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3D-printed mechanical metamaterials for bone repair: Advanced manufacturing, mechanical design, and biological functionalisation

Running title: 3D-printed mechanical metamaterials for bone repair

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Abstract

Repair of large segmental bone defects requires implanted scaffolds not only to provide sufficient structural stability but also to accommodate the pronounced spatial heterogeneity, anisotropy, and load-dependent nonlinear behaviour of native bone while establishing a local mechanical microenvironment conducive to tissue regeneration. Mechanical metamaterials offer a distinct design paradigm for precise mechanical regulation by tailoring microstructural topology and deformation mechanisms, including rotation, buckling, and configurational transitions, thereby enabling spatially differentiated responses, auxetic behaviour, nonlinear stiffness, multistability, and reconfigurability. This review first examines the mechanical adaptation requirements of metamaterial scaffolds for bone repair in the context of the heterogeneous, anisotropic, and nonlinear mechanical characteristics of native bone, and systematically summarises the capabilities and key constraints of advanced three-dimensional printing technologies, including powder bed fusion, vat photopolymerisation, and material extrusion, for fabricating complex metamaterial architectures. Building on this foundation, we critically review the structural mechanisms and bone-regenerative effects of spatially heterogeneous and anisotropic, auxetic, nonlinear, multistable, and reconfigurable metamaterials, and further discuss strategies for integrating functional ions, growth factors, and therapeutic agents with metamaterial architectures. We also examine the time-dependent mechanical evolution of degradable metamaterials, highlighting the coupling among material degradation, architectural evolution, and progressive bone regeneration after implantation. By elucidating the intrinsic relationships among structural design, mechanical response, and biological function, this review aims to provide a conceptual framework for the development of next-generation bone repair implants that combine precise mechanical adaptation with regenerative regulation.

Keywords: 3D printing; Mechanical metamaterials; Bone tissue engineering; Mechanical microenvironment; Bone regeneration

1. Introduction

Bone defects commonly arise from high-energy trauma, severe infection, tumour resection, and congenital deformities, and their treatment requires not only defect filling but also restoration of long-term mechanical stability and functional integrity¹. Critical-sized bone defects generally exceed the intrinsic regenerative capacity of bone tissue and therefore cannot achieve complete osseous healing through spontaneous repair. Their reconstruction becomes particularly challenging in the presence of compromised vascularisation, infection, and complex mechanical conditions, and surgical intervention is often required^{2,3}. At present, bone grafting remains an important clinical strategy for the reconstruction of large bone defects. However, its broader application continues to be constrained by limited graft availability, donor-site morbidity, risks of infection and immune-related complications, and variability in regenerative outcomes across patients and defect conditions⁴. Against this background, bone tissue engineering scaffolds have emerged as an important alternative to conventional bone grafting^{1,2}. As platforms that provide early mechanical support while facilitating tissue regeneration within the defect, these scaffolds must maintain structural stability and appropriate load transfer, provide a permissive environment for new bone formation and tissue ingrowth, and accommodate the continuously evolving local mechanical environment throughout the repair process⁵.

Three-dimensional (3D) printing has substantially expanded the manufacturable design space of complex porous scaffolds for bone tissue engineering through layer-by-layer fabrication and its high degree of geometric freedom⁶. A wide range of porous architectures, including regular lattices, triply periodic minimal surfaces, and trabecular bone-inspired structures, can therefore be fabricated, while scaffold stiffness, strength, mass transport, and tissue ingrowth can be selectively optimised by regulating pore size, porosity, and spatial distribution⁷. These approaches have established a direct relationship between pore architecture and the overall performance of scaffolds, but their mechanical optimisation has largely relied on predefined geometric parameters and static performance metrics^{5,7}. Importantly, the mechanical function of native bone is also characterised by pronounced spatial heterogeneity and directional dependence. Different regions and orientations exhibit distinct deformation, strain distributions, and load transfer in response to loading, together with complex nonlinear mechanical behaviour⁸. Accordingly, scaffold design for bone repair should move beyond matching overall stiffness and strength to account for mechanical responses across different regions, directions, and loading states, thereby positioning local

deformation, tissue strain, and load transfer as key targets of structural design^{5,9}. From the perspective of evidence level, biological validation remains uneven across different metamaterial strategies. Some designs have progressed to evaluation in animal bone-defect models, whereas multistable and some highly programmable architectures remain largely at the computational, mechanical, or in vitro validation stage.

Mechanical metamaterials provide a new structural design route for achieving the mechanical regulation described above. Their macroscopic mechanical behaviour is governed primarily by pore topology and associated deformation mechanisms. Structural responses such as unit-cell rotation, buckling, folding, and state transitions can generate distinctive mechanical characteristics, including auxeticity, nonlinear stiffness, tunable anisotropy, and multistability¹⁰. Compared with conventional porous structures, which mainly rely on pore parameters to achieve targeted bulk properties, mechanical metamaterials enable more precise regulation of structural deformation, local strain, and load transfer across different directions and loading states, thereby offering a broader design space for accommodating the spatial heterogeneity and complex mechanical environment of bone tissue^{5,10}. The defining feature of mechanical metamaterials lies in the use of tailored topologies and deformation mechanisms to generate architecture-dominated mechanical responses, with lattice topologies serving as one of their principal geometric realisation strategies. Lattice architectures can be classified as mechanical metamaterials when they are specifically engineered to produce targeted mechanical functionalities, such as anisotropy, auxeticity, nonlinearity, multistability, or reconfigurability. As bone repair research has progressed from mechanical adaptation towards greater consideration of post-implantation tissue responses, mechanical metamaterials have also begun to evolve towards the integration of biological functions, with material composition and functional components being exploited to further regulate osteogenesis, vascularisation, and the immune microenvironment¹¹. The incorporation of bioactive components, including functional ions, growth factors, and therapeutic agents, provides additional opportunities to modulate local biological signalling and achieve controlled release. Meanwhile, advances in stimuli-responsive materials and spatiotemporally programmed structures allow printed constructs to undergo predefined changes in morphology or performance in response to external stimuli, further expanding their capacity to adapt to the continuously evolving mechanical and biological environments encountered during bone repair^{12,13}.

Existing reviews have largely focused on the general structural mechanisms of mechanical metamaterials, the structure–property relationships of architected biomaterials, or the material systems and manufacturing strategies of 3D-printed bone scaffolds. However, a systematic framework that takes the complex mechanical characteristics of native bone as its foundation and further integrates advanced manufacturing, architecture-dominated mechanical responses, biological functionalisation, and time-dependent mechanical behaviour has yet to be established^{10,14}. Building on these considerations, this review systematically examines advanced 3D printing-enabled mechanical metamaterials for bone repair and their functional evolution. With the mechanical characteristics of native bone as the starting point for defining implant design requirements, particular emphasis is placed on the structural design, deformation mechanisms, and bone repair applications of spatially heterogeneous and anisotropic, auxetic, nonlinear, multistable, and reconfigurable mechanical metamaterials. We further discuss the integration of bioactive components, including functional ions, growth factors, and therapeutic agents, with metamaterial architectures, as well as the time-dependent mechanical behaviour of degradable metamaterials after implantation, which is jointly governed by material degradation, architectural evolution, and new bone formation. By clarifying the intrinsic relationships among structural design, mechanical response, and biological function, this review aims to establish a design framework for mechanical metamaterials in bone defect repair and to provide a theoretical basis and design guidance for the development of next-generation orthopaedic implants that combine precise mechanical adaptation with regenerative regulation.

To enhance the transparency of the literature identification and selection process, relevant studies were retrieved from the Web of Science Core Collection and PubMed databases. The search strategy employed combinations of terms including mechanical metamaterial, architected material, 3D printing, additive manufacturing, bone tissue engineering, bone scaffold, auxetic, anisotropic, nonlinear, multistable, and reconfigurable. The literature selection primarily focused on peer-reviewed studies published from 2020 onwards, while a limited number of earlier publications were retained when they provided foundational evidence for mechanical metamaterial theory, representative structural mechanisms, or the development of bone tissue engineering. Eligible studies primarily addressed the structural design and fabrication of 3D-printed mechanical metamaterials, architecture-dominated mechanical responses, bone-regenerative outcomes, and biological functionalisation. Additional relevant studies were identified by examining the

reference lists of representative publications. Studies with limited relevance to bone repair, those primarily concerning conventional porous scaffolds without clearly architecture-dominated mechanical behaviour, and those that did not provide direct evidence for the manufacturing, mechanical, or biological issues discussed in this review were excluded.

2. Key Mechanical Characteristics of Native Bone and Their Implications for Scaffold Design

The mechanical behaviour of native bone is not determined by a single material parameter but emerges from its multiscale hierarchical architecture and spatial organisation, giving rise to pronounced spatial heterogeneity, directional dependence, and load-dependent nonlinear responses. These characteristics result in distinct patterns of stiffness, load transfer, and damage evolution across different anatomical regions, loading directions, and stages of deformation, thereby creating a highly complex local mechanical environment. Accordingly, the design of metamaterial scaffolds for bone repair should extend beyond matching bulk elastic modulus or strength and should further account for regional mechanical variations, anisotropic responses, and load-dependent mechanical behaviour, translating these features into tunable structural design parameters. This section therefore focuses on the heterogeneous, anisotropic, and nonlinear mechanical characteristics of native bone and discusses their implications for the mechanical adaptation of metamaterial scaffolds.

2.1 Heterogeneity

The heterogeneity of native bone exists across multiple structural scales and is manifested as spatial variations in composition, microarchitecture, and mechanical properties¹⁵⁻¹⁷. Rodriguez-Palomo et al. systematically summarised the hierarchical organisation of bone from the nanoscale to the macroscale, highlighting that distinct structural levels possess different compositional and architectural characteristics that collectively underpin the overall mechanical performance of bone¹⁵. Micheletti et al. further delineated the hierarchical relationships among mineralised collagen, bone lamellae, osteons, and trabeculae, emphasising that the spatial organisation of mineral and organic matrices constitutes an important structural basis for the material properties of bone¹⁶. These compositional and structural differences are further translated into distinct mechanical behaviours at the tissue scale. Bittner-Frank et al. compared cortical bone and individual trabeculae derived from the human proximal femur and identified marked differences in tissue mineralisation as well as elastic, viscous, and damage-related behaviour¹⁸. Such heterogeneity is not restricted to the distinction between cortical and trabecular bone. Chen et al.

mechanically characterised the microenvironment of fresh murine femora and found substantial differences in elastic and viscoelastic properties among the endosteal surface of cortical bone, growth plate, metaphysis, and bone marrow, with modulus values within individual regions spanning several orders of magnitude¹⁷. Although this study primarily characterised the softer components of the bone microenvironment rather than the macroscopic load-bearing behaviour of mineralised bone, its findings nevertheless demonstrate pronounced local mechanical heterogeneity at cell-relevant length scales. In trabecular bone, both bone mass and the spatial organisation of the trabecular network contribute to its apparent mechanical properties. Bregoli et al. analysed human femoral head trabecular bone and reported substantial inter-sample variations in bone volume fraction, trabecular spacing, and connectivity density, with apparent stiffness being closely associated with bone density and connectivity density¹⁹. Turunen et al. further observed pronounced three-dimensional strain localisation within human trabecular bone, with higher tissue strains occurring in regions containing cracks and thinner trabeculae exhibiting greater susceptibility to fracture²⁰. These findings indicate that average bone volume fraction or porosity alone is insufficient to fully characterise the mechanical state of trabecular bone, as the spatial distribution of bone mass, trabecular dimensions, and network connectivity collectively govern load transfer and strain distribution within the tissue. Beyond trabecular architecture, local mineralisation and tissue maturation also represent important sources of mechanical heterogeneity in bone. Cisneros et al. identified spatial variations in local modulus across osteonal lamellae in bovine tibia, with modulus positively correlated with mineral content, demonstrating that regional differences in composition and mechanical properties also exist within individual osteons²¹. Kwon et al. performed nanomechanical characterisation of newly formed bone and pre-existing mature bone following implantation and found that newly formed bone exhibited a broader distribution of local modulus values. High-resolution atomic force microscopy further identified mechanically distinct regions corresponding to unmineralised, partially mineralised, and mature mineralised states²²(Fig.1A). Collectively, these findings demonstrate that the mechanical heterogeneity of bone is determined not only by anatomical location but also by the states of tissue formation, mineralisation, and remodelling. For bone tissue engineering scaffolds, homogeneous pore architectures or matching a single target modulus are therefore unlikely to adequately recapitulate the spatial mechanical heterogeneity of native bone. Scaffold design should additionally account for regional variations in mechanical properties and their spatial distribution.

2.2. Anisotropy

Native bone exhibits pronounced mechanical anisotropy, which is closely associated with the oriented organisation of multiscale structures, including mineralised collagen, bone lamellae, osteons, and trabeculae²³. In cortical bone, collagen fibres and mineral crystals exhibit preferential orientations, and this structural alignment extends across the lamellar and osteonal levels, giving rise to direction-dependent mechanical properties. Stockhausen et al. reported marked differences in mineralisation, stiffness, and deformability among osteons with distinct collagen orientations in the human femur. Osteons dominated by longitudinally aligned collagen exhibited greater stiffness, whereas those containing a higher proportion of obliquely oriented collagen showed enhanced deformability and energy dissipation, indicating a close relationship between collagen orientation and the local mechanical function of osteons²⁴. Cisneros et al. further identified differences between axial and transverse mechanical properties at the lamellar scale, with the magnitude of these differences varying according to lamellar position, demonstrating that direction-dependent mechanical heterogeneity is already present within individual osteons²¹. This directional dependence is also evident at the level of bulk cortical bone. Zhang et al. similarly found that long-bone cortical tissue exhibited distinct elastic and yielding responses under longitudinal and transverse loading, and that these differences were further influenced by anatomical location²⁵. Collectively, these studies demonstrate a consistent relationship between structural orientation and direction-dependent mechanical response across scales ranging from collagen fibres and bone lamellae to bulk cortical tissue, indicating that multiscale structural alignment provides a key architectural basis for the mechanical anisotropy of cortical bone. Trabecular bone likewise exhibits pronounced directional dependence, with its mechanical behaviour closely related to the spatial orientation of the trabecular network. Trabeculae are not randomly distributed but are typically organised along preferential directions within the three-dimensional network, resulting in direction-dependent stiffness and load-transfer capacity in trabecular bone²⁶(Fig.1B). Xiao et al. analysed trabecular bone from the human proximal femur and found that the trabecular network exhibited a distinct principal structural orientation that corresponded to direction-dependent apparent stiffness, indicating that a complete description of its mechanical behaviour requires consideration of elastic properties along multiple directions²⁷. Oefner et al. further showed that bone volume fraction and trabecular orientation jointly characterise the anisotropic elastic properties of trabecular bone, with the principal stiffness direction showing a clear correspondence

with the preferential trabecular orientation²⁸. He et al. similarly reported that the elastic response along the principal trabecular alignment was markedly greater than that in the transverse direction, further supporting the close relationship between trabecular orientation and the anisotropic mechanical behaviour of cancellous bone²⁹. Notably, the principal material directions of trabecular bone also exhibit pronounced spatial variability. Yan et al. found that the principal trabecular orientations in different regions of the distal femur do not consistently coincide with conventional anatomical axes, and that characterising local mechanical properties according to the actual principal material directions substantially improves the accuracy with which anisotropic responses are described. Subsequent studies have further supported the close association between trabecular microarchitecture and anisotropic elastic properties^{30,31}. Taken together, these studies demonstrate that native bone exhibits distinct structural orientation across multiple hierarchical scales, from mineralised collagen and bone lamellae to osteons and trabecular networks, with corresponding mechanical responses varying substantially with loading direction. For bone tissue engineering scaffolds, matching mechanical properties along a single direction or reproducing only average bulk mechanical parameters is therefore insufficient to recapitulate the directional dependence of native bone. Scaffold design should instead account for mechanical responses along multiple directions and their correspondence with local load-bearing requirements.

2.3. Nonlinearity of Load Response

In addition to spatial heterogeneity and anisotropy, the stress–strain response of native bone varies with loading and deformation levels. Within the low-strain regime, bone tissue generally exhibits an approximately linear elastic response, whereas beyond yielding, plastic deformation and progressive damage may occur, giving rise to increasingly nonlinear stress–strain behaviour³². Peruzzi et al. reported in compression experiments at the cortical bone lamellar scale that axially oriented tissue predominantly exhibited post-yield strain softening, whereas transversely oriented tissue showed strain hardening, with both post-yield responses being influenced by strain rate³³. A three-dimensional nonlinear model developed by Alizadeh et al. further demonstrated that mineralised collagen fibril arrays exhibit distinct post-yield mechanisms under different loading modes. Under tension, the response involved interfacial sliding and debonding between the fibrils and extrafibrillar matrix, whereas compression was dominated by plastic deformation³⁴. Compression experiments on trabecular bone have similarly demonstrated pronounced changes in the stress–strain relationship with increasing deformation. Soltanihafshejani et al. observed in

compression tests of human tibial trabecular bone that the characteristic stress–strain curve progressed from the elastic regime to post-yield behaviour, followed by a plateau and subsequent hardening, and their constitutive model reproduced the experimentally observed post-yield mechanical response with good agreement³⁵. These curve characteristics indicate that the initial elastic modulus captures only the mechanical response of trabecular bone within the elastic regime and is insufficient to describe its post-yield stress–strain behaviour. Peña Fernández et al. further observed that the evolution of local strain during compression was closely associated with damage initiation and propagation and was accompanied by bending, buckling, and plastic deformation of trabeculae and other microstructural elements³⁶(Fig.1C). These findings suggest that the macroscopic nonlinear response of trabecular bone is closely associated with local deformation and damage evolution within the trabecular network. Bone tissue also exhibits markedly different mechanical responses under varying loading rates and loading histories. Albert et al. compared the compressive behaviour of human rib cortical bone across different strain rates and found significant differences in elastic modulus, yield stress, yield strain, ultimate stress, and ultimate strain³⁷. Uniyal et al. further found that inelastic strain accumulated during cyclic loading reduced the subsequent compressive strength of human tibial cortical bone at lower strain rates, whereas this effect was no longer significant at higher strain rates³⁸. This finding indicates that the strain-rate sensitivity of cortical bone is also modulated by prior inelastic deformation, with this effect being more pronounced at lower strain rates. The mechanical response of trabecular bone is likewise influenced by loading duration. Gersie et al. performed uniaxial compression tests on trabecular bone from the human distal femur and proximal tibia and observed a continuous decay in stress over time under constant strain. Based on these observations, they developed a nonlinear viscoelastic model to describe the time-dependent response of trabecular bone³⁹. Collectively, these findings demonstrate that a single elastic modulus or strength parameter is insufficient to fully characterise the mechanical behaviour of native bone. With increasing strain, bone tissue may transition from an approximately linear elastic response to yielding, plastic deformation, and progressive damage, resulting in pronounced nonlinearity in its stress–strain relationship⁴⁰. Strain rate, loading history, and timescale can further alter the corresponding elastic, yielding, and post-yield mechanical characteristics⁴¹. For bone tissue engineering scaffolds, matching only the initial elastic modulus of native bone within the small-strain regime is therefore insufficient to reproduce

its complete mechanical response. Structural design should also account for strain-dependent stiffness evolution, post-yield behaviour, and energy dissipation.

2.4 Mechanical Adaptation Requirements for Metamaterial Scaffolds

The complex mechanical characteristics of native bone require metamaterial scaffolds to provide sufficient mechanical stability within the defect while simultaneously establishing an appropriate local mechanical microenvironment. Conventional porous scaffolds typically regulate effective stiffness through porosity, but this is often accompanied by a reduction in strength. Zhang et al. altered the axial distribution of strut diameter and thereby modulated the effective elastic modulus and yield strength of the structure while maintaining an approximately constant porosity⁴². Shum et al. optimised porous titanium implants according to the local strain environment at the implantation site and observed more homogeneous bone ingrowth and a higher bone–implant contact ratio in vivo⁴³. These findings further indicate that the evaluation of scaffold mechanical adaptation should extend beyond in vitro effective mechanical properties to the local stress–strain environment established after implantation⁴⁴. The spatial heterogeneity of native bone requires scaffolds to exhibit spatially differentiated mechanical responses that accommodate regional variations in tissue architecture and local loading conditions. Even when homogeneous porous scaffolds possess appropriate overall stiffness, they may still generate local stress concentrations under complex physiological loading. Heins et al. optimised the spatial density distribution of metamaterial implants according to patient-specific loading and boundary conditions, reducing stress concentrations within the implant while increasing stress transfer to the surrounding bone⁴⁵. This study demonstrates that spatial heterogenisation of the microarchitecture can regulate local stiffness and stress transfer within an implant, providing a basis for the spatially differentiated design of mechanical responses. The anisotropy of native bone further requires scaffolds to exhibit tunable direction-dependent elastic and strength responses. Chen et al. modulated strut orientation within a parametric lattice to regulate elastic modulus and yield strength along three orthogonal directions and achieved elastic anisotropy ratios comparable to those of trabecular bone from different anatomical sites⁴⁶. Accordingly, directional scaffold design should aim to match elastic, yielding, and deformation characteristics along multiple directions while aligning these responses with the principal load-bearing directions of the surrounding bone. Because the stiffness and post-yield response of native bone vary with strain level, the constitutive design of scaffolds should also account for the evolution of mechanical behaviour across different deformation regimes⁴⁰.

Conventional lattices are commonly designed primarily according to their initial effective modulus and therefore cannot adequately capture stiffness evolution and post-yield mechanical behaviour with increasing strain. Qin et al. developed a mechanical metamaterial in which configurational evolution of the structural units produced a low-stiffness response at relatively small strains followed by a transition to a higher-stiffness state. In a bone defect model, this design increased callus strain and enhanced both bone formation and vascularisation⁵. This study provides in vivo evidence that nonlinear stiffness evolution in metamaterials can regulate mechanical responses across different deformation ranges and thereby enable dynamic modulation of the mechanical environment during bone repair. The realisation of such distinctive mechanical responses must nevertheless be balanced against structural safety and fatigue stability. Heins et al. found that a metamaterial mandibular reconstruction plate improved stress distribution within the surrounding bone but exhibited a lower failure load than a solid titanium reconstruction plate, indicating that the mitigation of stress shielding remains constrained by structural strength⁴⁷. Repeated loading may further induce local damage accumulation within complex architectures, making fatigue performance another critical mechanical requirement for the long-term application of metamaterial scaffolds⁴⁸. Liu et al. showed that unit-cell dimensions and manufacturing-induced surface defects in additively manufactured porous scaffolds can alter fatigue crack initiation and structural lifetime⁴⁹. For mechanical metamaterials that rely on buckling, contact, or configurational transitions to generate specialised responses, fatigue assessment should therefore consider not only cyclic life but also the stability of the predefined stress-strain response and deformation mechanisms after repeated loading⁵. Accordingly, the mechanical design of metamaterials for bone repair should ensure sufficient structural strength and cyclic stability while enabling spatially, directionally, and deformation-dependent mechanical responses that are adapted to the local bone tissue and physiological loading environment. Their evaluation should likewise extend beyond single effective modulus and strength values to include local stress-strain distributions, directional dependence, and the complete stress-strain response.

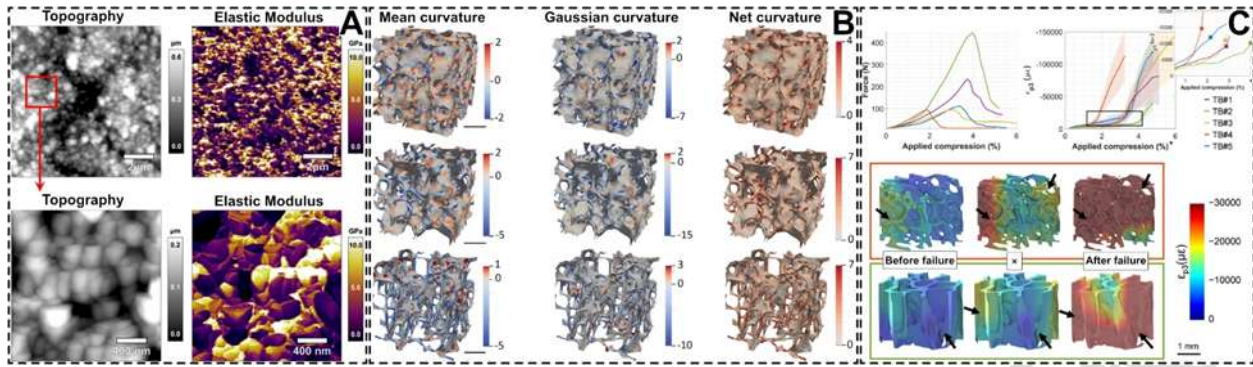


Figure 1. Multiscale mechanical heterogeneity, local geometric characteristics, and strain evolution under loading in native bone. (A) Nanoscale morphology and elastic modulus distribution of newly formed bone tissue. Bimodal atomic force microscopy (AFM) reveals distinct morphological features and spatial variations in local elastic modulus across different length scales, reflecting the nanomechanical heterogeneity arising during bone formation and mineralisation. Adapted from Kwon et al. ²². Copyright 2023, Springer Nature. (B) Spatial distribution of local surface geometry in human trabecular bone. Mean curvature, Gaussian curvature, and curvedness were used to characterise trabecular surfaces from different anatomical sites, revealing distinct local concave, convex, saddle-shaped, and highly curved regions, together with substantial spatial variations in curvature within individual trabecular networks. These features illustrate the complex and heterogeneous three-dimensional geometry of native cancellous bone. Adapted from Callens et al. ²⁶. Copyright 2021, Elsevier. (C) Global load-bearing behaviour and three-dimensional local strain evolution of human trabecular bone during continuous compression. Trabecular specimens with different microarchitectures exhibit distinct force–deformation responses and evolution of the minimum principal strain. Digital volume correlation analysis demonstrates a highly heterogeneous local strain distribution throughout the trabecular network, with strain preferentially accumulating in regions where cracks and structural failure subsequently develop. Rod-like and plate-like trabecular architectures further exhibit distinct local strain-bearing characteristics, demonstrating the direct contribution of trabecular microarchitecture to local load transfer, strain localisation, and damage evolution. Adapted from Peña Fernández et al. ³⁶. Copyright 2021, Elsevier.

3. Advanced 3D Printing Strategies

The mechanical functionality of metamaterials is highly dependent on unit-cell topology and local geometry, making manufacturing precision fundamental to the reliable realisation of predefined structural responses. Three-dimensional printing enables the fabrication of complex architectures incorporating fine-scale struts, continuous surfaces, internal channels, and spatial gradients, and therefore provides essential manufacturing routes for auxetic, nonlinear, multistable, and anisotropic metamaterials. However, different printing technologies vary in material compatibility, achievable feature size, and fabrication accuracy, while geometric deviations and manufacturing defects can further alter local stress distributions and deformation mechanisms. Bioprinting offers an additional manufacturing strategy by enabling the spatial organisation of cells, bioinks, and bioactive components, thereby facilitating the integration of mechanical and biological functions within metamaterial systems. This section focuses on powder bed fusion, vat

photopolymerisation, material extrusion, and bioprinting, with particular emphasis on their capabilities for realising complex architectures and the key manufacturing constraints associated with each process.

3.1. Powder Bed Fusion (PBF)

PBF selectively melts metal powders using a laser or electron beam and builds components layer by layer, enabling the integrated fabrication of complex nodes, fine-scale struts, and internal channels. It has therefore become an important manufacturing technology for metallic mechanical metamaterials^{5,50}. Wanniarachchi et al. used laser PBF to fabricate five CoCrMo auxetic scaffolds with different unit-cell configurations, achieving Poisson's ratios of approximately -0.10 to -0.24⁵¹. This study demonstrated the manufacturability of complex auxetic unit cells in biomedical metals and showed that their predefined transverse deformation characteristics could be retained in the fabricated structures. Beyond unit-cell topology, structural regulation enabled by PBF can be extended to the strut scale. Zhong et al. redesigned the strut architecture of Ti6Al4V lattices and achieved a compressive strength exceeding 400 MPa at a density of approximately 1.6 g cm⁻³⁵². This approach extended structural regulation in metallic metamaterials from the unit-cell level to the strut scale and exploited PBF to realise metallic structural elements with complex cross-sections and internal features. Noronha et al. further embedded thin-plate features within hollow-strut Ti6Al4V lattices to create multi-topology metallic metamaterials, reducing the nodal stress concentration factor by approximately 56% while achieving approximately 99% geometric agreement between the PBF-fabricated metamaterials and their digital models⁵⁰. As metamaterial design progresses from individual unit cells towards strut-level reconfiguration and multi-topology integration, mechanical responses become increasingly sensitive to local geometric features, thereby imposing more stringent requirements on fabrication accuracy and structural manufacturability in PBF⁵³. Strut inclination, minimum feature size, and complex boundary geometries can all affect geometric fidelity and local structural integrity, while hollow or highly enclosed internal architectures are additionally constrained by the removal of unmelted powder⁵⁴. For mechanical metamaterials that rely on local rotation, buckling, or configurational transitions to generate specific responses, geometric deviations may alter predefined deformation pathways and cause the mechanical behaviour of the printed structure to deviate from predictions based on the idealised model⁵⁵. To address these challenges, Zhong et al. developed a design framework for complex lattices fabricated by laser PBF, incorporating process constraints including strut

orientation, manufacturable feature size, boundary conformity, and powder removal into the structure-generation process, thereby improving the consistency between the designed and fabricated geometries of complex Ti6Al4V lattices⁵⁴. This approach further demonstrates that the structural design of complex metallic metamaterials must be coordinated with the practical processing boundaries of PBF to maintain consistency between the intended architecture and the realised structure. Accordingly, PBF-enabled manufacturing of metallic metamaterials has evolved from the fabrication of complex unit cells towards strut-level reconfiguration and multi-topology integration, with manufacturability becoming an increasingly important constraint in complex structural design^{50,54}. For mechanical metamaterials intended for bone repair, the key requirement is to ensure consistency among the digital design, the as-fabricated architecture, and the predefined mechanical response, so that complex local geometries and their associated deformation mechanisms can be reliably realised in physical implants. This provides a robust manufacturing basis for engineering mechanical functionalities including auxeticity, nonlinear stiffness, anisotropy, and multistability (Fig. 2A).

3.2. Vat Photopolymerisation (VPP)

VPP fabricates materials layer by layer through selective photopolymerisation and primarily includes stereolithography (SLA), digital light processing (DLP), and liquid crystal display (LCD)-based photopolymerisation⁵⁶. Compared with PBF, which primarily relies on thermal energy to sinter or melt powder feedstocks, VPP is more suitable for the high-resolution fabrication of photosensitive polymers and ceramic suspensions and offers considerable geometric freedom for producing continuous surfaces, thin-walled features, and fine-scale structures⁵⁶. Yao et al. used DLP to fabricate hydroxyapatite TPMS scaffolds with highly porous and geometrically complex curved architectures, demonstrating the capability of VPP to realise complex topologies in bioceramic systems⁵⁷. Shen et al. subsequently fabricated magnesium-doped calcium silicate scaffolds with different TPMS topologies using DLP while maintaining comparable porosity and pore dimensions. Distinct topology-dependent differences in mechanical performance and early bone regeneration were observed, further demonstrating the controllable fabrication of complex curved architectures by VPP⁵⁸. Roohani et al. employed high-resolution LCD-based photopolymerisation to fabricate TPMS bioceramic structures with a minimum wall thickness of approximately 38 μm , further extending the manufacturable feature size of complex curved architectures into the micrometre regime⁵⁹. These fabrication capabilities provide a manufacturing

basis for mechanical metamaterial architectures with complex geometries, enabling local geometric parameters to be further translated into tunable structural mechanical responses. Li et al. fabricated microlattice metamaterials using DLP and altered local deformation and stress-transfer modes by varying the degree of strut hollowness, thereby achieving different compressive moduli, strengths, and plateau stresses. These findings demonstrate that fine geometric design can be translated into tunable structural mechanical responses through photopolymerisation-based fabrication⁶⁰. However, as structural feature size decreases, manufacturing errors become increasingly significant relative to local geometric dimensions, while structural fidelity becomes more susceptible to constraints imposed by the material system and photopolymerisation process. Studies have shown that refractive-index mismatch, particle size, and exposure conditions in ceramic suspensions can alter light scattering and curing depth, thereby affecting lateral overcuring and dimensional fidelity⁶¹. In addition, photopolymerised ceramics generally require subsequent post-curing, debinding, and sintering, during which shrinkage, deformation, and defect evolution may further alter the designed pore dimensions, wall thickness, and local connectivity. Wu et al. optimised the calcium phosphate ceramic suspension, exposure conditions, and post-curing process, increasing the degree of curing of the green body from 69.78% to 93.91% and improving the mechanical strength of the final ceramic structure by 46.34%⁶². For mechanical metamaterials intended for bone repair that rely on local geometric units to generate specific stress-transfer pathways and deformation mechanisms, such manufacturing-induced geometric deviations affect not only fabrication quality but may also alter local stress distributions, buckling pathways, and deformation modes, ultimately causing the realised mechanical response to deviate from the intended design⁶³. Accordingly, the key challenge of VPP for bone-repair mechanical metamaterials is no longer limited to the manufacturability of complex architectures but increasingly concerns geometric fidelity throughout the transition from the digital model and green body to the final sintered structure, so that predefined configurations and their associated deformation mechanisms can be reliably reproduced in the final construct (Fig. 2B).

3.3. Material Extrusion (MEX)

MEX fabricates three-dimensional structures by extruding material through a nozzle and depositing it layer by layer along predefined toolpaths. In bone tissue engineering, the most commonly used MEX approaches include fused filament fabrication (FFF) and direct ink writing (DIW). Compared with PBF and VPP, which rely on powder beds and photosensitive resin systems,

respectively, MEX offers relatively simple equipment requirements and broad feedstock flexibility. However, because geometric construction depends on the sequential deposition of material filaments with finite dimensions, fabrication accuracy is more strongly constrained by nozzle size, material rheology, and deposition parameters⁶⁴. FFF has been used to fabricate diverse mechanical architectures, including honeycombs, auxetic lattices, strut-based lattices, and TPMS structures, providing a flexible manufacturing platform for degradable mechanical metamaterials⁶⁵. Liu et al. used FFF to fabricate regular, Gyroid, and Diamond PLA scaffolds with different porosities, demonstrating the manufacturability of complex TPMS architectures⁶⁶. Kladovasilakis et al. further integrated Schwarz Diamond structures and hybrid lattices combining Schwarz Diamond with FCC architectures into patient-specific tibial defect scaffolds, demonstrating that FFF can simultaneously realise complex lattice geometries and patient-specific external contours⁶⁷. However, the deformation mechanisms of mechanical metamaterials are highly dependent on local strut and nodal geometries, meaning that the manufacturability of a complex architecture does not necessarily ensure accurate reproduction of the intended design geometry. Bappy et al. systematically evaluated the effects of nozzle temperature, extrusion pressure, and printing speed on the strut width of PLGA/nHA scaffolds and, through iterative process optimisation, achieved printed dimensions within a predefined $\pm 5\%$ tolerance range⁶⁸. For mechanical metamaterials that rely on strut aspect ratio, connection angle, and nodal position to generate specific deformation mechanisms, deviations in extrusion width and interlayer overlap may further alter local stiffness and load-transfer pathways, causing the realised structural response to deviate from the intended design⁶⁹. The manufacturing advantages of MEX are further reflected in the broad range of compatible material systems. Compared with FFF, which primarily processes thermoplastic filaments, DIW can directly incorporate ceramics, bone cements, and multiphase composites into extrusion-based fabrication through control of the rheological behaviour of slurries or pastes⁷⁰. del Mazo Barbara et al. used PCL as a binding phase in a self-setting α -TCP ink. The optimised composite ink exhibited both favourable printability and interlayer bonding and increased the flexural strength of the hardened scaffold from approximately 2 MPa in the hydrogel-based control to approximately 4 MPa, demonstrating that DIW ink composition can simultaneously influence fabrication stability and structural mechanical performance⁷¹. DIW can also enable spatially graded fabrication through in-line multimaterial mixing. Guo et al. continuously varied the local proportions of two ceramic foams, generating spatial gradients in scaffold composition, pore

architecture, and mechanical properties and thereby providing a new manufacturing route for bone repair structures with regionally differentiated mechanical performance⁷². It should be noted that material rheology, nozzle dimensions, and toolpath geometry collectively influence the width and continuity of deposited filaments as well as nodal morphology. Frequent acceleration and deceleration along high-curvature paths may lead to mismatches between material flow rate and nozzle motion, while particle-containing suspensions additionally require appropriate matching between nozzle diameter and particle size to minimise clogging and local geometric distortion⁷³. Accordingly, the application of MEX to mechanical metamaterials for bone repair depends not only on the manufacturability of complex architectures but also on coordinated control of material rheology, extrusion parameters, and path planning to preserve the geometric fidelity of critical struts, nodes, and continuous surfaces and to ensure reliable realisation of the predefined local deformation and load-transfer mechanisms in the final structure (Fig. 2C).

3.4. Bioprinting

Bioprinting is an additive manufacturing approach that spatially organises living cells, biomaterials, and bioactive components into three-dimensional constructs according to predefined distributions. Unlike conventional scaffold fabrication followed by subsequent cell seeding, bioprinting enables simultaneous control over the spatial arrangement of cells and biological cues during structure fabrication, providing a new route for constructing bone tissue engineering scaffolds with complex cellular microenvironments and biological functions⁷⁴. For mechanical metamaterials, the principal value of bioprinting lies not in replacing conventional structural manufacturing technologies, but in further introducing cells and bioactive components into predefined architectures so that structural mechanical function and local biological regulation can be integrated within the same fabrication system¹⁴. Hydrogels suitable for cell encapsulation generally exhibit favourable cytocompatibility but limited mechanical performance, whereas increasing polymer concentration or crosslinking density may compromise cell viability and function. Balancing structural load-bearing capacity with biological compatibility therefore remains a major challenge in bone bioprinting. Rodrigues et al. employed a multimaterial co-extrusion strategy to simultaneously print structurally supportive PLGA or PLGA-HA with MSC-laden bioinks, providing a feasible route for reconciling structural stability with cellular activity⁷⁵. Functionalisation of bioinks further enables the printing process to modulate the bone-regenerative microenvironment. Yu et al. incorporated Sr-doped calcium silicate nanowires into hydrogels

containing BMSCs for bioprinting and found that nanowire incorporation improved printing fidelity and hydrogel mechanical properties while enhancing osteogenic differentiation of BMSCs and promoting macrophage polarisation towards a reparative phenotype⁷⁶. Beyond the spatial integration of cells and bioactive components, bioprinted constructs can also be combined with mechanical stimulation. Zhang et al. subjected hMSC-laden 3D-bioprinted composite scaffolds to long-term cyclic mechanical loading and found that sustained loading during the early stage significantly increased construct mineralisation and overall stiffness, while promoting type I collagen maturation, osteocytic differentiation, formation of the lacuno-canalicular network, and YAP expression⁷⁷. This study demonstrates that bioprinting not only enables the fabrication of three-dimensional constructs with predefined cellular compositions but also provides a controllable platform for investigating the relationships among structural deformation, mechanical stimulation, and cellular function, thereby supporting further integration of mechanical metamaterials with cellular mechanobiology. Nevertheless, studies that deeply integrate bioprinting with mechanical metamaterials for bone repair remain limited in the strict sense. At present, most bone bioprinting research continues to focus primarily on cell incorporation, enhancement of bioactivity, and tissue biomimicry, whereas the coordinated design of specialised structural deformation mechanisms and spatial cellular organisation has not yet been sufficiently explored. Meanwhile, bioinks must typically balance printing fidelity, mechanical performance, rheological behaviour, and cellular activity, and adjustments in material composition or crosslinking degree often influence both printing stability and cell function⁷⁸. Future studies should therefore preserve the predefined topology and deformation mechanisms of metamaterials while further coordinating the spatial organisation of load-bearing materials, bioinks, and cells, and should exploit structural responses to regulate the local cellular mechanical microenvironment. Such efforts may advance bioprinting from the fabrication of bioactive scaffolds towards the coordinated construction of mechanical and biological functions (Fig. 2D). A quantitative comparison of the manufacturing capabilities and constraints of representative 3D-printing technologies is summarised in Table 1.

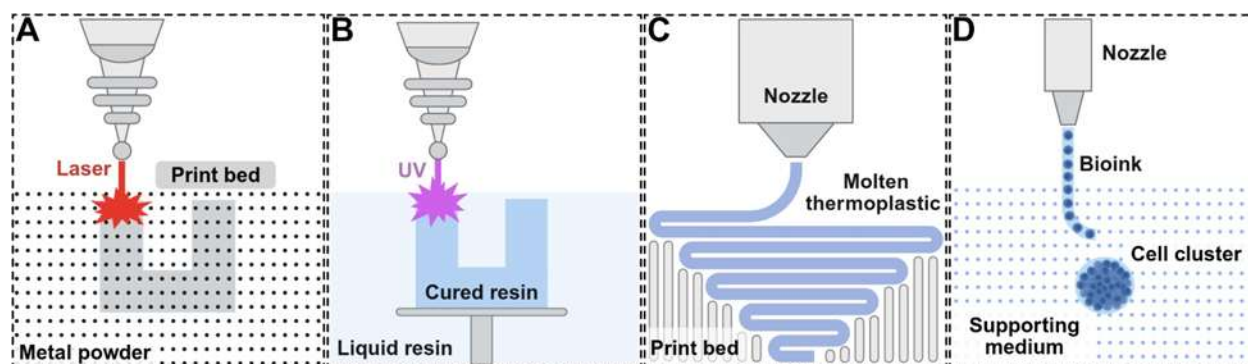


Figure 2. Advanced 3D printing strategies for the fabrication of mechanical metamaterials and their fundamental processing principles. (A) Powder bed fusion (PBF). High-energy beams, such as lasers, selectively melt metal powders along predefined scanning paths, while sequential powder recoating and layer-by-layer fusion enable the integrated fabrication of complex metallic metamaterials, including structures with fine struts, intricate nodes, and internal channels. (B) Vat photopolymerisation (VPP). Liquid photosensitive resins are selectively cured by ultraviolet light and sequentially constructed layer by layer, enabling high-resolution fabrication of structures with continuous curved surfaces, thin walls, and high geometric complexity. (C) Material extrusion (MEX). Thermoplastic materials or extrudable pastes are continuously extruded through a nozzle and deposited layer by layer along predefined toolpaths, providing a flexible manufacturing approach for polymeric and composite metamaterials. (D) 3D bioprinting. Cell-laden bioinks are deposited through a nozzle according to predefined spatial trajectories, enabling the spatial organisation of cells, biomaterials, and bioactive components during fabrication and providing a manufacturing platform for integrating structural mechanical functions with biological regulation in mechanical metamaterials.

Table 1 Manufacturing capabilities and constraints of 3D printing and bioprinting for bone repair metamaterials

Process family / subtype	Printable material systems	Feature size and pore accessibility	Layer thickness / optical scale	Geometric accuracy and fidelity	Surface quality	Major defects and constraints	Implications for mechanical behaviour	Architectural suitability	Post-processing / cell compatibility	Representative evidence
A Powder bed fusion										
Laser PBF Biomedical metals	Ti6Al4V and CoCrMo; other alloys require their own process qualification.	CoCrMo auxetic lattice: designed strut thickness 300 µm. Ti hollow-strut example: 1.15 mm internal channels selected for powder removal.	CoCrMo example: 40 µm layers and 100 µm laser spot. Spot size is not strut size.	Mean strut-thickness variation approximately 50 µm in the CoCrMo study. Inclination, melt-pool size and node geometry affect local deviations.	Partially fused powder and stair-stepping give orientation-dependent surfaces; internal faces are difficult to finish uniformly.	Lack of fusion; attached particles; thermal distortion; unsupported-span deformation; inaccessible trapped powder.	Oversized struts and nodes change relative density and stiffness. Local notches and internal defects can compromise fatigue and intended deformation paths.	Load-bearing metallic lattices, graded architectures, auxetic cells and hollow-strut designs. Thin walls and moving joints require geometry-specific qualification.	Depowdering and cleaning; support removal where required; alloy-specific heat treatment or surface finishing. Validate removal of particles from interconnected pores.	Wanniarachchi et al., 2022 ⁵¹ ; Noronha et al., 2024 ⁵⁰
High-precision laser PBF Thin metallic shells	316L stainless steel in the cited thin-wall study.	Reported system feature capability approximately 50-60 µm; compensation validated on 135 and 185 µm walls. These are different metrics.	10 µm layers; 25 µm laser spot.	Pre-compensated 135 and 185 µm walls had deviations below 10 µm under the tested conditions; not a general tolerance for all overhangs.	Roughness and wall thickness depend on inclination; small feature size does not remove down-facing surface irregularities.	Powder adhesion; recoil/recoating interactions; scrape-induced thinning; non-compensable geometric regions.	Relative wall error becomes large in thin shells, changing shell stiffness, buckling loads and stress concentration.	Thin-shell TPMS and fine metallic lattices; demonstrated Schwarz Primitive compensation. Fragile overhangs remain process-limited.	Geometry pre-compensation, micro-CT or optical dimensional checks, and careful cleaning; finishing must not erase thin features.	Ding et al., 2022 ⁵³
Electron-beam PBF	Ti6Al4V in the cited study; conductive metal powders compatible with electron-beam processing.	Combined SC/BCC/FCC lattice: designed strut diameter 500 µm and unit-cell length 6.4 mm. No universal minimum established.	50 µm layers; 100 µm beam diameter; approximately 75 µm mean powder diameter.	CT revealed strut-thickness variation, waviness and eccentricity; geometric imperfections were incorporated into mechanical modelling.	Adhered/sintered powder and non-uniform strut surfaces complicate the definition of the load-bearing cross-section.	Strut waviness; eccentricity; thickness variation; removal of the surrounding sintered powder cake from narrow channels.	As-built imperfections affect collapse patterns and static/dynamic compressive response; ideal CAD models can misrepresent deformation.	Metallic interconnected lattices and bone-like porous architectures. Fine hinges and tightly enclosed channels require particular caution.	Powder-cake removal and cleaning; validate open channels and structural geometry. In the cited hot-build protocol, separate stress relief was omitted.	Yu et al., 2022 ⁵⁵
Polymer selective laser sintering	PA12 (PA 2200) in the cited auxetic demonstration.	Re-entrant cells: designed 600 × 600 µm strut cross-sections within 3.75 mm unit cells. These are demonstrated designs, not minimum limits.	100 µm layers; feedstock particles 20-40 µm.	Fabricated negative-, near-zero- and positive-Poisson-ratio designs; a numerical dimensional tolerance was not established in this comparison.	Powder-derived granular texture and layer steps; narrow concave regions retain particles more readily.	Incomplete fusion; local porosity; thermal shrinkage/warpage; powder entrapment and feature coalescence.	Fusion quality and local geometry can change stiffness and hinge rotation, obscuring the response predicted from ideal unit cells.	Re-entrant and spatially graded polymer lattices; useful for structural demonstrations. Implant suitability is not established by printability alone.	Controlled cooling, depowdering and cleaning; any smoothing must preserve re-entrant angles and connecting struts. Biological suitability requires separate evaluation.	Yao et al., 2023 ⁷⁹
B Vat photopolymerisation and high-resolution photopolymerisation										
Micro-SLA Photopolymer lattices	Biocompatible RG photopolymer in the cited study; compatibility is resin-specific.	Re-entrant design: 60 µm nominal strut widths and 500 µm nominal aperture.	Layer thickness not specified here; 2.5 µm in the article is the micro-CT voxel resolution, not printing resolution.	Measured strut widths were approximately 71-99 µm; measured apertures approximately 459-464 µm across designs.	Layer-stacking traces remained visible. Optical curing can improve contour continuity but does not eliminate local overgrowth.	Lateral overcuring; strut thickening; pore narrowing; incomplete curing and retained resin in internal spaces.	Strut overgrowth changes porosity, effective modulus and re-entrant deformation; designed and measured geometry should both inform models.	Fine auxetic lattices and cell-mechanobiology test structures. Demonstrated cyclic-loading studies; long-term load-bearing use is a separate question.	Resin removal, washing and resin-specific post-cure; cytocompatibility testing after processing. Cells were seeded after printing, not printed within the resin.	Geng et al., 2025 ⁸⁰

Process family / subtype	Printable material systems	Feature size and pore accessibility	Layer thickness / optical scale	Geometric accuracy and fidelity	Surface quality	Major defects and constraints	Implications for mechanical behaviour	Architectural suitability	Post-processing / cell compatibility	Representative evidence
DLP Ceramic suspensions	HA and biphasic calcium phosphate slurries; related calcium-silicate systems require material-specific exposure control.	Interconnected ceramic TPMS are demonstrated. Minimum final wall/pore dimensions cannot be inferred from projector pixel size alone.	HA example: 50 µm projected pixels and 50 µm printed layers.	Assess CAD-green body-sintered geometry. Light scattering, exposure and thermal shrinkage can alter walls, pores and connectivity.	Continuous curved surfaces are feasible; final finish also reflects ceramic particle size, exposure, grain growth and residual microporosity.	Over/undercuring; trapped slurry; interlayer cracks; debinding defects; differential sintering shrinkage.	Cure and thermal defects alter brittle strength and local stress transfer. Optimised CaP post-curing raised final strength by 46.34% in one study.	Ceramic TPMS, curved surfaces and fine lattices. Reversible snapping requires a suitably compliant material/geometry and is not guaranteed by print resolution.	Washing, post-curing, debinding and sintering. CaP green-body conversion increased from 69.78% to 93.91% after post-curing. Live-cell encapsulation is incompatible with sintering.	Yao et al., 2021 ⁵⁷ ; Wu et al., 2023 ⁶²
LCD mask-based VPP Fine bioceramic TPMS	HA and baghdadite ceramic suspensions in the cited work.	Measured sintered Gyroid wall as thin as 38 µm; reported pore sizes below 200 µm and porosity up to 92%.	22 µm nominal LCD pixel size; 50 µm layers selected for printing.	Applied scale factors 1.1 in x-y and 1.3 in z to compensate shrinkage. These are model scaling factors, not residual error or shrinkage percentages.	Reducing median particle size from 9.0 to 0.5 µm improved surface finish and attainable fine features.	Particle scattering; refractive-index mismatch; insufficient cure in thin features; washing damage and anisotropic thermal shrinkage.	Thin-wall variation changes local stress and stiffness. A demonstrated minimum wall is not a validated fatigue-safe design limit.	Highly porous Gyroid, Diamond and Schwarz-type ceramic surfaces; suitable when fine continuous walls and open pores can survive post-processing.	Optimise suspension and exposure; gentle cleaning, debinding and sintering; verify final thickness and connectivity rather than relying on green-body appearance.	Roohani et al., 2023 ⁵⁹
Two-photon polymerization Micro-scale lattices	IP-Q methacrylate photoresist; other photoresists require separate cytocompatibility and mechanical calibration.	Demonstrated microarchitectures with 36 µm designed struts and approximately 175-184 µm designed pores. These are not the optical voxel limit.	Voxel writing, slicing, hatching and stitching govern construction; a single macroscopic layer-thickness value is not directly comparable with DLP.	Segment overlaps and contour settings were adjusted to preserve fine struts. CAD dimensions must be distinguished from measured structural response.	Fine contours are accessible; writing paths and segment junctions can leave local surface/shape discontinuities.	Stitching mismatch; incomplete polymerisation; development-induced shrinkage or collapse; capillary damage; limited throughput.	Local defects alter slender-beam compliance and Poisson's ratio; the polymer's intrinsic response must also be measured.	Micro-scale auxetic/non-auxetic lattices and mechanobiology platforms. Scale and throughput constrain direct translation to large bone defects.	Develop in PGMEA and rinse in IPA; control drying deformation and substrate adhesion. Biological tests used post-seeded MC3T3-E1 cells.	Yarali et al., 2024 ⁸¹
C Material extrusion										
Fused filament fabrication Thermoplastic scaffolds	PLA in the cited comparison; PCL, PEEK and other polymers need their own thermal and extrusion windows.	250 µm nozzle in the PLA study; nozzle diameter is not a measured minimum wall. Regular, Gyroid and Diamond architectures were printed.	250 µm layers in the cited PLA protocol; nozzle temperature 210 °C.	Deposited roads and intersections differ from smooth CAD surfaces; local overlap/underfill depends on path, pore shape and porosity.	At 15% porosity, top-surface Sa was 47.7 µm (regular), 52.8 µm (Gyroid) and 97.1 µm (Diamond). Areal values vary with topology.	Inter-road voids; weak interlayer bonding; staircase texture; bead overlap; sagging over unsupported pores.	Layer bonding and toolpath create process anisotropy in addition to designed anisotropy; surface and overlap defects modify load paths.	Polymer strut lattices, auxetic cells and coarse TPMS. Very thin curved walls and freely moving joints are restricted by deposition width and support access.	Dry feedstock, optimise temperature/flow and remove supports where used. Sterilisation must preserve polymer shape and properties; hot extrusion is not live-cell printing.	Liu et al., 2023 ⁶⁶

Process family / subtype	Printable material systems	Feature size and pore accessibility	Layer thickness / optical scale	Geometric accuracy and fidelity	Surface quality	Major defects and constraints	Implications for mechanical behaviour	Architectural suitability	Post-processing / cell compatibility	Representative evidence
Pressure-driven melt extrusion Particle-filled polymer	95 wt% PLGA / 5 wt% nHA composite in the cited study.	Designed strut width 400 μm ; designed open square pores 750 μm .	400 μm designed layer height; evaluated temperatures 115-125 $^{\circ}\text{C}$.	Iterative parameter optimisation brought strut widths within $\pm 5\%$ of the 400 μm target, equivalent to $\pm 20 \mu\text{m}$ for that target only.	Bead contours and layer junctions remain; width repeatability does not by itself establish surface roughness or internal pore fidelity.	Over/under-extrusion; filler-related flow variation; pressure/speed mismatch; discontinuous or widened struts.	Rod width and node overlap alter local stiffness and porosity. The reported dimensional tolerance is not a guarantee of mechanical equivalence.	Composite lattices and spatially prescribed pore networks; high-curvature paths and thin joints require local flow calibration.	Prepare homogeneous feedstock and remove preparation solvent before melt processing. Optimise pressure, speed and temperature; cell seeding follows fabrication.	Bappy et al., 2024 ⁶⁸
Direct ink writing Self-setting calcium phosphate	α -TCP/PCL composite ink; aqueous hardening generates an apatite-containing scaffold.	410 μm dispensing tip; 250 μm designed inter-filament spacing. Neither value establishes a minimum printed feature.	335 μm layer height with 20% designed z-overlap.	Rheology and interlayer overlap determine strut continuity and shape retention; evaluate the hardened, not only freshly printed, structure.	Setting produces micro/nanotexture within deposited roads; assess roughness in the hydrated/hardened state relevant to use.	Filament spreading; sedimentation or nozzle blockage; poor interlayer contact; incomplete setting and formulation-dependent shrinkage.	Inter-road bonding and setting control bending strength; optimised PCL-containing inks approximately doubled flexural strength versus hydrogel-based controls.	Open extruded lattices and graded composites; continuous thin TPMS walls are more path-constrained than in VPP.	Controlled self-hardening and washing/conditioning according to formulation. No high-temperature sintering is needed for this route; live-cell compatibility cannot be assumed.	del-Mazo-Barbara and Ginebra, 2024 ⁷¹
Direct ink writing Graded ceramic foams	Online mixtures of zirconia-based and alumina-based ceramic foams.	1.2 mm nozzle in the demonstrated gradient scaffold. Hierarchical microporosity is foam-derived, not the printer's minimum feature.	1.2 mm layers; printing speed 30 mm/s .	Composition gradients and pore organisation were fabricated by changing mixing ratio; an absolute dimensional tolerance is not supplied here.	Hierarchical pores and ceramic surface texture remain after firing; surface appearance depends on foam structure and sintering.	Foam destabilisation by shear; flow/mixing lag; drying cracks; mismatch in shrinkage during co-sintering.	Spatial composition and porosity jointly influence stiffness; process-generated defects can interrupt the intended smooth property gradient.	Regionally graded load-supporting scaffolds and hierarchical porosity. Coarse deposited roads limit fine hinges and small re-entrant details.	Controlled-humidity drying for at least 3 days, followed by validated co-sintering. Remove organics and verify interface continuity; cells are introduced subsequently.	Guo et al., 2025 ⁷²
D Bioprinting and multimaterial biofabrication										
Cell-laden extrusion Hydrogel and composite bioinks	GelMA/Sr-substituted calcium-silicate nanowires with BMSCs; GO/alginate/gelatin with hMSCs.	22G needle or 27G nozzle. Gauge identifies the delivery tool; do not equate it with final filament width or open-pore size.	Layer height not specified here. Example settings: 0.15-0.20 MPa and 8 mm/s; 30-40 kPa and 2 mm/s.	Shape retention depends on ink yield behaviour, temperature and crosslinking. Nanowire reinforcement improved printing fidelity in the GelMA system.	Hydrated gel surfaces and filament junctions evolve with swelling and cell remodelling; dry-scaffold roughness is not an equivalent measure.	Shear-related cell injury; filament spreading/fusion; pore closure; heterogeneous crosslinking; inadequate initial load support.	Gel stiffness and architecture change during culture. Increasing crosslinking to improve stability can also restrict cell spreading and transport.	Cell-bearing lattices, bioactive infills and mechanobiology models. Special auxetic or multistable behaviour must be demonstrated separately.	405 nm for 60 s; 2% CaCl_2 for 10 min. The GO composite retained >85% viability on days 9 and 31, not an immediate-print survival metric.	Yu et al., 2024 ⁷⁶ ; Zhang et al., 2022 ⁷⁷
Multimaterial coextrusion Structural polymer and bioink	PLGA or PLGA/HA ink in DMSO, combined with MSC-laden GelMA.	Two-channel printhead constructed from 23G needles. Final filament dimensions depend on both flow streams and solvent exchange.	Layer height not specified here; channel geometry, deposited height and flow ratio need joint calibration.	Solvent-exchanged polymer components showed volume shrinkage of $27.6 \pm 2.6\%$ (PLGA) and $25.2 \pm 5.4\%$ (PLGA/HA) ; not linear shrinkage values.	Microporous polymer phase adjacent to a hydrated hydrogel phase; interfaces and pore opening must be assessed after conditioning.	Flow mismatch; interfacial discontinuity; solvent-associated cellular stress; shrinkage and redistribution of the two phases.	The polymer phase supplies structural reinforcement while the gel carries cells; printing a hybrid does not automatically preserve a designed metamaterial deformation mode.	Reinforced cell-bearing scaffolds and prospective biohybrid lattices. Verify component alignment, interface integrity and functional deformation.	Photocrosslink GelMA, then wash/exchange solvent and culture. Cell viability was slightly lower on day 1 than GelMA alone; longer-term proliferation/differentiation were supported.	Rodrigues et al., 2024 ⁷⁵

Abbreviations. BCC, body-centred cubic; BMSCs, bone marrow mesenchymal stromal cells; CAD, computer-aided design; CaP, calcium phosphate; CT, computed tomography; DLP, digital light processing; DMD, digital micromirror device; DMSO, dimethyl sulfoxide; FCC, face-centred cubic; FFF, fused filament fabrication; GelMA, gelatin methacryloyl; GO, graphene oxide; HA/nHA, hydroxyapatite/nanohydroxyapatite; hMSCs, human mesenchymal stromal cells; IPA, isopropyl alcohol; LCD, liquid crystal display; LPBF, laser powder bed fusion; MEX,

material extrusion; MSCs, mesenchymal stromal cells; PA12, polyamide 12; PBS, phosphate-buffered saline; PCL, polycaprolactone; PEEK, polyether ether ketone; PGMEA, propylene glycol methyl ether acetate; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); SC, simple cubic; SLA, stereolithography; TCP, tricalcium phosphate; TPMS, triply periodic minimal surface; VPP, vat photopolymerisation.

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4. 3D-Printed Metamaterials for Bone Tissue Engineering Scaffolds

Mechanical metamaterials are designed such that their macroscopic mechanical responses are governed predominantly by internal architecture and associated deformation mechanisms, thereby moving beyond conventional design strategies that regulate mechanical properties primarily through material composition and pore parameters. For bone tissue engineering scaffolds, spatially heterogeneous and anisotropic designs can impart region- and direction-dependent mechanical responses, whereas auxetic architectures modulate the mechanical state of both the scaffold and the bone-scaffold interface through characteristic transverse deformation. Nonlinear, multistable, and reconfigurable structures further exploit mechanisms such as buckling, rotation, contact, and state transitions to enable scaffold stiffness, deformation, and load transfer to evolve with loading conditions. These architecture-dominated mechanical responses expand the capacity of scaffolds to accommodate the complex mechanical characteristics of native bone, while further integration of bioactive components can extend their function from mechanical adaptation towards regenerative regulation. Accordingly, this section focuses on representative mechanical design strategies, including spatial heterogeneity and anisotropy, auxeticity, nonlinearity, multistability, and reconfigurability, together with the biological functionalisation of mechanical metamaterials, and discusses the structural mechanisms and recent advances of 3D-printed metamaterials in bone tissue engineering. In discussing these design strategies, we further distinguish computational and mechanical proof-of-concept studies, in vitro biological evaluations, and in vivo animal validation to reflect the current stage of biological validation achieved by different mechanical metamaterial strategies.

4.1. Spatially Heterogeneous and Anisotropic Metamaterials

Native bone exhibits pronounced spatial and directional dependence in its composition, microarchitecture, and mechanical properties, making conventional homogeneous periodic structures insufficient to reproduce its complex mechanical requirements. By spatially regulating microstructural topology and orientation, 3D-printed metamaterials can further modulate local load transfer, stress–strain distributions, and mass transport, thereby influencing cellular behaviour and bone regeneration⁸². Spatially heterogeneous designs generate region-specific mechanical and transport properties through local modulation of microstructural parameters, whereas anisotropic designs regulate load-bearing and deformation responses along different loading directions by controlling structural orientation and direction-dependent topology⁸³.

Spatially heterogeneous metamaterials primarily achieve region-specific mechanical and mass-transport properties through spatial variation in unit-cell size, geometry, and relative density. Zhang et al. modulated the dimensions and aspect ratios of Diamond-type unit cells and combined distinct microlattices into a hierarchical architecture containing trabecular-like and dense regions, thereby achieving regional regulation of elastic modulus and permeability and providing a structural basis for simultaneously accommodating local load-bearing and mass-transfer requirements⁸⁴ (Fig. 3A). In subsequent work, the same group developed pentamode metamaterials incorporating pore gradients and tapered struts. These structures increased permeability and cell-seeding efficiency while enhancing the expression of osteogenic markers, including COL I, RUNX2, and OCN, in BMSCs. In a rabbit femoral condyle defect model, they also promoted new bone formation, indicating that spatially heterogeneous design can improve cellular osteogenesis and tissue ingrowth by modulating the local mechanical and transport microenvironment⁸⁵. These approaches primarily generate regional differences in performance through predefined microstructural gradients. In the actual implantation environment, however, load distribution is also influenced by patient-specific anatomy, fixation configuration, and physiological loading. Spatially heterogeneous design has therefore begun to evolve towards structural configurations driven by local mechanical conditions. Heins et al. developed a patient-specific mandibular metamaterial reconstruction plate based on a Gyroid TPMS microarchitecture. By reducing local effective stiffness, the design improved load transfer to bone adjacent to the defect and mitigated stress shielding, although its failure load was reduced, indicating that local mechanical adaptation must still be balanced against overall load-bearing safety⁴⁷. The same group subsequently employed density-based topology optimisation to determine a spatially non-uniform density distribution according to patient-specific masticatory loads, fixation conditions, and implant loading states, thereby reducing stress concentrations within the implant and increasing load transfer to the surrounding bone⁴⁵. This strategy advances spatially heterogeneous design from predefined structural gradients towards region-specific property allocation driven by local mechanical conditions, thereby improving the capacity of scaffolds to accommodate spatial variations in the mechanical environment at the implantation site. Because the mechanical characteristics of native bone exhibit not only pronounced spatial heterogeneity but also strong directional dependence, anisotropic design represents a further important strategy for regulating the direction-dependent mechanical response of scaffolds.

The significance of anisotropic architectures lies not only in their ability to accommodate the direction-dependent mechanical characteristics of native bone, but also in their capacity to regulate load transfer, fluid flow, and nutrient transport along different directions through structural orientation and pore-channel geometry⁸⁶. Liu et al. constructed orthotropic TPMS architectures by modifying implicit functions, enabling distinct mechanical responses and fluid-transport characteristics along three orthogonal directions. Among these structures, the ratios of elastic moduli along the three orthogonal directions of the orthotropic Gyroid were comparable to those of trabecular bone, providing a structural basis for coordinating direction-dependent load bearing with local mass transport⁸⁷. Subsequent studies have begun to investigate how such direction-dependent architectures influence cellular behaviour and osteogenesis. Tian et al. constructed orthotropic scaffolds by modulating and integrating Schwarz P and Gyroid topologies. In addition to generating direction-dependent mechanical responses, these structures promoted the adhesion, proliferation, and osteogenic differentiation of MC3T3-E1 preosteoblasts. The observed biological effects were associated with cytoskeletal reorganisation and activation of the MEK/ERK and Wnt/ β -catenin signalling pathways, suggesting that structural anisotropy may further contribute to regulation of the osteogenic microenvironment⁸⁸ (Fig. 3B). With advances in computational design, anisotropic regulation is progressively shifting from simply generating directional differences in mechanical performance towards quantitative matching of the mechanical characteristics of target bone tissue. Wang et al. combined a backpropagation neural network with a genetic algorithm to inversely design aperiodic spinodoid architectures, achieving simultaneous matching of elastic responses along multiple directions⁸⁹. Beyond mechanical matching, direct evidence is also emerging for the relationship between anisotropic pore topology and osteogenic responses. Karali et al. developed Schwarz Diamond Ti6Al4V TPMS scaffolds with anisotropic pore topology and found that these structures not only supported the adhesion, proliferation, migration, and colonisation of MC3T3-E1 preosteoblasts but also promoted cellular maturation, osteogenic marker expression, and mineralisation, indicating that three-dimensional pore topology can further modulate the osteogenic microenvironment⁹⁰. Collectively, these studies indicate that the objective of anisotropic structural design is evolving from merely reproducing the direction-dependent mechanical characteristics of native bone towards coordinated regulation of directional load bearing and the osteogenic microenvironment.

In addition to the anisotropy intentionally introduced through structural topology and

orientation, additive manufacturing itself may also generate unintended anisotropic behaviour⁹¹. Hossain et al. investigated Ti6Al4V micro-struts fabricated by LPBF at different build angles and found that lower build angles were associated with greater surface roughness and more pronounced cross-sectional irregularities, while the yield strength exhibited clear directional dependence⁹². To address this issue, Karami et al. further demonstrated that laser scanning strategies can influence the fatigue behaviour of LPBF-fabricated Ti6Al4V lattices by modifying grain orientation and internal defects, whereas post-processing treatments including hot isostatic pressing, sandblasting, and chemical etching can further improve fatigue performance⁹³. Beyond process optimisation, appropriate selection of structural topology may also reduce the influence of additive manufacturing-induced anisotropy on the overall mechanical performance. Barber et al. compared the compressive responses of Ti6Al4V porous architectures tested along different orientations and found that Diamond structures exhibited more pronounced compressive anisotropy, whereas Schwarz D and Gyroid architectures showed relatively lower directional sensitivity⁹⁴. Collectively, these findings indicate that the direction-dependent mechanical behaviour of 3D-printed scaffolds is not determined solely by the prescribed topology, but arises from the combined effects of structural design and the manufacturing process. Accordingly, the design and application of mechanical metamaterials should jointly consider unit-cell topology, build orientation, and the principal loading direction at the implantation site to minimise the influence of manufacturing-induced anisotropy on the intended mechanical response and to improve consistency between the digital design and the mechanical performance of the as-fabricated structure.

Current evidence indicates that 3D-printed spatially heterogeneous and anisotropic metamaterials are evolving from predefined geometric gradients and directionally organised architectures towards precise structural configurations tailored to local loading conditions and the mechanical characteristics of target bone tissue¹⁰. The level of biological validation remains uneven across different design strategies. Spatially heterogeneous designs have been supported by *in vivo* evidence, whereas studies of anisotropic architectures remain focused primarily on computational and mechanical characterisation and *in vitro* cellular evaluation, with direct validation of their regenerative effects in animal bone-defect models still lacking^{85,88,90}. Future studies should further establish quantitative relationships among structural parameters, local mechanical and transport characteristics, and bone-regeneration outcomes, thereby advancing

heterogeneous and anisotropic metamaterials from mechanical biomimicry towards precision structural design for bone regeneration.

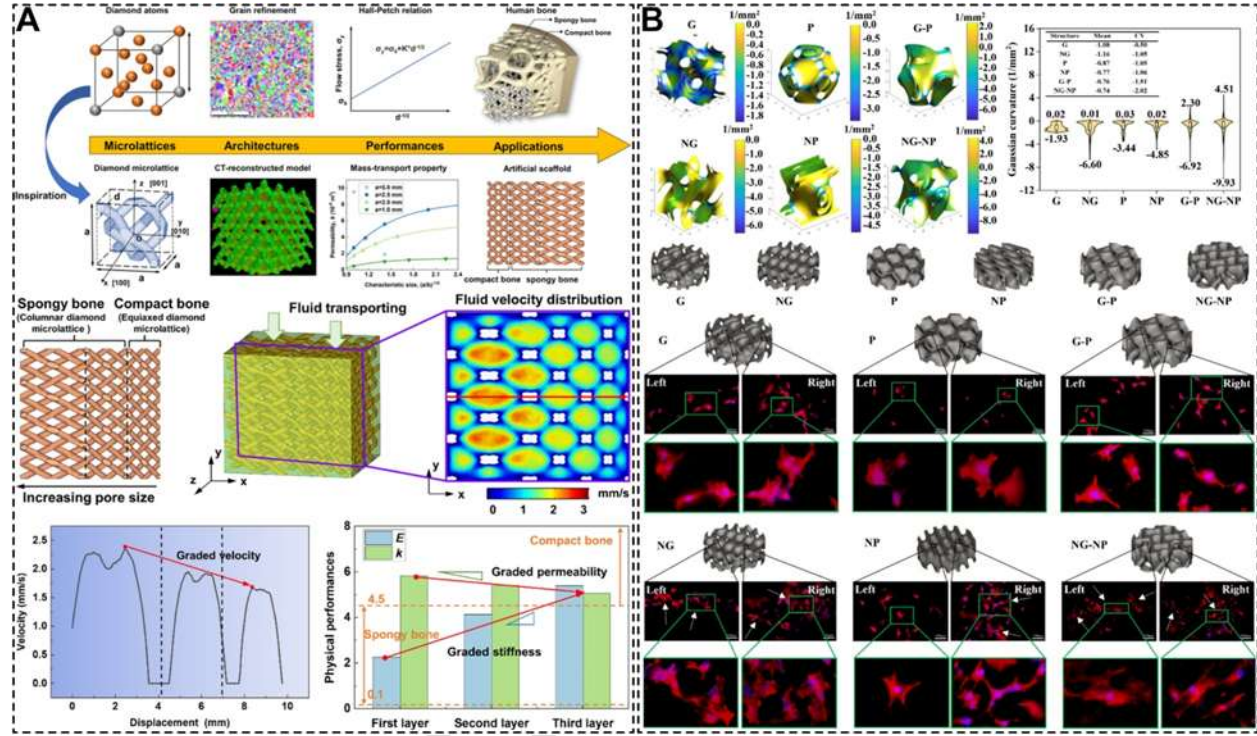


Figure 3. Structural design of spatially heterogeneous and anisotropic metamaterials and their mechanical and biological effects. (A) Inspired by the hierarchical organisation of cancellous and cortical bone, heterogeneous hierarchical structures were constructed by regulating the unit size, aspect ratio, and spatial arrangement of Diamond micro-lattices. This design enabled graded modulation of stiffness, permeability, and fluid velocity distributions across different regions, thereby balancing local load-bearing requirements with mass transport demands. Adapted from Zhang et al. ⁸⁴. Copyright 2022, Elsevier. (B) Anisotropic TPMS scaffolds were constructed through geometric modulation of Gyroid and Schwarz P topologies and their dual-topology fusion. Different topologies and their modified structures exhibited distinct Gaussian curvature distributions, which further influenced cell adhesion, spreading, and cytoskeletal organisation on the scaffold surface, demonstrating the regulatory role of anisotropic pore topology in the local osteogenic microenvironment. Adapted from Tian et al. ⁸⁸. Copyright 2026, Elsevier.

4.2. Auxetic Metamaterials

Auxetic metamaterials exhibit characteristic transverse deformation through unit-cell rotation, bending, or re-entrant deformation, expanding laterally under axial tension and contracting laterally under axial compression, thereby generating deformation modes distinct from those of conventional porous scaffolds^{10,95}. In bone tissue engineering, such deformation can not only regulate the effective stiffness and energy absorption of scaffolds, but also alter the contact state

between the implant and surrounding bone, local strain transfer, and the fluid environment within the pores, thereby modifying how external loads are transmitted to cells and newly formed tissue^{10,96}. Auxetic behaviour has also been observed in trabecular bone under specific loading and orientation conditions, and auxetic architectures have therefore been explored as a means of extending the capacity of scaffolds to accommodate the complex mechanical responses of native bone^{95,97}. However, auxeticity is not a universal or invariant material property of bone, and its magnitude is influenced by tissue architecture, loading direction, and strain level. Scaffold design should therefore not simply aim to maximise the magnitude of negative Poisson's ratio, but should instead focus on whether the local mechanical environment generated under physiological loading is favourable for bone regeneration.

With advances in additive manufacturing, complex re-entrant unit cells can now be fabricated with high geometric precision in three dimensions, allowing auxetic responses to be controllably tuned through geometric parameters. Yao et al. varied the re-entrant angle of three-dimensional re-entrant honeycomb unit cells to tune the structures across negative, near-zero, and positive Poisson's ratios, and verified their manufacturability using selective laser sintering. This work provided a structural basis for further investigating how scaffolds with different Poisson's ratios influence bone-cell and tissue responses⁷⁹. Building on this capability, subsequent studies have gradually shifted from the geometric realisation of auxeticity towards investigating its effects on cell adhesion, proliferation, and mechanotransduction. Jin et al. fabricated multiscale PCL auxetic scaffolds using melt electrowriting and showed that auxetic architectures could be integrated with microscale fibrous networks favourable for cellular colonisation⁹⁸. To further isolate the influence of Poisson's ratio itself on bone-cell behaviour, Yarali et al. computationally designed three-dimensional microarchitectures with Poisson's ratios ranging from -0.74 to +0.74 while maintaining pore size, porosity, and effective elastic modulus as similar as possible. All structures supported adhesion, infiltration, and osteogenesis-related responses of MC3T3-E1 preosteoblasts. Although the auxetic group showed trends towards increased RUNX2 expression and mineralisation, no clear statistically significant advantage was observed⁸¹. These findings indicate that differences in Poisson's ratio under static conditions are insufficient to directly determine osteogenic responses, and that the distinct biological effects of auxetic architectures may depend more strongly on their deformation under loading. On this basis, Geng et al. further evaluated cellular responses to structures with different re-entrant angles under cyclic compression and found

that the 75° auxetic scaffold promoted MC3T3-E1 cell proliferation and YAP nuclear translocation, suggesting that its dynamic deformation can contribute to the regulation of cellular mechanotransduction⁸⁰ (Fig. 4A).

Building on in vitro cellular studies, the effects of auxetic architectures on bone ingrowth and interfacial osseointegration have also been further evaluated in vivo. Wang et al. compared porous titanium bone screws with identical porosity but either auxetic or non-auxetic architectures and found higher BV/TV, trabecular number, and bone mineral density within the auxetic structures. Dynamic tensile loading further increased new bone formation and the mineral apposition rate around the auxetic bone screws⁹⁹ (Fig. 4B). These findings suggest that the characteristic deformation generated by auxetic structures under loading may help maintain mechanical stimulation at the bone–implant interface, thereby promoting bone ingrowth and osseointegration. However, these favourable interfacial mechanical effects did not translate into improved structural durability, as the fatigue strength of the auxetic structures was markedly lower than that of their non-auxetic counterparts⁹⁹. Optimisation of auxetic bone implants therefore requires a careful balance among osseointegration, structural strength, and fatigue life. Kolken et al. investigated additively manufactured auxetic titanium metamaterials under cyclic loading and found that their fatigue behaviour was strongly dependent on microstructural design, with cracks preferentially initiating and propagating in local high-strain regions around re-entrant nodes and peripheral struts^{100,101}. Future design should therefore move beyond optimisation of Poisson’s ratio alone towards precise regulation of the local mechanical environment under loading. While controlling pore architecture and overall stiffness, it will be necessary to clarify the relationships between structural deformation, cellular mechanotransduction, osteogenic differentiation, and in vivo new bone formation, while simultaneously optimising fatigue performance and long-term structural stability. Such an approach may establish auxeticity as a controllable structural design parameter tailored to the requirements of bone regeneration.

Collectively, current evidence indicates that research on auxetic metamaterials is shifting from the regulation of deformation itself towards understanding the relationships among auxetic responses, osteocellular mechanosensing, interfacial osseointegration, and long-term load-bearing stability^{10,95}. Existing in vitro studies suggest that, under dynamic loading, auxetic architectures can modulate cellular responses such as proliferation and YAP nuclear translocation, whereas in vivo evidence indicates their potential to improve bone ingrowth and interfacial integration. The role of auxeticity in bone repair is therefore likely to depend more strongly on the local mechanical responses generated under loading than

on Poisson's ratio alone. Future studies should further establish quantitative relationships between structural deformation and bone-regeneration outcomes while simultaneously accounting for structural strength and fatigue life, thereby defining an auxetic design window appropriate for bone regeneration.

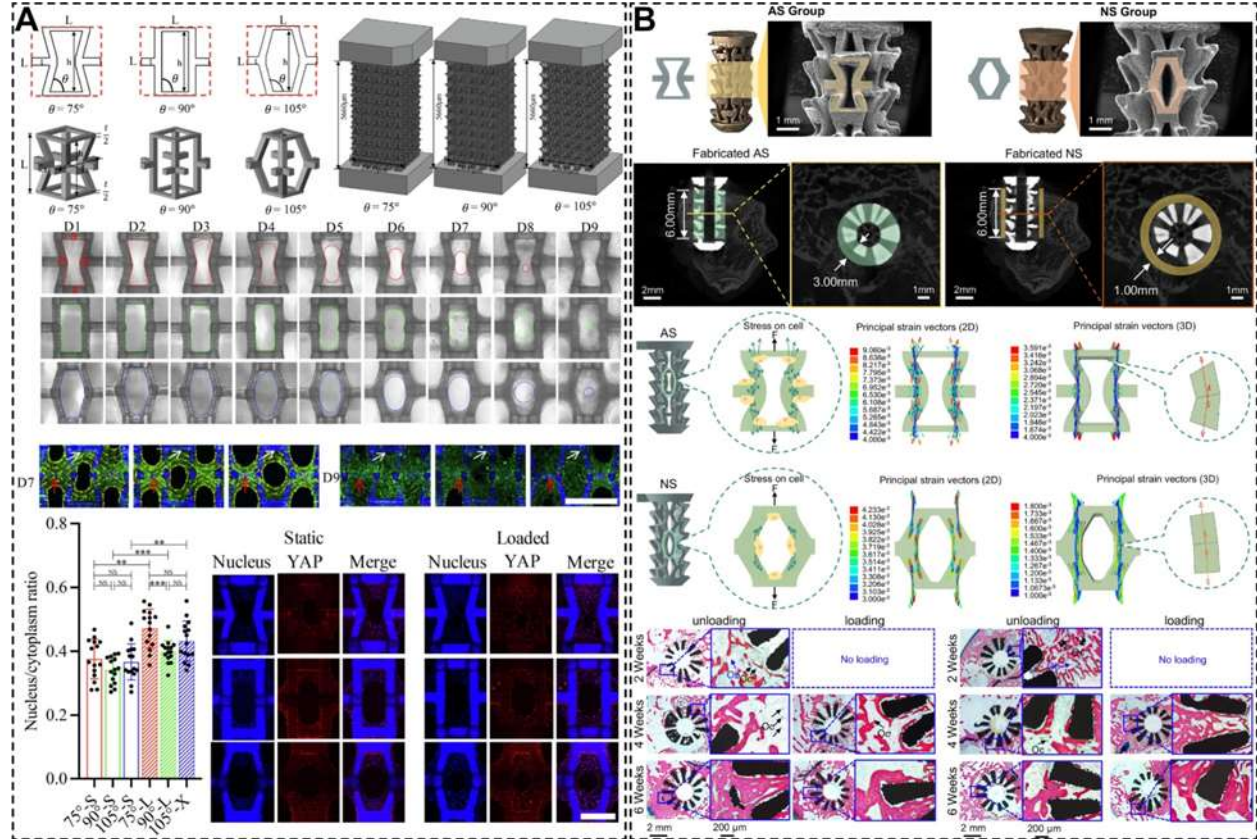


Figure 4. Dynamic deformation, cellular mechanotransduction, and in vivo osseointegration effects of 3D-printed auxetic metamaterials. (A) Scaffolds with different Poisson's ratio responses were constructed by regulating the re-entrant angle of three-dimensional re-entrant honeycomb unit cells, and their continuous deformation behaviour was examined during cyclic compression. Compared with near-zero- or positive-Poisson's-ratio structures, the 75° auxetic scaffold exhibited characteristic lateral contraction under loading and promoted cytoskeletal responses and YAP nuclear translocation in MC3T3-E1 cells, indicating that the dynamic deformation of auxetic structures can regulate cellular mechanotransduction. Adapted from Geng et al.⁸⁰. Copyright 2025, Elsevier. (B) Structural design, in vivo bone ingrowth, and local mechanical environment of the auxetic screw (AS) and non-auxetic screw (NS). Micro-CT revealed distinct patterns of bone ingrowth within the two implants, while finite element analysis further demonstrated differences in the magnitude and orientation of principal strain under loading. Histological evaluation showed that the auxetic structure, in combination with dynamic mechanical loading, promoted new bone formation and interfacial osseointegration around the implant, suggesting that its characteristic deformation can modulate the bone regenerative microenvironment by altering local strain transfer. Adapted from Wang et al.⁹⁹. Copyright 2023, Elsevier.

4.3. Nonlinear, Multistable, and Reconfigurable Metamaterials

Nonlinear mechanical metamaterials exploit structural mechanisms such as bending, buckling, contact, and rotation to enable stiffness and deformation modes to vary with loading level¹⁰². Multistable structures employ instability-driven transitions to establish multiple stable configurations and can switch between distinct mechanical states under external loading¹⁰³. Reconfigurable structures, in contrast, alter their overall configuration through predefined kinematic degrees of freedom, enabling functions such as deployment, contraction, and morphological adaptation¹⁰⁴. These structural responses expand the capacity of 3D-printed scaffolds to accommodate different loading states and complex bone-defect geometries, while providing additional structural design routes for regulating the local mechanical environment.

Load-dependent changes in stiffness and deformation represent an important application of nonlinear design in bone repair. To address the relatively fixed stiffness of conventional fracture fixation devices, Hashemi et al. developed a 3D-printed tunable-stiffness metamaterial fixation structure with a two-stage mechanical response. Under low loads, deformation was primarily accommodated by the peripheral compliant elements, whereas closure of the internal gap brought structural components into contact and markedly increased the overall stiffness, thereby limiting further deformation¹⁰⁵. This study demonstrated the feasibility of using geometric contact to regulate mechanical responses across different loading stages, although direct evaluation of bone-related biological effects was not performed. Taleb Alashkar et al. increased the curvature of interlayer connecting walls along the scaffold height, transforming carbonate apatite scaffolds from global instability to sequential layer-by-layer collapse. The graded curved walls simultaneously reduced flow velocity within the pores and generated wall shear stress distributions more favourable for cell adhesion and early proliferation, while more pronounced new bone formation was observed at both 4 and 12 weeks after implantation¹⁰⁶ (Fig. 5A). These findings indicate that nonlinear scaffold deformation can simultaneously regulate load-bearing behaviour and local fluid stimulation, thereby modifying the mechanical microenvironment relevant to bone regeneration. When instability generates multiple configurations that can remain mechanically stable, the structural response can extend from continuous load-dependent variation to transitions between distinct stable states, thereby giving rise to multistability. Liang et al. used topology optimisation to tune the critical instability forces of bistable curved-beam units and combined units with different instability thresholds, enabling 3D-printed structures to sequentially cross multiple

predefined load thresholds and undergo successive state transitions during compression. This approach achieved staged and programmable mechanical responses¹⁰⁷ (Fig. 5B). Xiu et al. further coupled bistable mechanisms with topological state transitions in Maxwell lattices, such that different stable configurations exhibited markedly different boundary stiffnesses, providing a new strategy for reversible regulation of structural mechanical states¹⁰⁸. At the biological level, Wang et al. demonstrated that three-dimensional microtissues formed by mesenchymal cells could induce snap-through instability in 3D-printed metamaterials through their intrinsic contractile forces, while distinct structural states were accompanied by pronounced differences in tissue morphology and cellular alignment¹⁰⁹. These findings show that endogenous cellular forces can actively participate in metamaterial state transitions and suggest that multistable structures may regulate the local mechanical microenvironment through reciprocal interactions with cellular mechanical behaviour. Existing studies have therefore begun to reveal bidirectional mechanical coupling between living tissues and instability-based metamaterials, although whether distinct stable states and their transition processes generate differential cellular mechanical environments and subsequently influence osteogenic differentiation and new bone formation remains to be established.

Building on the ability of multistable structures to switch between different stable configurations, reconfigurable metamaterials further extend local state changes to regulation of the overall implant morphology, enabling printed structures to actively adapt to complex bone defects during implantation. Kolken et al. introduced a plastically deformable porous outer layer into additively manufactured acetabular implants, allowing local deformation during press-fit insertion, with functionally graded designs exhibiting improved defect conformity¹¹⁰. Leeftang et al. further developed deployable implants using integrally printed kinematic mechanisms, enabling the implant to enter the defect in a compact configuration and subsequently transform into an expanded, load-bearing state after implantation¹¹¹. de Jong et al. employed multi-degree-of-freedom joint networks to achieve continuous adaptation to both singly and doubly curved surfaces, demonstrating that reconfigurable design has progressed from simple dimensional expansion towards conformity with complex anatomical geometries¹¹² (Fig. 5C). Such structures may reduce geometric mismatch between the implant and defect boundaries, improve interfacial contact and defect-space occupancy, and thereby provide more favourable structural conditions for subsequent tissue ingrowth. Recent studies have begun to further evaluate the performance of reconfigurable

scaffolds in bone-regenerative environments. Choudhury et al. combined configurational adaptation with direct assessment of bone regeneration by developing a near-infrared-responsive 3D-printed self-adapting scaffold. In vitro experiments showed that the scaffold increased ALP secretion and mineral deposition, indicating favourable osteogenic support. In a rabbit critical-sized calvarial defect model, the pre-compressed scaffold recovered its original configuration after near-infrared stimulation and conformed to the defect boundary, while micro-CT analysis demonstrated near-complete osseous repair at 12 weeks¹¹³. These studies indicate that reconfigurable metamaterials can not only improve morphological adaptation to complex bone defects, but also support subsequent osteogenesis and new bone formation while maintaining structural conformity, thereby expanding their potential applications in bone tissue engineering.

Current evidence indicates marked differences in the level of validation among nonlinear, multistable, and reconfigurable metamaterials. Nonlinear architectures have progressed from computational and mechanical validation towards in vivo evaluation of bone formation, whereas multistable designs remain largely at the stage of mechanical proof-of-concept and in vitro investigation of interactions with living tissues, with their direct effects on osteogenic differentiation and new bone formation yet to be established. By contrast, reconfigurable architectures have advanced from mechanical shape adaptation to in vitro osteogenic evaluation and animal bone-defect repair. Future studies should further distinguish the effects arising from structural responses themselves from those attributable to material bioactivity, while simultaneously examining local mechanical stimulation after state transitions, fatigue stability, and the influence of tissue ingrowth on structural motion. These considerations will be essential for defining the appropriate application domains of different dynamic metamaterial architectures in bone repair.

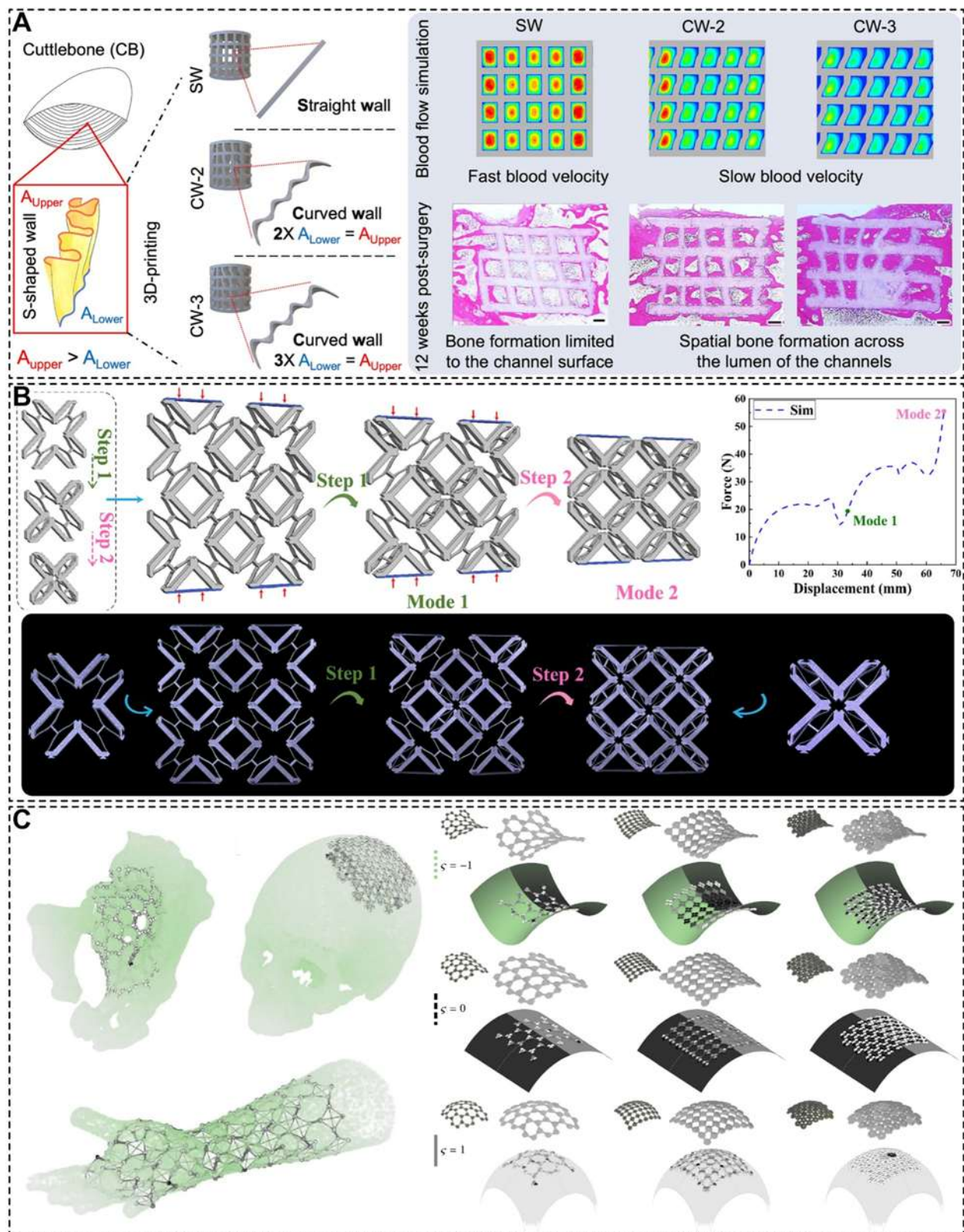


Figure 5. Dynamic structural responses and shape adaptability of nonlinear, multistable, and reconfigurable metamaterials. (A) Inspired by the hierarchical architecture of cuttlebone, nonlinear carbonate apatite scaffolds were constructed using wall structures with different curvatures. Compared with straight-wall structures, scaffolds with progressively curved walls exhibited

sequential layer-by-layer collapse during compression rather than global structural failure. Structural deformation also altered the distribution of blood flow velocity within the internal channels and promoted spatially distributed bone formation within the defect, demonstrating the capacity of nonlinear deformation to modulate the local mechanical environment and bone regeneration. Adapted with permission from Taleb Alashkar et al. ¹⁰⁶. Copyright 2026, Elsevier. (B) Multistable metamaterials were constructed using bistable unit cells with precisely tailored instability thresholds. By integrating bistable cells with different critical snap-through loads, the 3D-printed structures underwent sequential snap-through transitions under external compression, enabling programmable switching between multiple stable configurations. Adapted with permission from Liang et al. ¹⁰⁷. Copyright 2023, Elsevier. (C) Reconfigurable metallic metamaterials were constructed from networks of kinematic units, in which structural degrees of freedom enabled shape transformation from an initially planar configuration into single- and doubly-curved surfaces. Such structures can conform to complex three-dimensional surfaces and improve geometric matching between implants and irregular anatomical defects, providing a potential design strategy for dynamically shape-adaptive bone repair implants. Adapted from de Jong et al. ¹¹². Copyright 2025, Elsevier.

4.4 Biological Functionalisation of Metamaterials

The structural design of metamaterials can regulate scaffold effective stiffness, load transfer, and mass-transport characteristics through unit-cell topology and associated deformation modes. However, bone defect repair is also governed by multiple biological factors, including osteogenic induction, vascularisation, infection control, and the local biochemical microenvironment¹¹⁴. Structural regulation alone is therefore insufficient to meet the regenerative requirements of complex bone defects. Incorporating bioactive components, such as functional ions, growth factors, and therapeutic agents, into mechanical metamaterials and related 3D-printed architectures can preserve their structural mechanical functions while endowing scaffolds with the capacity to directly modulate cellular responses and the local regenerative microenvironment. The highly interconnected porous architectures and large effective surface areas of these systems also provide a structural basis for compositional incorporation, surface immobilisation, and local delivery of bioactive components, thereby enabling coordinated integration of structural design and biological regulation within a single scaffold¹¹⁵.

Functional ions represent a relatively direct strategy for the biological functionalisation of metamaterials. Their principal advantage lies in the potential for sustained release through bulk material composition or surface coatings, while avoiding the limited stability commonly associated with protein-based factors¹¹⁶. Shan et al. fabricated Sr-doped β -TCP Gyroid TPMS scaffolds and found that increasing Sr content enhanced ALP activity, matrix mineralisation, and the expression of RUNX2 and OCN in MC3T3-E1 cells. In a rat femoral condyle defect model, the 10Sr-TCP group exhibited the highest BV/TV and BMD, together with increased OPN expression and a

greater number of CD31-positive vessels, indicating that sustained Sr^{2+} release can further enhance vascularised osteogenesis on the basis of the cell- and vessel-ingrowth capacity provided by TPMS channels¹¹⁷ (Fig. 6A). Beyond providing sustained ionic stimulation through compositional doping, degradable metals can also directly contribute to the functional behaviour of metamaterials. Qin et al. constructed a metallic metamaterial consisting of a Zn primary structure and Mg constraining elements, in which shape recovery was driven by Mg degradation. Mg degradation increased the local Mg^{2+} concentration, while material extracts enhanced MC3T3-E1 mineralisation and promoted HUVEC migration. As the Mg constraints gradually disappeared, structural recovery generated additional sustained mechanical stimulation. In a rabbit femoral defect model, the Zn-Mg group formed denser newly generated trabecular bone and achieved superior bone regeneration compared with control structures without shape recovery, demonstrating that bioactive ion release can act synergistically with the dynamic structural behaviour of metamaterials to regulate bone regeneration¹¹⁸ (Fig. 6B). These findings indicate that integrating functional ions with metamaterials should not be viewed merely as a means of enhancing the intrinsic osteogenic activity of the material. More importantly, ion dosage and release kinetics should be coordinated with structural characteristics so that biochemical stimulation can act synergistically with the mechanical and spatial microenvironments provided by the metamaterial architecture.

Beyond functional ions, growth factors and therapeutic agents can also be integrated with metamaterials, extending structural mechanical functionality towards osteogenic induction and infection control. Lee et al. incorporated magnesium-decorated nanospiked hydroxyapatite and adhesive DNA into 3D-printed PLA scaffolds, enabling modulation of mechanical and degradation properties while simultaneously providing antibacterial and antitumour activity and promoting angiogenesis and osteogenesis¹¹⁹. These findings demonstrate that coordinated design of material composition and functional components can simultaneously regulate the physical properties, therapeutic activity, and regenerative performance of printed scaffolds. When extended to mechanical metamaterials, this functionalisation strategy can exploit their complex porous architectures and large effective surface areas to integrate growth factors and therapeutic agents, thereby expanding structural mechanical functionality towards osteogenic induction and infection control. Amin Yavari et al. developed a functional coating on the surface of 3D-printed Gyroid titanium metamaterials and simultaneously incorporated BMP-2 and antibiotics, both of which exhibited sustained release for approximately 2-3 weeks. BMP-2 increased ALP activity in

mesenchymal stem cells by approximately twofold and enhanced matrix mineralisation by up to approximately fourfold, whereas antibiotic loading reduced the numbers of both planktonic and scaffold-adherent bacteria by up to approximately eight orders of magnitude and effectively prevented biofilm formation¹²⁰. These findings demonstrate that the large effective surface area of metamaterials not only facilitates cell and tissue interactions but can also support the integration of bioactive components with distinct biological functions, thereby simultaneously enhancing osteogenic and antibacterial performance. More advanced designs have begun to exploit the spatial architecture of metamaterials to regulate the temporal actions of different bioactive components. Zhao et al. developed a graded TPMS titanium scaffold in which antibiotics were predominantly localised to the peripheral region, whereas BMP-2 was incorporated within the interior, enabling sustained antibacterial release during the early stage while relatively delaying BMP-2 release. In a rabbit model of infected calvarial defects, the composite scaffold reduced local infection while promoting greater new bone formation. Newly formed bone extended from the scaffold surface into the internal pores, with both bone coverage and ingrowth depth exceeding those observed in scaffolds lacking the corresponding bioactive components¹²¹. These findings indicate that graded architectures can serve not only as carriers for bioactive agents but also as spatially organised delivery platforms capable of coordinating different therapeutic functions over time, thereby aligning early infection control with subsequent bone formation during the repair of infected bone defects. The combined incorporation of multiple regulators of bone metabolism can further expand this biological functionality. Yan et al. co-delivered BMP-2 and an anti-resorptive agent within 3D-printed Gyroid scaffolds and found increased expression of the osteogenic markers COL1 and OCN, together with enhanced angiogenic marker expression and migratory activity in endothelial cells¹²². These findings indicate that integrating bioactive components with distinct biological functions into metamaterial architectures can further regulate osteogenesis, bone resorption, and angiogenesis while the underlying structure provides space for tissue ingrowth and mechanical support. Current studies also suggest that such strategies are evolving from simply increasing bioactive-agent loading towards exploiting metamaterial surface area, pore distribution, and spatial compartmentalisation to regulate local biological activity, thereby establishing more direct synergy between structural design and biological function.

Current evidence indicates that the biological functionalisation of mechanical metamaterials and related 3D-printed architectures is evolving from the simple loading of bioactive components

towards the coordinated design of architecture, material composition, and delivery behaviour¹². Some functionalised strategies have progressed from in vitro cellular evaluation to validation in animal bone-defect models, but the overall evidence remains predominantly preclinical, and the respective contributions of structural effects and bioactive components have not yet been fully disentangled. Early studies mainly exploited the large surface area of metamaterials to support functional coatings, while the structural architecture and bioactive components remained relatively independent in terms of function. Accordingly, future design should move beyond simply increasing the loading capacity of bioactive agents and instead simultaneously consider unit-cell topology, local surface area, pore connectivity, and the dosage and release windows of bioactive components, so that biochemical regulation can be matched to the evolving mechanical and biological requirements of different stages of bone repair¹²³. Representative mechanical metamaterial architectures and their corresponding levels of biological validation are summarised in Table 2.

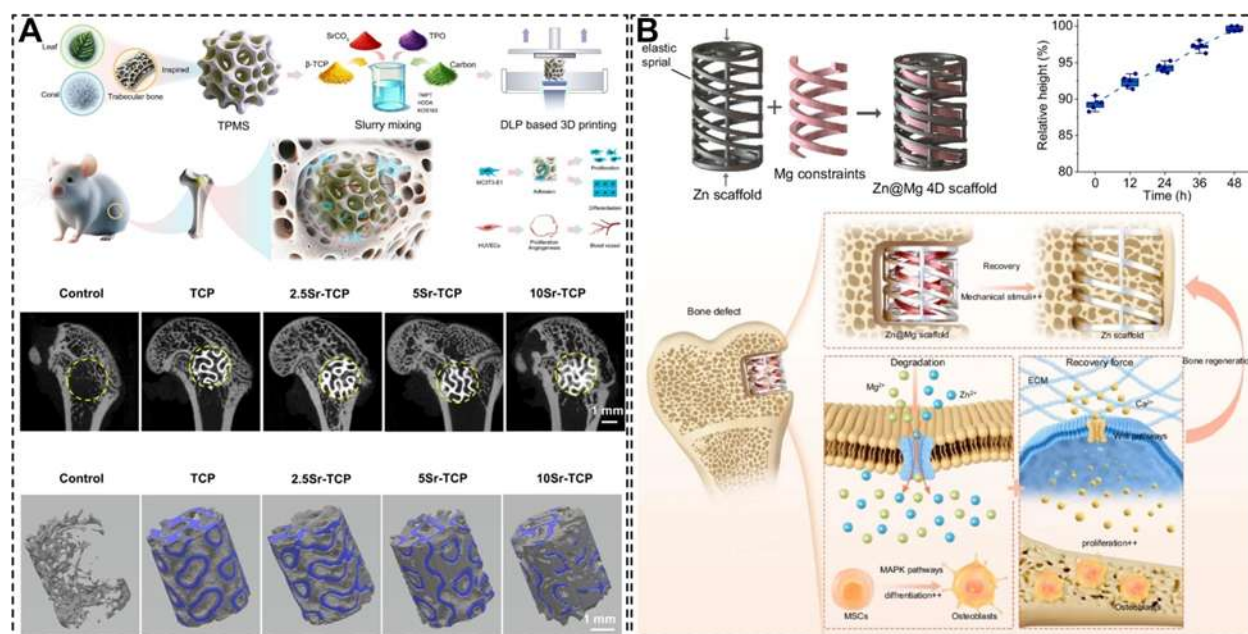


Figure 6. Biofunctionally integrated metamaterials promote bone regeneration through ionic regulation and dynamic structural responses. (A) Construction and vascularised osteogenic effects of Sr-incorporated β -TCP Gyroid TPMS bioceramic metamaterials. Incorporation of Sr^{2+} into a TPMS architecture with continuously interconnected pores enables the integration of bioactive ion release with a biomimetic porous geometry. Sr-TCP metamaterials promote MC3T3-E1 cell adhesion, proliferation, and osteogenic differentiation while enhancing the angiogenic activity of HUVECs. In a bone defect model, the Sr-functionalised TPMS scaffolds further enhanced vascularised new bone formation and bone defect filling, demonstrating the synergistic regulation of bone regeneration by bioactive ionic cues and architected porosity. Adapted from Shan et al.¹¹⁷. Copyright 2025, Oxford University Press. (B) An Mg-constrained Zn 4D bone scaffold was constructed using biodegradable metallic metamaterials. Progressive degradation of the Mg constraint released Mg^{2+} and gradually removed the structural confinement, allowing the pre-deformed Zn scaffold to recover its original geometry while generating sustained mechanical stimulation. Within the bone defect microenvironment, this dynamic metamaterial integrates ionic regulation, structural recovery, and mechanical stimulation to promote mesenchymal stem cell osteogenic differentiation and new bone formation. Adapted with permission from Qin et al.¹¹⁸. Copyright 2026, Springer Nature.

Table 2 Representative mechanical metamaterials and related architected scaffolds

Metamaterial category	Representative unit-cell / topological design	Constituent material	Fabrication method	Key mechanical mechanism / property	Validation level / Biological model	Intended function in bone repair	Major outcome	Reference
Heterogeneous / anisotropic	Graded pentamode lattice with tapered struts	Ti6Al4V	LPBF (SLM)	Porosity gradients and strut tapering jointly tune stiffness and permeability.	In vitro + in vivo; BMSCs; Rabbit femoral condyle defects (4 and 12 weeks).	Coordinate load support, cell seeding and bone ingrowth.	Improved permeability and cell-seeding efficiency; increased osteogenic markers and new bone formation relative to uniform designs.	Zhang et al. (2023) ⁸⁵
Heterogeneous / anisotropic	Orthotropic hybrid Schwarz P-Gyroid TPMS	Ti6Al4V	LPBF (SLM)	Topology fusion produces direction-dependent mechanical responses and pore geometry.	In vitro; MC3T3-E1 preosteoblasts.	Combine directional mechanical adaptation with an osteogenic microenvironment.	Supported adhesion, proliferation and osteogenic differentiation; associated with cytoskeletal reorganisation and MEK/ERK and Wnt/ β -catenin signalling.	Tian et al. (2026) ⁸⁸
Heterogeneous / anisotropic	Schwarz Diamond TPMS; unit-cell sizes 2.5-3.0 mm	Ti6Al4V ELI	LPBF	Asymmetric tension–compression response; compressive modulus 14-20 Gpa and tensile modulus 38-55 Gpa across tested designs.	In vitro; MC3T3-E1 preosteoblasts.	Provide cortical-bone-oriented mechanical support and a cell-accessible pore network.	Supported adhesion, migration, maturation and mineralisation; linked pore topology with mechanical asymmetry and early osteogenic responses.	Karali et al. (2025) ⁹⁰
Auxetic	3D re-entrant and non-auxetic microarchitectures with controlled Poisson's ratios	IP-Q methacrylate photoresist	Two-photon polymerisation	Designed Poisson's ratio -0.74 to $+0.74$; pore size, porosity and effective modulus controlled as closely as practicable.	In vitro; MC3T3-E1 preosteoblasts under static culture.	Isolate the influence of transverse deformation on bone-cell responses.	All designs supported cellular attachment and infiltration. Higher RUNX2/mineralisation trends in auxetic structures did not establish a statistically significant osteogenic advantage.	Yarali et al. (2024) ⁸¹
Auxetic	Re-entrant lattices with varied re-entrant angles	Biocompatible RG photopolymer	Micro-SLA (VPP)	Angle-dependent auxetic deformation and compressive response under cyclic loading.	In vitro; MC3T3-E1 preosteoblasts under cyclic compression.	Transmit dynamic mechanical cues to osteogenic cells.	The 75° auxetic design enhanced proliferation and YAP nuclear translocation under cyclic compression; in vivo bone repair was not evaluated.	Geng et al. (2025) ⁸⁰
Auxetic	Re-entrant porous bone screw; non-auxetic control at matched 51% porosity	Ti6Al4V	LPBF (SLM)	Negative Poisson's ratio modifies interfacial strain transfer; fatigue strength approximately 43% below the non-auxetic control.	In vivo; Rabbit femoral condyle implantation; With/without dynamic tensile loading.	Improve bone ingrowth and screw osseointegration.	Higher BV/TV, trabecular number and BMD; tensile loading further enhanced bone formation and mineral apposition. Improved integration accompanied reduced fatigue resistance.	Wang et al. (2023) ⁹⁹
Nonlinear	Compliant peripheral arms surrounding a contact-closing internal gap in a bone rod	17-4 PH stainless steel	Metal powder-bed fusion (ProX 300)	Gap closure activates a mechanical stop and a stiffer load-bearing stage; measured stiffness ratio approximately 3.8.	Computational + mechanical; Finite-element analysis and mechanical tests.	Allow low-load micromotion while limiting excessive deformation during fracture fixation (proposed).	Demonstrated two-stage stiffness and geometry-based tunability; fracture healing and biological benefit were not tested.	Hashemi et al. (2021) ¹⁰⁵
Nonlinear	Cuttlebone-inspired layered scaffold with progressively curved connecting walls	Carbonate apatite	VPP of CaCO ₃ precursor; heat treatment and hydrothermal conversion	Curved walls promote sequential layer-by-layer collapse rather than global failure; geometry also modifies flow and wall shear.	Computational + in vitro + in vivo; MC3T3-E1 cells; Rabbit femoral condyle defects (4 and 12 weeks).	Combine controlled collapse with a pore environment favourable for bone formation.	Curved-wall designs supported early cellular responses and greater new bone formation at both implantation times; flow effects were assessed computationally.	Taleb Alashkar et al. (2026) ¹⁰⁶

Metamaterial category	Representative unit-cell / topological design	Constituent material	Fabrication method	Key mechanical mechanism / property	Validation level / Biological model	Intended function in bone repair	Major outcome	Reference
Multistable	Arrays of topology-optimised bistable curved-shell cells	Nylon	Multi Jet Fusion	Prescribed instability thresholds generate sequential snap-through and multiple stable configurations.	Computational + mechanical; Finite-element analysis and quasi-static mechanical tests.	Provide staged structural switching for future adaptive support (proposed).	Validated designed snapping sequences and programmable multistability; no osteogenic or bone-defect evidence.	Liang et al. (2023) ¹⁰⁷
Instability-based / multistability-related	Octet-truss and re-entrant bowtie microarchitectures	SZ2080 organic-inorganic hybrid photoresist	Multiphoton lithography	Cell-generated contraction induces architecture-dependent buckling and snap-through.	In vitro; Human iPSC-derived mesenchymal stromal cell microtissues.	Explore reciprocal tissue–structure mechanical interactions relevant to adaptive scaffolds.	Demonstrated tissue-driven structural instability and distinct tissue morphology/cell alignment. Osteogenesis and stable-state-dependent bone repair were not established.	Wang et al. (2022) ¹⁰⁹
Reconfigurable	Non-assembly bicapped cube and antiprism deployment mechanisms	Ti6Al4V ELI	LPBF (SLM)	Integrated moving joints convert compact configurations into expanded load-bearing structures.	Mechanical; Deployment and compression testing.	Enable compact insertion and subsequent filling of large bone defects (proposed).	Demonstrated deployable metal mechanisms and post-deployment load support; biological integration and bone regeneration were not assessed.	Leeflang et al. (2021) ¹¹¹
Reconfigurable / 4D-responsive	Pre-compressed shape-memory porous scaffold with NIR-triggered self-fitting	PLMC copolymer with polydopamine nanoparticles	Melt-extrusion 3D printing; shape programming	Photothermal shape recovery >99% within 30 s under tested NIR conditions.	In vitro + ex vivo + in vivo; Primary hMSCs; Rabbit critical-sized calvarial defect model.	Conform to irregular defect boundaries and support bone regeneration.	Enhanced ALP and mineral deposition versus neat PLMC; near-complete bone regeneration at 12 weeks by micro-CT. Material bioactivity and self-fitting act together.	Choudhury et al. (2024) ¹¹³
Reconfigurable / biofunctional	Pre-deformed elastic Zn body with a degradable Mg constraint; stretching-type scaffold	Zn–1Mg body and WE43 Mg-alloy constraint	Separate LPBF fabrication followed by assembly	Preferential Mg degradation releases the constraint, driving shape recovery and sustained mechanical stimulation.	In vitro + in vivo; MC3T3-E1 cells; HUVECs; Rabbit femoral condyle defect model (6 weeks).	Couple endogenous shape recovery with osteogenic/angiogenic ionic cues.	Enhanced mineralisation and endothelial migration in extract assays; denser trabeculae and greater bone regeneration than non-recovering controls in vivo.	Qin et al. (2026) ¹¹⁸
Biofunctionally integrated	Gyroid TPMS with controlled Sr substitution	Sr-doped β -TCP (0–10 mol% Sr)	DLP (VPP), debinding and sintering	Interconnected architecture provides structural support and transport pathways; Sr release adds biochemical activity.	In vitro + in vivo; MC3T3-E1 cells; HUVECs; Rat femoral condyle defects.	Promote vascularised bone regeneration through topology and ion delivery.	10Sr-TCP showed the highest BV/TV and BMD among tested groups, with increased osteogenic markers and CD31-positive vessels.	Shan et al. (2025) ¹¹⁷
Biofunctionally integrated	Sheet Gyroid TPMS with layer-by-layer bioactive coatings	Commercially pure Ti; gelatin/chitosan; BMP-2 and vancomycin	LPBF (SLM); layer-by-layer coating	Porous architecture provides a coating carrier; functionalisation adds controlled release rather than a demonstrated new deformation mode.	In vitro + in vivo; MSCs; Staphylococcus aureus; Rat subcutaneous implantation model (8 weeks).	Combine osteogenic stimulation, antibacterial protection and tissue ingrowth.	Release over 2–3 weeks; approximately 2-fold ALP and up to 4-fold mineralisation increases; up to 8-log bacterial reduction. In vivo endpoint was connective-tissue ingrowth, not bone-defect repair.	Amin Yavari et al. (2020) ¹²⁰
Biofunctionally integrated	Graded TPMS with peripheral antibiotic delivery and internal BMP-2 localisation	Ti6Al4V; GelMA; antibiotic-loaded PLGA microspheres; BMP-2	LPBF (SLM); spatial loading of drug carriers and hydrogel	Spatially graded architecture supports compartmentalised delivery and load support; release timing is coordinated by carrier placement.	In vitro + in vivo; MC3T3-E1 cells; antibacterial assays; Rabbit infected calvarial defect model.	Coordinate early infection control with subsequent osteogenesis.	Reduced infection and increased new bone coverage and ingrowth relative to scaffolds lacking the corresponding active components.	Zhao et al. (2025) ¹²¹

Abbreviations: ALP, alkaline phosphatase; BMD, bone mineral density; BMP-2, bone morphogenetic protein-2; BMSCs, bone marrow mesenchymal stromal cells; BV/TV, bone volume/total volume; DLP, digital light processing; ELI, extra-low interstitial; GelMA, gelatin methacryloyl; hMSCs, human mesenchymal stromal cells; HUVECs, human umbilical vein endothelial cells; iPSC, induced pluripotent stem cell; LPBF, laser powder-bed fusion; MSCs, mesenchymal stromal cells; NIR, near-infrared; PLGA, poly(lactic-co-glycolic acid); PLMC, polylactide-co-trimethylene carbonate; RUNX2, runt-related transcription factor 2; SLA, stereolithography; SLM, selective laser melting; β -TCP, beta-tricalcium phosphate; TPMS, triply periodic minimal surface; VPP, vat photopolymerisation; YAP, Yes-associated protein.

5. Time-Dependent Mechanical Evolution of Degradable Metamaterial Scaffolds

The mechanical behaviour of degradable bone-repair scaffolds evolves continuously after implantation¹²⁴. Ideally, the mechanical support provided by the scaffold should progressively decrease as bone formation proceeds, thereby maintaining temporal coordination between initial post-implantation stability and the gradual replacement of the scaffold by newly formed bone tissue¹²⁵. Previous studies have shown that excessively rapid degradation can compromise scaffold structural integrity before sufficient tissue replacement has occurred. Liu et al. reported substantial loss of structural integrity in 3D-printed WE43 porous scaffolds during both in vitro immersion and in vivo implantation¹²⁶. This issue is particularly critical for mechanical metamaterials because their macroscopic mechanical responses are governed predominantly by local topology and specific deformation mechanisms. Degradation-induced strut thinning, wall damage, node failure, and disruption of structural connectivity can not only reduce overall stiffness and strength but also alter architecture-dominated mechanical responses, including buckling, contact interactions, auxetic behaviour, and configuration transitions^{10,127}. Aghabarari et al. systematically evaluated the structural and mechanical evolution of PLA/PEG/Mg metamaterial scaffolds during degradation and found that void formation, interlayer damage, and disruption of load paths were accompanied by substantial reductions in compressive modulus and strength. These findings further demonstrate that material degradation can reshape architecture-dominated mechanical responses through progressive microstructural evolution¹²⁸.

Compared with conventional porous scaffolds, mechanical metamaterials require greater attention to the time-dependent evolution of their mechanical behaviour during degradation. Because their distinctive mechanical responses arise from unit-cell geometry and coordinated deformation, even localised or early-stage degradation may alter characteristic dimensions and structural connectivity, thereby shifting the prescribed mechanical response¹⁰. Shi et al. investigated auxetic mechanical metamaterials fabricated from Zn and demonstrated configuration-dependent differences in degradation and mechanical evolution, with some configurations even exhibiting transient increases in elastic modulus or yield strength during degradation¹²⁷. These findings indicate that the time-dependent mechanical behaviour of mechanical metamaterials should be evaluated not only in terms of changes in bulk mechanical properties but also with respect to how local geometrical degradation affects the prescribed deformation mechanisms. Mincheva et al. further showed that the mechanical response of PLLA-

based auxetic metamaterials is highly sensitive to unit-cell dimensions, structural orientation, and material composition, suggesting that degradation-induced changes in geometry and material properties may progressively perturb the intended deformation mechanisms¹²⁹. For nonlinear and multistable metamaterials, such effects may further manifest as changes in critical instability loads, deformation sequences, and stable configurations¹³⁰. In spatially heterogeneous and anisotropic architectures, degradation may instead alter regional stiffness gradients or progressively divert load transfer from the initial design⁶. Accordingly, the central challenge for degradable mechanical metamaterials is not simply to delay strength loss, but to preserve the prescribed architecture-dominated mechanical response throughout continuous material and geometrical evolution. Research addressing this process remains limited. Existing studies have predominantly focused on global parameters such as modulus, strength, and mass loss, whereas the long-term evolution of key metamaterial-specific mechanical characteristics, including Poisson's ratio, instability thresholds, directional dependence, and configuration-transition capability, has yet to be systematically characterised¹⁰.

The above discussion primarily concerns the effects of degradation on the mechanical response of the scaffold itself. However, the actual mechanical state within the defect after implantation also depends on the progressive formation of new bone and its increasing contribution to load bearing¹³¹. Using a multiphysics coupled model, Yang et al. analysed the time-dependent mechanical interplay between magnesium scaffold degradation and bone regeneration, showing that scaffold stiffness progressively decreased with degradation, whereas newly formed bone gradually compensated for the resulting mechanical loss and contributed to recovery of the overall structural stiffness at later stages¹³² (Fig. 7). Long-term in vivo studies by Putra et al. further showed that some degradable scaffolds could retain yield strength and elastic modulus close to their pre-implantation values despite material degradation and substantial osseointegration, indicating that material degradation, structural preservation, and tissue replacement need to be temporally coordinated¹³³. Accordingly, the time-dependent mechanical behaviour of degradable scaffolds should not be characterised solely by deterioration of the scaffold itself, but should also account for the dynamic balance between scaffold mechanical loss and the increasing load-bearing capacity of regenerated bone. This process is more complex for mechanical metamaterials. Bone ingrowth and interfacial integration can progressively alter pore occupancy, boundary constraints, and local load paths, thereby reshaping architecture-dominated mechanical responses and coupling

degradation-driven structural evolution with regeneration-induced mechanical remodelling¹⁰. Therefore, the design of degradable mechanical metamaterials should not be limited to prolonging mechanical retention, but should instead seek to temporally coordinate the decline in scaffold load-bearing capacity with the establishment of mechanical function in regenerated bone.

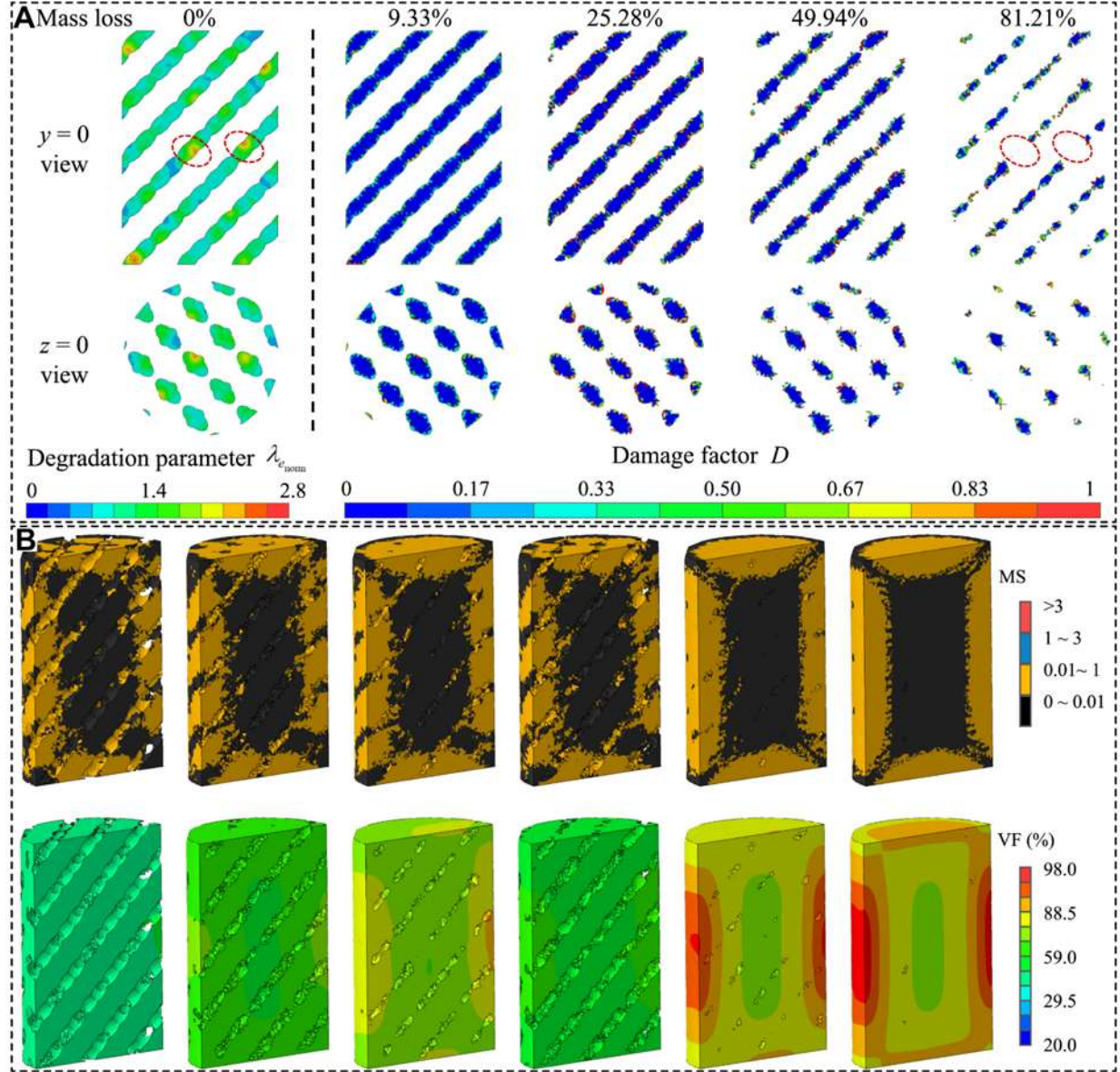


Figure 7. Computational modelling of the time-dependent coupling between magnesium scaffold degradation and bone regeneration. (A) Spatial evolution of scaffold degradation at increasing levels of mass loss. Cross-sectional views illustrate the progressive development of material damage and loss of structural continuity, quantified by the degradation parameter and damage factor [D]. (B) Predicted spatial distributions of the mechanobiological stimulus [MS] and regenerated tissue volume fraction [VF] during the coupled degradation-regeneration process, demonstrating the progressive redistribution of the local mechanical environment and tissue formation as scaffold degradation proceeds. Adapted from Yang et al.¹³². Copyright 2025, Elsevier.

Based on these considerations, the design of degradable mechanical metamaterials should extend beyond achieving mechanical matching at the time of implantation towards maintaining time-dependent mechanical compatibility throughout the entire repair process¹³⁴. An ideal architecture should not only provide sufficient early-stage stability but also coordinate material degradation and architectural evolution with the progressive mechanical maturation of newly formed bone¹³⁵. Accordingly, evaluation of these structures should not be restricted to modulus, strength, or mass loss measured at a single time point, but should instead incorporate longitudinal assessment of geometrical integrity, retention of stiffness and strength, fatigue durability, and load sharing within the scaffold-bone construct across different stages of degradation¹³⁶. For mechanical metamaterials, the temporal evolution of architecture-dominated mechanical responses should also be specifically monitored¹⁰. Future design should therefore focus not simply on slowing degradation, but on coordinating material composition, local topology, and spatial organisation so that the trajectory of mechanical-function loss is matched to the recovery of load-bearing capacity in regenerating bone, thereby shifting the design paradigm from initial mechanical adaptation towards temporally coordinated mechanical adaptation. The overall relationships among advanced manufacturing, metamaterial architecture, mechanical regulation, biological responses, and bone regeneration are summarised in Fig. 8.

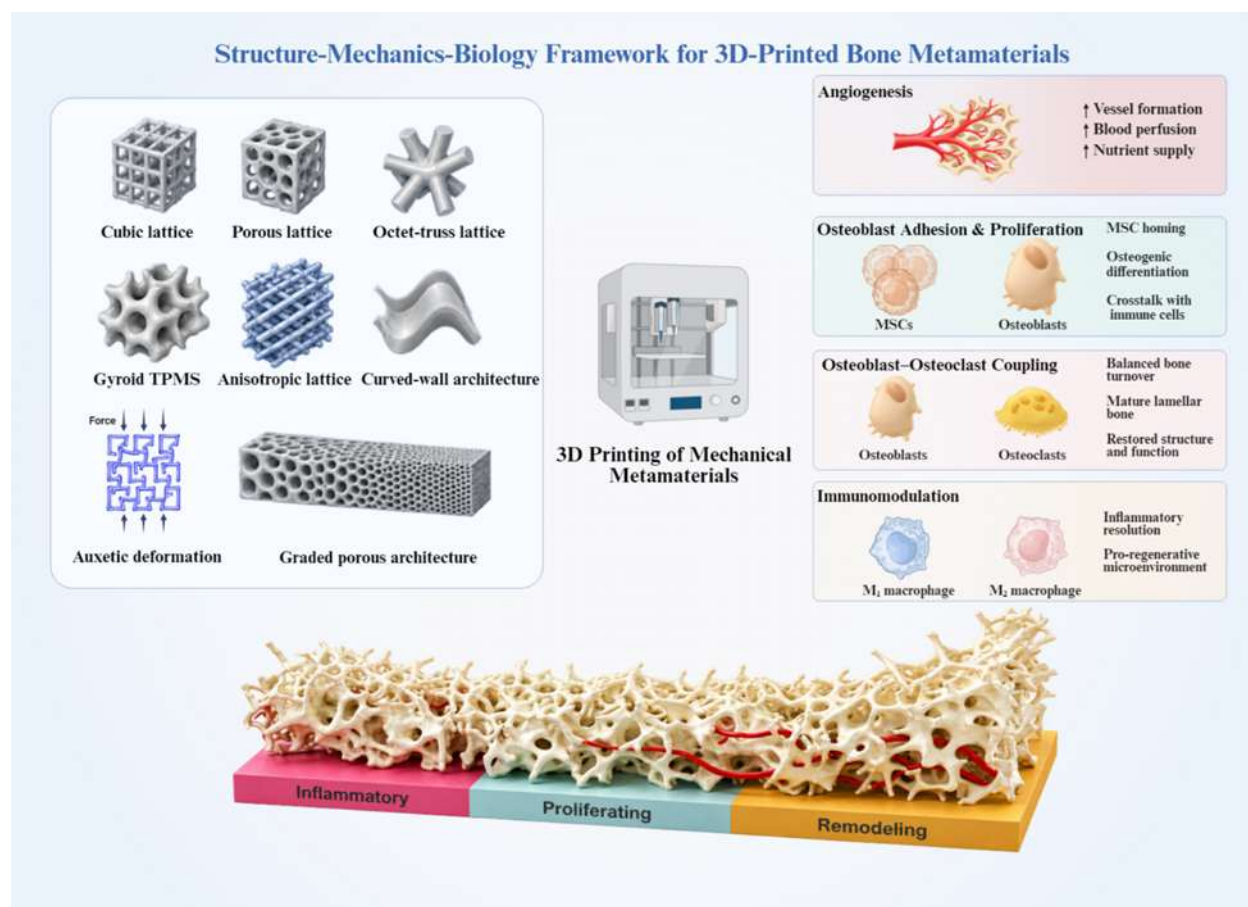


Figure 8. Integrated framework linking structural design, mechanical regulation, and biological responses in 3D printed mechanical metamaterials for bone repair.

6. Conclusions and Perspectives

Native bone exhibits pronounced spatial heterogeneity, anisotropy, and load-dependent nonlinearity, and these complex mechanical characteristics provide important inspiration for the metamaterial design of bone repair scaffolds. Enabled by 3D printing, mechanical metamaterials can exploit microstructural topology and deformation mechanisms such as rotation, buckling, contact, and configurational transitions to generate region-specific, direction-dependent, and load-responsive mechanical behaviours, thereby moving beyond the conventional design paradigm of porous scaffolds that primarily relies on matching bulk modulus and strength. Current research has progressively expanded from the creation of distinctive mechanical properties towards coordinated regulation of mechanical responses and biological functions, indicating a shift in metamaterial

design for bone repair from mechanical adaptation alone towards multifunctional regenerative regulation.

However, several key challenges still hinder the predictable and reproducible application of 3D-printed mechanical metamaterials in bone repair. From the perspective of evidence level, biological validation remains uneven across different metamaterial strategies. Some designs have progressed to evaluation in animal bone-defect models, whereas multistable and some highly programmable architectures remain largely at the computational, mechanical, or in vitro validation stage. First, clear quantitative relationships between structural responses and in vivo bone regeneration remain insufficiently established. Future studies should further resolve the local strain, interfacial micromotion, and fluid shear generated by unit-cell deformation and determine how these mechanical cues are associated with cellular mechanotransduction, vascularisation, and new bone formation^{5,10}. Second, mechanical metamaterials are highly sensitive to local geometric features, and manufacturing deviations and defects may alter predefined stress distributions, instability pathways, and configurational transitions. Greater consistency is therefore required among digital designs, as-fabricated structures, and target mechanical responses^{137,138}. At the same time, new bone ingrowth, material degradation, and cyclic loading continuously alter the mechanical boundary conditions of scaffolds, and the long-term functional stability of auxetic, multistable, and reconfigurable structures therefore requires systematic validation^{13,100}. With the increasing incorporation of bioactive components, future designs should also strengthen the coordinated optimisation of structural parameters, bioactive-agent dosage, and release timing so that mechanical regulation can be aligned with stage-specific biological requirements, including inflammation, vascularisation, and bone maturation^{12,123}. By further clarifying the intrinsic relationships among architecture, manufacturing, the local mechanical microenvironment, and bone regeneration, 3D-printed metamaterials may evolve from complex structures with distinctive mechanical properties into bone repair implants that integrate precise mechanical adaptation with regenerative regulation.

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Conflict of interest

The authors declare they have no competing interests.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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