = F/A$, $\epsilon = \Delta L/L$, where A is the apparent cross-sectional area of the metamaterial, and L is the initial height. The following metrics were extracted: (i) initial elastic modulus (E_{lin})—via linear regression over the first elastic region; (ii) buckling stress (σ_b)—defined as the local maximum of the curve, or, in case of no maximum, the stress associated to a deviation (20%) from the initial stiffness; (iii) energy absorption during the loading phase (W_{abs})—quantified as the area under the stress–strain curve for positive strain value densification stress, and (iv) the amplitude of the progressive instability plateau (A_p)—identified as the strain interval between the strain at which the mechanical response transitions from linear to nonlinear behavior (i.e., where the instantaneous stiffness drops below 20% E_{lin}) and the strain associated to the intersection point of two linear fits (bilinear regression) which describe the low-stiffness region (fitted from the local minimum or inflection point onward), and the subsequent stiffening regime. Both lines were obtained by minimizing the residuals between the piecewise linear model and the corresponding portions of the experimental curve.

Statistical descriptors (median and IQR) and comparative plots were generated for all materials and geometries.

4.9 | Finite Element Modeling

Finite element (FE) simulations were executed in Abaqus 2023 (Dassault Systèmes, France). Solid models were formed by full 3D continuum representation using linear tetrahedral elements (average dimension between 0.05–0.1 mm, to guarantee a minimum number of three elements on the shell thickness. Mesh density was refined in regions of high curvature to ensure numerical stability in post-buckling regimes. A minimum of 4000 elements per unit cell was reached, to provide an adequate number able to correctly mimic the phenomenon [45, 76].

Contact between internal septa was modeled with finite friction ($\mu = 0.5$). The bottom platen was fully constrained; the upper platen was restricted from rotation and lateral displacement and assigned a prescribed vertical displacement of 5.6 mm, to simulate the experimental test.

A linear buckling analysis (Abaqus/Standard) provided the first eigenmode which was then scaled (assuming a coefficient between 0.1–0.3) and introduced as an imperfection to trigger realistic buckling. Then, the compression phase was simulated using the explicit solver, enabling efficient convergence during large deformations and septal contact events. Previous validation was carried out also through an implicit procedure (Riks method, Figure S10). The computational analyses were performed on an HPC server equipped with 8 Intel Xeon Platinum 8260, 2 TB RAM and SSD HD. The number of variables in the model (approximately 3,000,000) suggested the use of at least 20 cores for both implicit and explicit simulations.

4.10 | Multivariate Regression Framework and Monte Carlo Robustness Assessment

A multivariate regression framework was employed to quantify the relationship between the geometrical and material descriptors of the cellular structures and their effective mechanical response. Given the strictly positive nature of the mechanical outputs and the observed heteroscedasticity in the raw data, the response variables were log-transformed before regression analysis, thereby improving linearity and the statistical validity of the regression assumptions. Accordingly, the models were formulated as linear relationships in log-space, such that the regression coefficients describe multiplicative effects on the mechanical responses in the original physical domain, such as $\log y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \epsilon$. The vector of output variables y states for $[E_{lin}; \sigma_b; W_{abs}; A_p]$, while $\bar{X} = [x_1; x_2; x_3; x_4] = [\bar{D}; \bar{r}; \bar{E}_s; \bar{\alpha}]$ states for the predictors, that have been standardized prior to regression analysis to ensure comparable scaling across inputs:

$$\bar{X} = \frac{X - \mu_X}{\sigma_X}$$

Thus, the regression model for each dependent variable is expressed as follows:

$$\begin{cases} \log E_{lin} = \beta_{0,E} + \beta_{1,E}\bar{D} + \beta_{2,E}\bar{S} + \beta_{3,E}\bar{E}_s + \beta_{4,E}\bar{\theta} + \epsilon_E \\ \log \sigma_b = \beta_{0,b} + \beta_{1,b}\bar{D} + \beta_{2,b}\bar{S} + \beta_{3,b}\bar{E}_s + \beta_{4,b}\bar{\theta} + \epsilon_b \\ \log W_{abs} = \beta_{0,W} + \beta_{1,W}\bar{D} + \beta_{2,W}\bar{S} + \beta_{3,W}\bar{E}_s + \beta_{4,W}\bar{\theta} + \epsilon_W \\ \log A_p = \beta_{0,A} + \beta_{1,A}\bar{D} + \beta_{2,A}\bar{S} + \beta_{3,A}\bar{E}_s + \beta_{4,A}\bar{\theta} + \epsilon_A \end{cases}$$

Regression was implemented in MATLAB [77] using the *fitlm* function. Coefficient significance was assessed via standard error, t-statistics, and p-values (threshold $p < 0.05$).

The robustness of the confidence interval of the predictors coefficients was evaluated using a Monte Carlo resampling approach. The dataset was randomly partitioned 2000 times into training (80%) and test (20%) subsets. At each iteration, regression coefficients and goodness-of-fit metrics were computed, enabling the construction of empirical confidence intervals for the model parameters. Model performance was primarily evaluated in log-space using the coefficient of determination, adjusted to account for the number of predictors ($p = 4$) relative to the limited sample size ($n = 24$) $R^2_{adj} = 1 - (1 - R^2)(n-1)/(n-p-1)$, ensuring consistency with the statistical assumptions of the fitted models. Predicted responses were subsequently back-transformed to physical units for visualization and interpretation, allowing direct comparison with experimental measurements. Statistical significance of individual predictors was assessed via two-sided t-tests on the regression coefficients, with p-values computed in the transformed space and confidence intervals for each coefficient were obtained from the 2.5th – 97.5th percentiles of their respective distributions.

4.11 | Leave-One-Out Cross-Validation

LOOCV was performed to provide an estimate of the predictive accuracy of the adopted model, given the modest dataset ($n = 24$). In this framework, each observation was iteratively excluded from the dataset, the model was re-fitted on the remaining data, and the excluded point was predicted [78]. This procedure yielded a set of out-of-sample predictions for all configurations. Predictive accuracy was quantified using the cross-validated coefficient of determination $R^2_{CV} = 1 - \frac{\sum (y_i - \hat{y}_i^{CV})^2}{\sum (y_i - \bar{y})^2}$, where $\hat{y}_i^{CV}$ denotes the prediction obtained when the i-th observation is excluded from model calibration. Details of this procedure are reported in Figure S11 and Table S5.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. L. J. Gibson, “Biomechanics of Cellular Solids,” *Journal of Biomechanics* 38 (2005): 377–399, <https://doi.org/10.1016/j.jbiomech.2004.09.027>.
2. B. Liu, Y. Liao, Y. Yang, C. Yang, Y. Tian, and H. Yin, “Design and Analysis of Reconfigurable and Deployable Thin-walled Architectural Equipment Inspired by Mirror-Miura Origami Patterns,” *Engineering Structures* 286 (2023): 116059, <https://doi.org/10.1016/j.engstruct.2023.116059>.
3. M. Kazim, A. Pal, and D. Goswami, “Mechanical Metamaterials for Bioengineering: in Vitro, Wearable, and Implantable Applications,” *Advanced Engineering Materials* 27 (2025): 2401806.
4. Y. Wu, J. Yang, A. van Teijlingen, et al., “Disinfector-Assisted Low Temperature Reduced Graphene Oxide-Protein Surgical Dressing for the Postoperative Photothermal Treatment of Melanoma,” *Advanced Functional Materials* 32 (2022): 2205802.
5. M. Vafaefar, K. M. Moerman, and T. J. Vaughan, “Experimental and Computational Analysis of Energy Absorption Characteristics of Three Biomimetic Lattice Structures under Compression,” *Journal of the Mechanical Behavior of Biomedical Materials* 151 (2024): 106328, <https://doi.org/10.1016/j.jmbbm.2023.106328>.
6. N. Karathanasopoulos and O. Al-Ketan, “Towards Biomimetic, Lattice-based, Tendon and Ligament Metamaterial Designs,” *Journal of the Mechanical Behavior of Biomedical Materials* 134 (2022): 105412, <https://doi.org/10.1016/j.jmbbm.2022.105412>.
7. P. Zhang, X. Chen, P. Yu, et al., “Shell-lattice Metamaterials with Intrinsic Contact Stabilization for Exceptional Mechanical Performance and Nonlinear Stability,” *Journal of the Mechanics and Physics of Solids* 208 (2026): 106467, <https://doi.org/10.1016/j.jmps.2025.106467>.
8. E. L. Carniel, C. G. Fontanella, M. V. Mascolini, S. Pettenuzzo, I. Toniolo, and A. Berardo, “An in Silico Approach to the Mechanical Design of Meta-materials for Adipose Tissue Engineering,” *Heliyon* 11 (2025): 43430.
9. L. Dong, J. Wang, and D. Wang, “Modeling and Design of Three-dimensional Voxel Printed Lattice Metamaterials,” *Additive Manufacturing* 69 (2023): 103532.
10. Y. M. Luo, C. He, Z. Tao, et al., “A Surface-wave Seismic Metamaterial Filled with Auxetic Foam,” *International Journal of Mechanical Sciences* 262 (2024): 108715, <https://doi.org/10.1016/j.ijmecsci.2023.108715>.
11. M. Kang, H. G. Choi, K. Park, and S. Pyo, “Additively Manufactured 3D Auxetic Metamaterials for Structurally Guided Capacitive and Resistive Tactile Sensing,” *Advanced Functional Materials* 09704 (2025): 1.
12. C. T. Wanniarachchi, A. Arjunan, A. Baroutaji, and M. Singh, “3D printing Customised Stiffness-matched Meta-biomaterial with near-zero Auxeticity for Load-bearing Tissue Repair,” *Bioprinting* 33 (2023): e00292, <https://doi.org/10.1016/j.bprint.2023.e00292>.
13. D. Jiang, H. Thissen, T. C. Hughes, et al., “Advances in Additive Manufacturing of Auxetic Structures for Biomedical Applications,” *Materials Today Communication* 40 (2024): 110045.
14. Y. Bai, Z. Wang, and Y. Shi, “Design and Mechanical Properties Analysis of a Cellular Waterbomb Origami Structure,” *Theoretical and Applied Mechanics Letters* 14 (2024): 100509, <https://doi.org/10.1016/j.taml.2024.100509>.
15. J. P. McInerney, D. Misseroni, D. Z. Rocklin, G. H. Paulino, and X. Mao, “Coarse-grained Fundamental Forms for Characterizing Isometries

- of Trapezoid-based Origami Metamaterials,” *Nature Communications* 16 (2025): 1823, <https://doi.org/10.1038/s41467-025-57089-x>.
16. D. Misseroni, P. P. Pratapa, K. Liu, et al., “Origami Engineering,” *Nature Reviews Methods Primers* 4 (2024): 40, <https://doi.org/10.1038/s43586-024-00313-7>.
17. Y. Sun, W. Ye, Y. Chen, W. Fan, J. Feng, and P. Sareh, “Geometric Design Classification of Kirigami-inspired Metastructures and Metamaterials,” *Structures* 33 (2021): 3633.
18. K. Bertoldi, V. Vitelli, J. Christensen, and M. van Hecke, “Flexible Mechanical Metamaterials,” *Nature Reviews Materials* 2 (2017): 17066, <https://doi.org/10.1038/natrevmats.2017.66>.
19. H. Haag, P. D. Dalton, and V. Bloemen, “The Synergy of Biomimetic Design Strategies for Tissue Constructs,” *Advanced Functional Materials* 32 (2022): 1, <https://doi.org/10.1002/adfm.202201414>.
20. C. Wang, Z. Vangelatos, C. P. Grigoropoulos, and Z. Ma, “Micro-engineered Architected Metamaterials for Cell and Tissue Engineering,” *Materials Today Advances* 13 (2022): 100206, <https://doi.org/10.1016/j.mtadv.2022.100206>.
21. L.-Q. Wang, J. Shen, R. Lincoln, et al., “Re-programmable Mechanical Metamaterials for Tunable Energy Dissipation through Pre-stressing: Concept, Mechanics and Data-driven Design,” *Thin-Walled Structures* 216 (2025): 113601, <https://doi.org/10.1016/j.tws.2025.113601>.
22. S. Ravanbod, K. Rahmani, C. Branfoot, et al., “Biomimetic Composite Meta-stabilisers with Programmable Multi-directional Quasi-zero Stiffness and Vibration Isolation,” *Materials Today Advances* 28 (2025): 100661, <https://doi.org/10.1016/j.mtadv.2025.100661>.
23. M. Mohammadi, A. Z. Kouzani, M. Bodaghi, and A. Zolfagharian, “3D-printed Programmable Bistable Mechanisms for Customized Wearable Devices in Tremor Attenuation,” *Journal of the Mechanical Behavior of Biomedical Materials* 168 (2025): 107006, <https://doi.org/10.1016/j.jmbbm.2025.107006>.
24. Y. Berkane, H. Oubari, L. van Dieren, et al., “Tissue Engineering Strategies for Breast Reconstruction: a Literature Review of Current Advances and Future Directions,” *Annals of Translational Medicine* 12 (2024): 15, <https://doi.org/10.21037/atm-23-1724>.
25. R. Pugliese and S. Graziosi, “Biomimetic Scaffolds Using Triply Periodic Minimal Surface-based Porous Structures for Biomedical Applications,” *SLAS Technology* 28 (2023): 165.
26. H. Zhang, X. Guo, J. Wu, D. Fang, and Y. Zhang, “Soft Mechanical Metamaterials with Unusual Swelling Behavior and Tunable Stress-strain Curves,” *Science Advances* 4 (2018): 8535.
27. A. Sensini, F. Giacomini, O. Stamati, et al., “Revealing the Auxetic Behavior of Biomimetic Multimaterial and Region-Specific Nanofibrous Fascicle-Inspired Scaffolds via Synchrotron Multiscale Digital Volume Correlation: Innovative Building Blocks for the Enthesis Regeneration,” *Advanced Functional Materials* 36 (2025): 11660.
28. N. Munding, M. Fladung, Y. Chen, et al., “Bio-Metamaterials for Mechano-Regulation of Mesenchymal Stem Cells,” *Advanced Functional Materials* 34 (2024): 2301133.
29. E. Dogan, A. Bhusal, B. Cecen, and A. K. Miri, “3D Printing Metamaterials towards Tissue Engineering,” *Applied Materials Today* 20 (2020): 100752, <https://doi.org/10.1016/j.apmt.2020.100752>.
30. H. Wang, Y. Lyu, S. Bosiakov, H. Zhu, and Y. Ren, “A Review on the Mechanical Metamaterials and Their Applications in the Field of Biomedical Engineering,” *Frontiers in Materials* 10 (2023): 1.
31. F. Karamaouna, V. Kati, N. Volakakis, et al., “Ground Cover Management with Mixtures of Flowering Plants to Enhance Insect Pollinators and Natural Enemies of Pests in Olive Groves,” *Agriculture, Ecosystems & Environment* 274 (2019): 76–89, <https://doi.org/10.1016/j.agee.2019.01.004>.
32. M. Wan, K. Yu, and H. Sun, “4D printed Programmable Auxetic Metamaterials with Shape Memory Effects,” *Composite Structures* 279 (2022): 114791, <https://doi.org/10.1016/j.compstruct.2021.114791>.
33. J. Zhou, J. Chang, X. Song, et al., “Bio-inspired Design and Unusual Mechanical Properties of 3D Horseshoe-shaped Soft Network Metamaterials,” *Composites Part B: Engineering* 275 (2024): 111284, <https://doi.org/10.1016/j.compositesb.2024.111284>.
34. L. Zhang, B. Wang, B. Song, et al., “3D Printed Biomimetic Metamaterials with Graded Porosity and Tapering Topology for Improved Cell Seeding and Bone Regeneration,” *Bioact Mater* 25 (2023): 677.
35. R. Wu, Y. Li, M. Shen, et al., “Bone Tissue Regeneration: The Role of Finely Tuned Pore Architecture of Bioactive Scaffolds Before Clinical Translation,” *Bioact Mater* 6 (2021): 1242.
36. L. Tytgat, L. Van Damme, M. P. del Ortega Arevalo, et al., “Extrusion-based 3D Printing of Photo-crosslinkable Gelatin and κ -carrageenan Hydrogel Blends for Adipose Tissue Regeneration,” *International Journal of Biological Macromolecules* 140 (2019): 929–938, <https://doi.org/10.1016/j.jbiomac.2019.08.124>.
37. A. C. Weems, M. C. Arno, W. Yu, R. T. R. Huckstepp, and A. P. Dove, “4D polycarbonates via Stereolithography as Scaffolds for Soft Tissue Repair,” *Nature Communications* 12 (2021): 3771, <https://doi.org/10.1038/s41467-021-23956-6>.
38. A. A. Valencia-Lazcano, R. Román-Doval, E. De La Cruz-Burelo, E. J. Millán-Casarrubias, and A. Rodríguez-Ortega, “Enhancing Surface Properties of Breast Implants by Using Electrospun Silk Fibroin,” *Journal of Biomedical Materials Research—Part B Applied Biomaterials* 106 (2018): 1655.
39. M. Zhou, J. Hou, G. Zhang, et al., “Tuning the Mechanics of 3D-printed Scaffolds by Crystal Lattice-like Structural Design for Breast Tissue Engineering,” *Biofabrication* 12 (2020): 015023.
40. Y. Luo, X. Wei, Y. Wan, X. Lin, Z. Wang, and P. Huang, “3D printing of Hydrogel Scaffolds for Future Application in Photothermal Therapy of Breast Cancer and Tissue Repair,” *Acta Biomaterialia* 92 (2019): 37–47, <https://doi.org/10.1016/j.actbio.2019.05.039>.
41. Z. Zhao, Y. Liu, and P. Wang, “Computational Design of Bio-inspired Mechanical Metamaterials Based on Lipidic Cubic Phases,” *Jom Journal of the Minerals Metals and Materials Society* 75 (2023): 2126–2136, <https://doi.org/10.1007/s11837-023-05866-8>.
42. D. Coato, G. Dolino, A. Berardo, et al., “Synthetic 3D Printed Tibial Plateau with Gradient Material Properties for Biomechanical Accuracy,” *Frontiers in Bioengineering and Biotechnology* 13 (2025): 1707380.
43. K. Rahmani, K. Park, and M. Bodaghi, “Polyamide12-Meta-Composites with Excellent Mechanical Performance, Shape-Memory, Flame Retardancy and 3D/4D Printability,” *Macromolecular Materials and Engineering* 311 (2026): 70212.
44. S. Amin Yavari, S. M. Ahmadi, R. Wauthle, et al., “Relationship between Unit Cell Type and Porosity and the Fatigue Behavior of Selective Laser Melted Meta-biomaterials,” *Journal of the Mechanical Behavior of Biomedical Materials* 43 (2015): 91–100, <https://doi.org/10.1016/j.jmbbm.2014.12.015>.
45. O. Walker, T. Roland, D. Favier, A. Egele, M. Heymann, and C. Stubenrauch, “Mechanical Properties of Architected Polymer Lattice Materials: A Comparative Study of Additive Manufacturing and CAD Using FEM and μ -CT,” *Advanced Functional Materials* 12520 (2025): e12520.
46. R. Li, W. W. S. Ma, T. Niu, H. Liu, J. Ding, and X. Song, “Stiffness and Strength Enhancement of Hierarchical TPMS-based Shell Lattices via Inter-level Conformal Design,” *Addit Manuf* 105 (2025): 104802.
47. W. Hao, Z. Du, X. Hou, et al., “Intelligent Design of Mechanical Metamaterials: a GCNN-based Structural Genome Database Approach,” *National Science Review* 12 (2025): nwaf053.
48. J. Liu, B. Peng, W. Xu, Y. Wei, and P. Wen, “Highly Efficient Discovery of 3D Mechanical Metamaterials via Monte Carlo Tree Search,” *Advancement of Science* 12 (2025): 13771.
49. M. A. Bagheri, C. E. Aubin, M. L. Nault, and I. Villemure, “Mechanical Characterization of an Origami-inspired Super Deformable Metamaterial

- with High Tunability for Tissue Engineering,” *Materials & Design* 251 (2025): 113701, <https://doi.org/10.1016/j.matdes.2025.113701>.
50. K. H. Schneider, G. Oberoi, E. Unger, et al., “Medical 3D Printing with Polyjet Technology: Effect of Material Type and Printing Orientation on Printability, Surface Structure and Cytotoxicity,” *3D Printing in Medicine* 9 (2023): 27, <https://doi.org/10.1186/s41205-023-00190-y>.
51. M. J. Suta, A. Csík, S. Bodzás, et al., “A Comparative Evaluation of Vat-photopolymerization and PolyJet 3D Printers Using Multiple Measurement Methods,” *Journal of Dentistry* 166 (2026): 106352.
52. S. Pettenuzzo, E. Belluzzi, A. Pozzuoli, et al., “Mechanical Behaviour of Plantar Adipose Tissue: from Experimental Tests to Constitutive Analysis,” *Bioeng* 11 (2023): 42.
53. S. Pettenuzzo, A. Berardo, E. Belluzzi, et al., “Mechanical Insights into Fat Pads: a Comparative Study of Infrapatellar and Suprapatellar Fat Pads in Osteoarthritis,” *Connective Tissue Research* 66 (2025): 272–283, <https://doi.org/10.1080/03008207.2025.2502591>.
54. V. Macchi, E. E. E. Picardi, C. G. Fontanella, et al., “The Characteristics of the Lobular Arrangement Indicate the Dynamic Role Played by the Infrapatellar Fat Pad in Knee Kinematics,” *Journal of Anatomy* 235 (2019): 80–87, <https://doi.org/10.1111/joa.12995>.
55. K. M. Gaskin, G. E. Peoples, and D. E. McGhee, “The Fibro-Adipose Structure of the Female Breast: a Dissection Study,” *Clinical Anatomy* 33 (2020): 146–155, <https://doi.org/10.1002/ca.23505>.
56. K. Comley and N. A. Fleck, “The Toughness of Adipose Tissue: Measurements and Physical Basis,” *Journal of Biomechanics* 43 (2010): 1823–1826, <https://doi.org/10.1016/j.jbiomech.2010.02.029>.
57. H. Yang, B. E. Abali, D. Timofeev, and W. H. Müller, “Determination of Metamaterial Parameters by Means of a Homogenization Approach Based on Asymptotic Analysis,” *Continuum Mechanics and Thermodynamics* 32 (2020): 1251–1270, <https://doi.org/10.1007/s00161-019-00837-4>.
58. X. Wang, L. Zhang, B. Song, et al., “Tunable Mechanical Performance of Additively Manufactured Plate Lattice Metamaterials with Half-open-cell Topology,” *Composite Structures* 300 (2022): 116172, <https://doi.org/10.1016/j.compstruct.2022.116172>.
59. D. W. Abueidda, M. Bakir, R. K. Abu Al-Rub, J. S. Bergström, N. A. Sobh, and I. Jasiuk, “Mechanical Properties of 3D Printed Polymeric Cellular Materials with Triply Periodic Minimal Surface Architectures,” *Materials & Design* 122 (2017): 255–267, <https://doi.org/10.1016/j.matdes.2017.03.018>.
60. S. R. G. Bates, I. R. Farrow, and R. S. Trask, “Compressive Behaviour of 3D Printed Thermoplastic Polyurethane Honeycombs with Graded Densities,” *Materials & Design* 162 (2019): 130–142, <https://doi.org/10.1016/j.matdes.2018.11.019>.
61. X. Kuang, J. Wu, K. Chen, et al., “Grayscale Digital Light Processing 3D Printing for Highly Functionally Graded Materials,” *Science Advances* 5 (2019): 5790.
62. L. Valdevit, S. W. Godfrey, T. A. Schaedler, A. J. Jacobsen, and W. B. Carter, “Compressive Strength of Hollow Microlattices: Experimental Characterization, Modeling, and Optimal Design,” *Journal of Materials Research* 28 (2013): 2461–2473, <https://doi.org/10.1557/jmr.2013.160>.
63. M. Mohammadi, A. Z. Kouzani, M. Bodaghi, and A. Zolfagharian, “Inverse Design of Adaptive Flexible Structures Using Physical-enhanced Neural Network,” *Virtual Phys Prototyp* 20 (2025): 2530732.
64. A. Zolfagharian, M. Bodaghi, R. Hamzehei, L. Parr, M. Fard, and B. F. Rolfe, “3D-Printed Programmable Mechanical Metamaterials for Vibration Isolation and Buckling,” *Sustain* 14 (2022): 6831.
65. A. Zolfagharian, P. Picken, M. Bodaghi, M. Fard, and B. Rolfe, “Additive Manufacturing of Composite Foam Metamaterial Springs for Vibration Isolation,” *Advanced Engineering Materials* 25 (2023): 2300356.
66. M. Bodaghi, S. Jolaiy, K. Rahmani, S. Li, F. Gao, and A. Zolfagharian, “Bioinspired Auxetic Metamaterial Liners and Sockets for Transtibial Prostheses: Energy Absorption and Stress Redistribution,” *Journal of the Mechanical Behavior of Biomedical Materials* 175 (2026): 107305, <https://doi.org/10.1016/j.jmbbm.2025.107305>.
67. S. Ma, K. Song, J. Lan, and L. Ma, “Biological and Mechanical Property Analysis for Designed Heterogeneous Porous Scaffolds Based on the Refined TPMS,” *Journal of the Mechanical Behavior of Biomedical Materials* 107 (2020): 103727, <https://doi.org/10.1016/j.jmbbm.2020.103727>.
68. S. Tan, J. Gu, S. C. Han, D.-W. Lee, and K. Kang, “Design and Fabrication of a Non-clogging Scaffold Composed of Semi-permeable Membrane,” *Materials & Design* 142 (2018): 229–239, <https://doi.org/10.1016/j.matdes.2018.01.033>.
69. N. G. Ramião, P. S. Martins, R. Rynkevicius, A. A. Fernandes, M. Barroso, and D. C. Santos, “Biomechanical Properties of Breast Tissue, a state-of-the-art Review,” *Biomechanics and Modeling in Mechanobiology* 15 (2016): 1307–1323, <https://doi.org/10.1007/s10237-016-0763-8>.
70. A. Berardo, M. V. Mascolini, C. G. Fontanella, et al., “Mechanical Characterization of the Male Lower Urinary Tract: Comparison among Soft Tissues from the Same Human Case Study,” *Applied Sciences* 14 (2024): 1357.
71. G. Singh and A. Chanda, “Mechanical Properties of Whole-body Soft human Tissues: a Review,” *Biomedical Materials* 16 (2021): 062004, <https://doi.org/10.1088/1748-605X/ac2b7a>.
72. A. Zolfagharian, S. Gharai, A. Z. Kouzani, et al., “Silicon-based Soft Parallel Robots 4D Printing and Multiphysics Analysis,” *Smart Materials and Structures* 31 (2022): 115030.
73. G. Dolino, D. Coato, R. Forni, G. Boretti, F. K. Ciliberti, and P. Gargiulo, “Designing a Synthetic 3D-Printed Knee Cartilage: FEA Model, Micro-Structure and Mechanical Characteristics,” *Applied Science* 14 (2024): 331.
74. C. G. Fontanella, E. L. Carniel, A. Frigo, et al., “Investigation of Biomechanical Response of Hoffa’s Fat Pad and Comparative Characterization,” *Journal of the Mechanical Behavior of Biomedical Materials* 67 (2017): 1–9, <https://doi.org/10.1016/j.jmbbm.2016.11.024>.
75. A. N. Natali, C. G. Fontanella, and E. L. Carniel, “A Numerical Model for Investigating the Mechanics of Calcaneal Fat Pad Region,” *Journal of the Mechanical Behavior of Biomedical Materials* 5 (2012): 216–223, <https://doi.org/10.1016/j.jmbbm.2011.08.025>.
76. H. S. Abdulhadi, A. Fadeel, T. A. Alwattar, and A. Mian, “Developing Scaling Laws to Predict Compressive Mechanical Properties and Determine Geometrical Parameters of Modified BCC Lattice Structures,” *Engineering Reports* 5 (2023): 1, <https://doi.org/10.1002/eng.2.12566>.
77. The MathWorks, Inc., *MATLAB Version R2025b* (The MathWorks Inc, 2025).
78. Y. Pang, Y. Wang, X. Lai, S. Zhang, P. Liang, and X. Song, “Enhanced Kriging Leave-one-out Cross-validation in Improving Model Estimation and Optimization,” *Computer Methods in Applied Mechanics and Engineering* 414 (2023): 116194, <https://doi.org/10.1016/j.cma.2023.116194>.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File: adfm77047-sup-0001-SuppMat.pdf.