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Biomimetic structural design in 3D-printed scaffolds for bone tissue engineering

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ABSTRACT

The rising prevalence of bone diseases in an aging population underscores the urgent need for innovative and clinically translatable solutions in bone tissue engineering. While significant progress has been made in refining the chemical properties of biomaterials, the structural design of scaffolds-a critical determinant of repair success-remains comparatively underexplored. Structural parameters such as porosity, pore size, and interconnectivity are not only essential for achieving mechanical stability but also pivotal in regulating biological processes, including vascularization, osteogenesis, and immune modulation. This review systematically categorizes scaffold architectures documented in the literature and highlights how these design parameters can be optimized to enhance bone regeneration. Advanced fabrication technologies, particularly 3D printing, are emphasized for their transformative potential in creating precise, biomimetic scaffolds that align with the complex functional demands of native bone. Furthermore, this work synthesizes diverse findings to provide a comprehensive framework for designing next-generation scaffolds. By bridging the gap between structural innovation and clinical application, this review delivers actionable strategies and a strategic roadmap for advancing the field toward improved clinical outcomes and transformative breakthroughs in regenerative medicine.

1. Introduction

As the global population ages, the prevalence of debilitating bone diseases such as osteoporosis, fractures, and bone tumors is rising, significantly impacting individuals' mobility, independence, and quality of life [1–3]. These conditions not only burden patients but also strain healthcare systems worldwide, as traditional treatments like pharmacotherapy and surgery often fail to fully restore bone function or prevent recurrence [4,5]. This underscores the urgent need for innovative, patient-centered therapeutic strategies. Bone tissue engineering has emerged as a pioneering field, combining biology, mechanics, and materials science to develop bone substitutes that restore damaged tissue through advanced scaffold designs capable of mimicking natural bone's structural and functional complexities [6]. Biomimetics, inspired by natural structures and processes, is a transformative approach in bone tissue engineering [7]. By replicating the hierarchical, gradient, and porous architectures of natural bone, researchers create scaffolds that mimic native tissue's structural and functional properties. Natural bone's hierarchical structure-from nanoscale collagen fibers to macroscale cortical and trabecular bone-underpins its mechanical strength and

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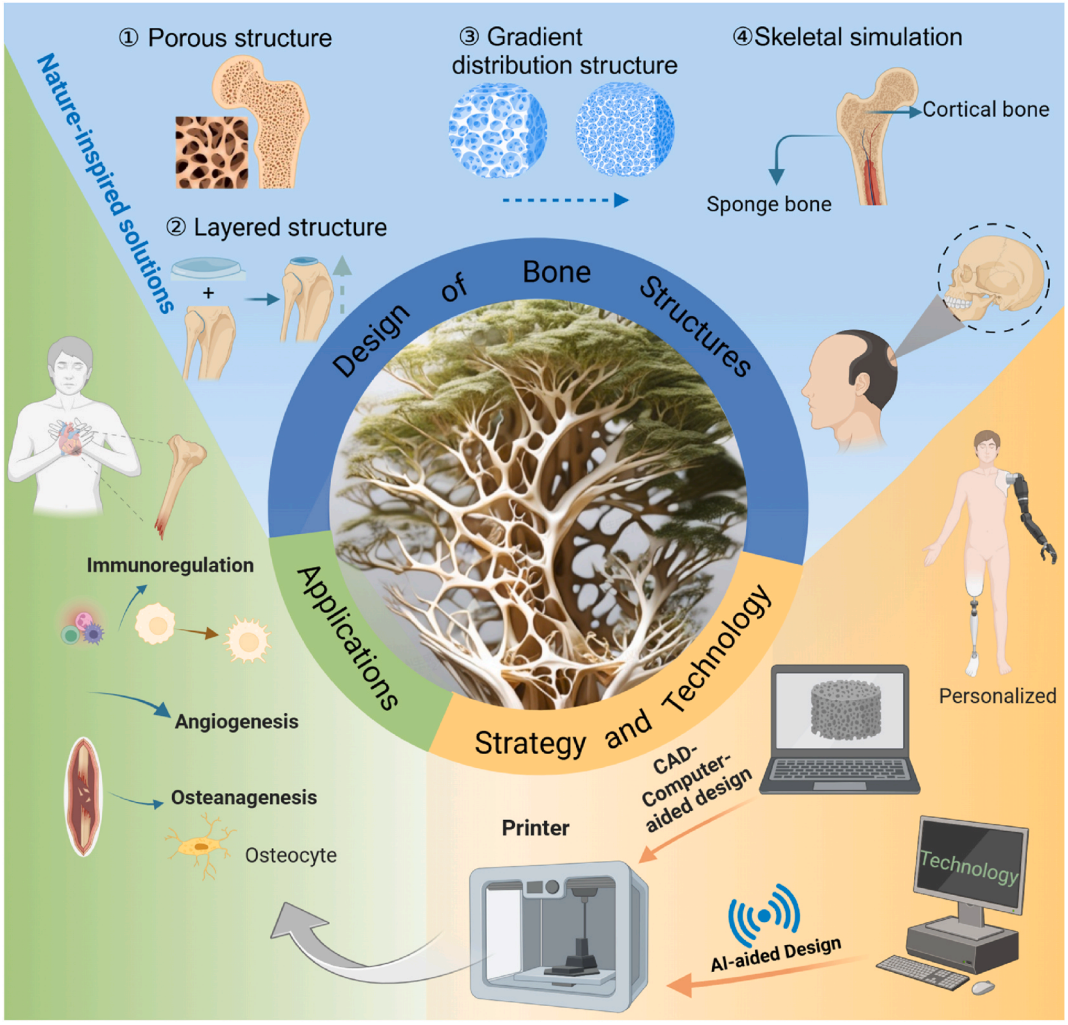

Fig. 1. Strategies and technologies in bone structure design, highlighting nature-inspired solutions, advanced fabrication tools, and their roles in personalized bone regeneration.

biological activity. Additionally, its gradient porosity and interconnected porous networks facilitate nutrient transport and vascularization, critical for bone regeneration. Biomimetic scaffolds emulate these features, improving host tissue integration, cell-material interactions, and bone regeneration, making them essential for advanced bone scaffold design.

At the core of bone tissue engineering lies the structural design of scaffolds, which play a crucial role in providing mechanical support and guiding biological processes such as cell attachment, proliferation, differentiation, and vascularization. From the microscale level, scaffold porosity is vital for enabling efficient nutrient and waste exchange and promoting cellular activity, while at the macroscale, the scaffold must exhibit mechanical robustness to withstand physiological loads and facilitate the integration of new bone tissue [8–10]. Furthermore, the structural complexity of scaffolds is essential to support processes such as vascularization, immune modulation, and tissue maturation, all of which contribute to successful bone regeneration. However, despite their importance, scaffold structural parameters have often been overlooked in favor of extensive research on the chemical properties of biomaterials [11–13]. Hutmacher et al. [14] noted that while extensive research has been conducted on the chemical properties of biomaterials, structural parameters such as porosity, pore size, and interconnectivity have been relatively underexplored. Similarly, Bose et al. [15]emphasized that the mechanical and biological performance of scaffolds is highly dependent on their structural design, yet systematic studies on optimizing these parameters remain limited. While these studies acknowledge the importance of scaffold structure, a comprehensive review that critically evaluates its influence on scaffold performance and translational potential is still lacking. This imbalance underscores the necessity of a systematic review that critically evaluates scaffold structural design strategies and their influence on functional performance, which this manuscript aims to address.

The advent of 3D printing technology has revolutionized scaffold fabrication, providing unparalleled precision in controlling the structural and mechanical properties of bone constructs [16,17]. This technology enables the creation of biomimetic architectures that replicate the hierarchical features of natural bone, including porous, layered, and gradient-distributed structures. Moreover, the integration of advanced computational tools, such as computer-aided design (CAD) and artificial intelligence (AI), has transformed the design and optimization processes, allowing for the development of patient-specific scaffolds tailored to meet diverse clinical needs [18–22]. These innovations have opened new avenues for bone tissue engineering, offering opportunities to bridge the gap between fundamental research and clinical application. Essential structural parameters such as pore size, porosity, and interconnectivity, combined with optimized mechanical properties, are increasingly recognized as pivotal for influencing cellular behavior and the overall success of bone regeneration [23].

This review provides a systematic examination of the key factors and strategies in the structural design of bone scaffolds, focusing on their

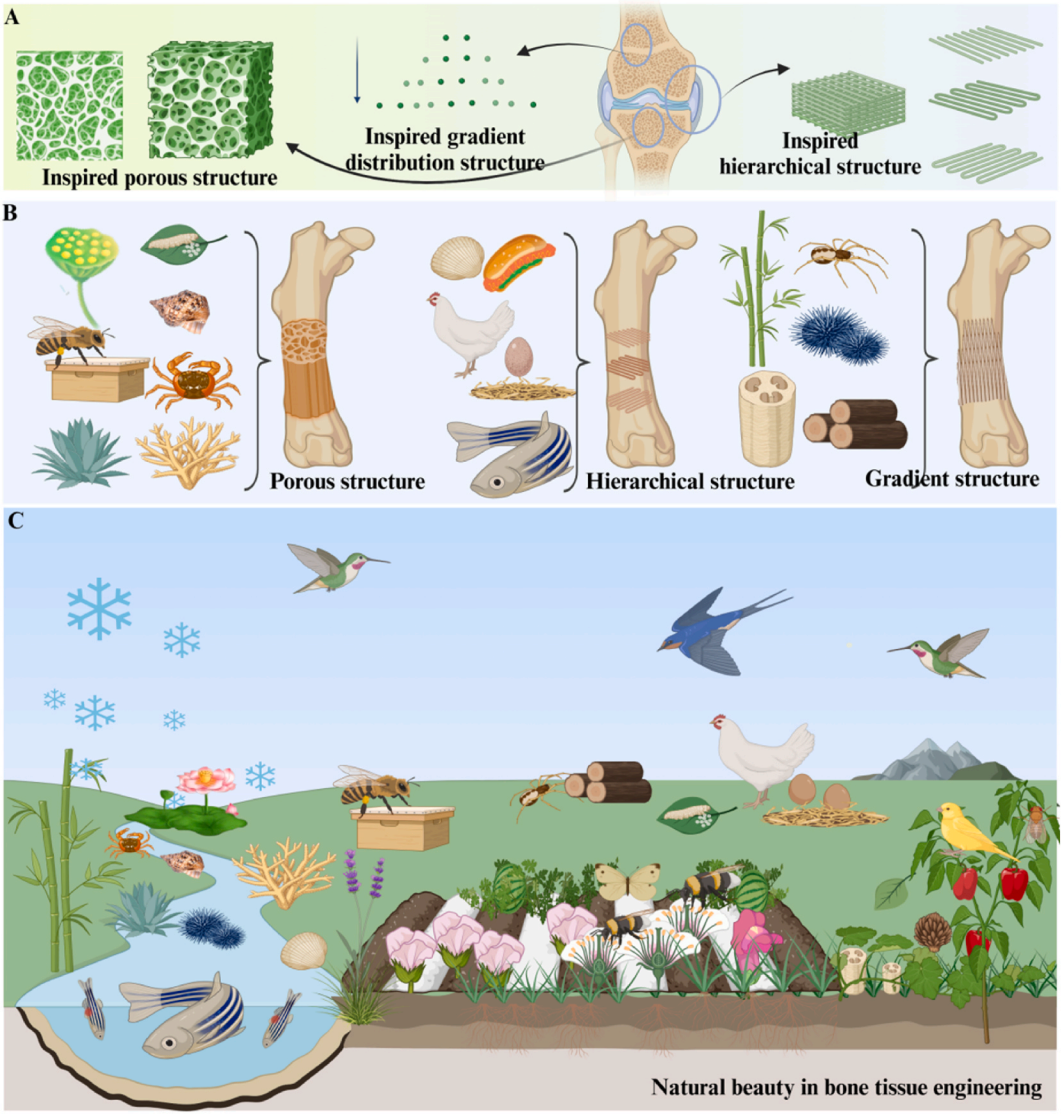

Fig. 2. Biomimetic design strategies for bone tissue engineering: from natural inspiration to scaffold structures. A) Translating natural features into scaffold structures, including porous, hierarchical, and gradient-distributed designs, for enhanced bone regeneration. B) Classification of porous, stratified and gradient distribution designs and associations of bone structure. C) Natural inspirations in bone tissue engineering, showcasing diverse natural forms and organisms that inspire biomimetic design strategies.

biomimetic applications and translational potential (Fig. 1). While recent advancements have explored nature-inspired scaffold designs, a systematic analysis of these diverse approaches remains underexplored in the literature. To address this gap, this review categorizes and analyzes biomimetic scaffold designs, integrating advanced fabrication technologies such as 3D printing and computational tools like AI and CAD. By synthesizing recent findings, we highlight structural parameters-including pore size, porosity, and connectivity-that critically influence cellular behavior and scaffold performance. Ultimately, this review provides a comprehensive framework for designing scaffolds that mimic the hierarchical and multifunctional properties of natural bone, paving the way for improved clinical applications in bone tissue engineering.

2. Biomimetic structure design in bone constructs

In bone tissue engineering, mimicking the complexity of natural structures and functions is pivotal for creating effective bone regeneration technologies. Biomimetic principles [24], inspired by natural organisms, are heavily employed in designing 3D bioprinted bone constructs. These designs incorporate intricate porous architectures, hierarchical arrangements, and gradient distributions similar to those found in nature, serving as innovative models for engineering bone tissue. By recreating the bone's natural environment, these biomimetic designs enhance cellular interactions and facilitate bone growth, making them highly effective in promoting tissue repair and regeneration.

2.1. Nature-inspired design strategies

The exquisite structures and functions of biological organisms, refined through eons of evolution, serve as powerful inspirations for the development of biomaterials dedicated to bone regeneration. These natural systems, known for their optimized features and adaptability, provide a rich foundation for biomimetic design in bone tissue engineering [25–27]. This field draws from the natural world's aesthetic and functional elegance, applying these principles to mimic the delicate structure and robust functionality of natural bone tissue (Fig. 2A). The intricate designs observed in nature, such as the porous structures of leaves, the hierarchical organization of eggshells, and the gradient patterns seen in fish scales, have been instrumental in shaping the

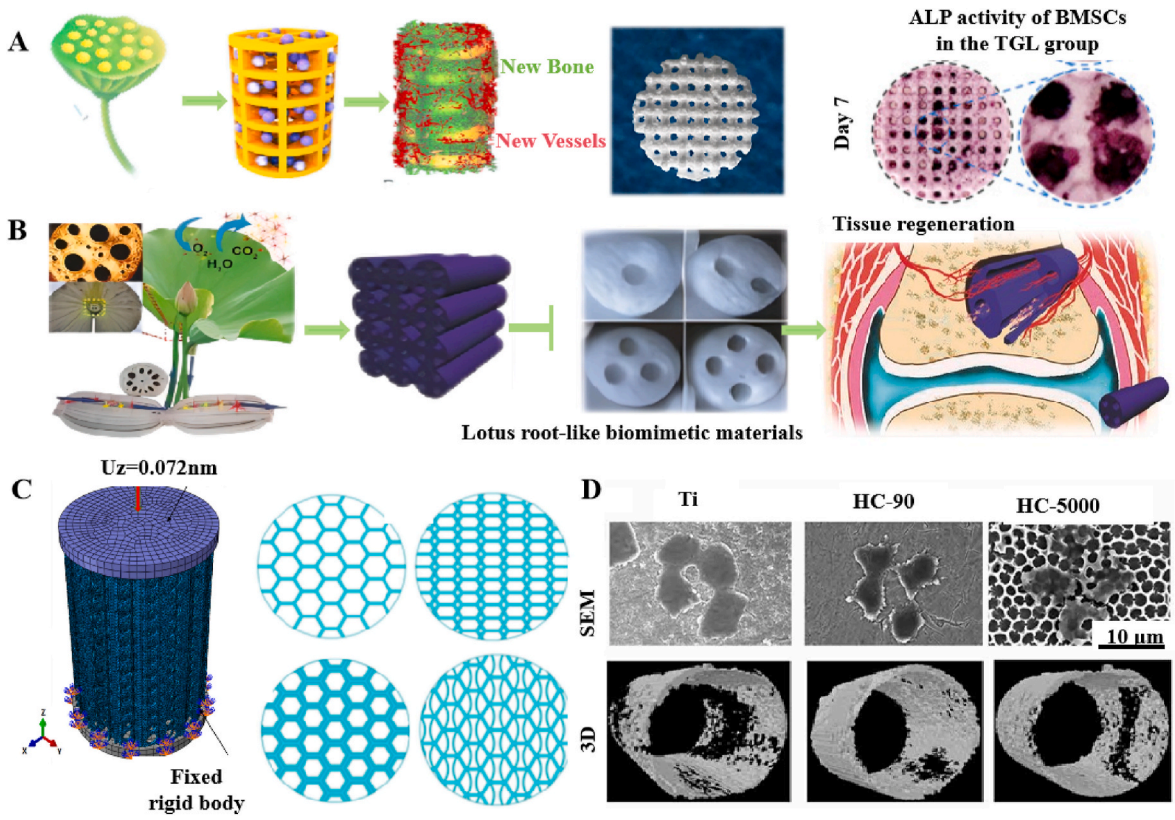

Fig. 3. Nature-inspired porous structures. A) Structure inspired by lotus seedpod. Reproduced with permission [32]. Copyright 2020, Elsevier. B) Inspired by lotus root microstructure. Reproduced with permission [33]. Copyright 2017, Wiley. C) Finite element analysis model of honeycomb structures porous scaffold. Reproduced with permission [35]. Copyright 2021, Elsevier. D) TiO_2 honeycomb structures. Reproduced with permission [36]. Copyright 2023, Elsevier.

biomimetic approaches used in bone tissue engineering (Fig. 2B). Biomimicry in bone tissue engineering does more than emulate the natural world-it expands the creative horizon for future biomaterial designs. The core principle of biomimicry involves replicating the structural and functional attributes of natural bone, enhancing the performance and biocompatibility of synthetic bone constructs. The design of 3D printed structures, in particular, is influenced by the architectural marvels found in natural ecosystems [28]. Fig. 2C displays a variety of natural elements that influence the design of structural supports in bone tissue engineering.These elements are incorporated to develop scaffolds with diverse pore sizes, hierarchical structures, and porous configurations. Such natural inspirations are critical in enhancing biocompatibility, mechanical integrity, and the osteogenic capacity of artificial bone scaffolds, thus offering substantial support for the regeneration and repair of bone tissues.

2.1.1. Porous architectures

The multi-level micro-porous structure of artificial bone is crucial for optimal osteogenesis [29]. This structure facilitates nutrient transportation, waste elimination, cellular behavior, and favorable mechanical properties, enhancing implant integration and bone regeneration [30,31]. Porous structures are widespread in nature, ranging from the sponges to the hexagonal layout of honeycombs, adopted by organisms to optimize their functions. These structures promote both mechanical strength and substance transfer and exchange.

The lotus seedpod is a spongy receptacle with honeycomb-like holes, each containing a lotus seed. Han et al. [32] utilized 3D-printed porous bioceramics as lotus seedpods and deferoxamine (DFO)-loaded gel microspheres as lotus seeds, constructing a vascularized lotus pod-shaped scaffold (Fig. 3A). This biomimetic design enhances bone regeneration by providing an interconnected porous network for cell adhesion and nutrient exchange, while the controlled release of DFO promotes vascularization, supporting bone repair. Additionally, the scaffold achieves mechanical strength comparable to cancellous bone, ensuring structural stability and creating a microenvironment conducive to new bone formation. The porosity and mechanical properties of the biomimetic lotus root scaffold can be tailored individually by manipulating the arrangement of elements within the 3D scaffold and adjusting the density of channel distribution [33] (Fig. 3B). The honeycomb structure, renowned for its exceptional mechanical properties, serves as a notable example [34]. Wang et al. [35] conducted a study where they fabricated four porous scaffold models based on the honeycomb structure (Fig. 3C), resulting in elastic moduli ranging from 1.6 to 3 GPa, closely aligning with the elastic moduli of human cancellous bone (0.1–4.5 GPa). Additionally, the wall shear stresses of these four scaffolds varied from 2.8 to 42.8 MPa, potentially stimulating cells to deposit mineralized extracellular matrix within the 3D scaffold, thereby promoting bone regeneration.

The four honeycomb-like distributed TiO_2 nanostructures, as depicted in Fig. 3D, induced scale-dependent osteoimmunomodulation, fostering a favorable microenvironment for osteocytes and macrophages, thereby accelerating the integration of the implant with the bone [36] (Fig. 3D). Cuttlefish possess a unique biomineralized shell known as cuttlebone, exhibiting an extensively developed internal pore structure with a porosity exceeding 90 %, thus forming a highly porous physical structure [37]. Leveraging the porous structure of cuttlebone in scaffold manufacturing can facilitate cell growth and tissue regeneration [38]. Moreover, the intricate calcareous teeth network structure of the sea urchin's pharyngeal tongue, Aristotle's lantern, has attracted considerable scientific interest [39]. The adequate porous structure, by ensuring ample space for oxygen and nutritional supply, has been demonstrated as the optimal choice for bone growth, further bolstering cell regeneration in new bone tissue [40,41]. Therefore, in the realm of bone tissue engineering, researchers continuously explore biomimetic

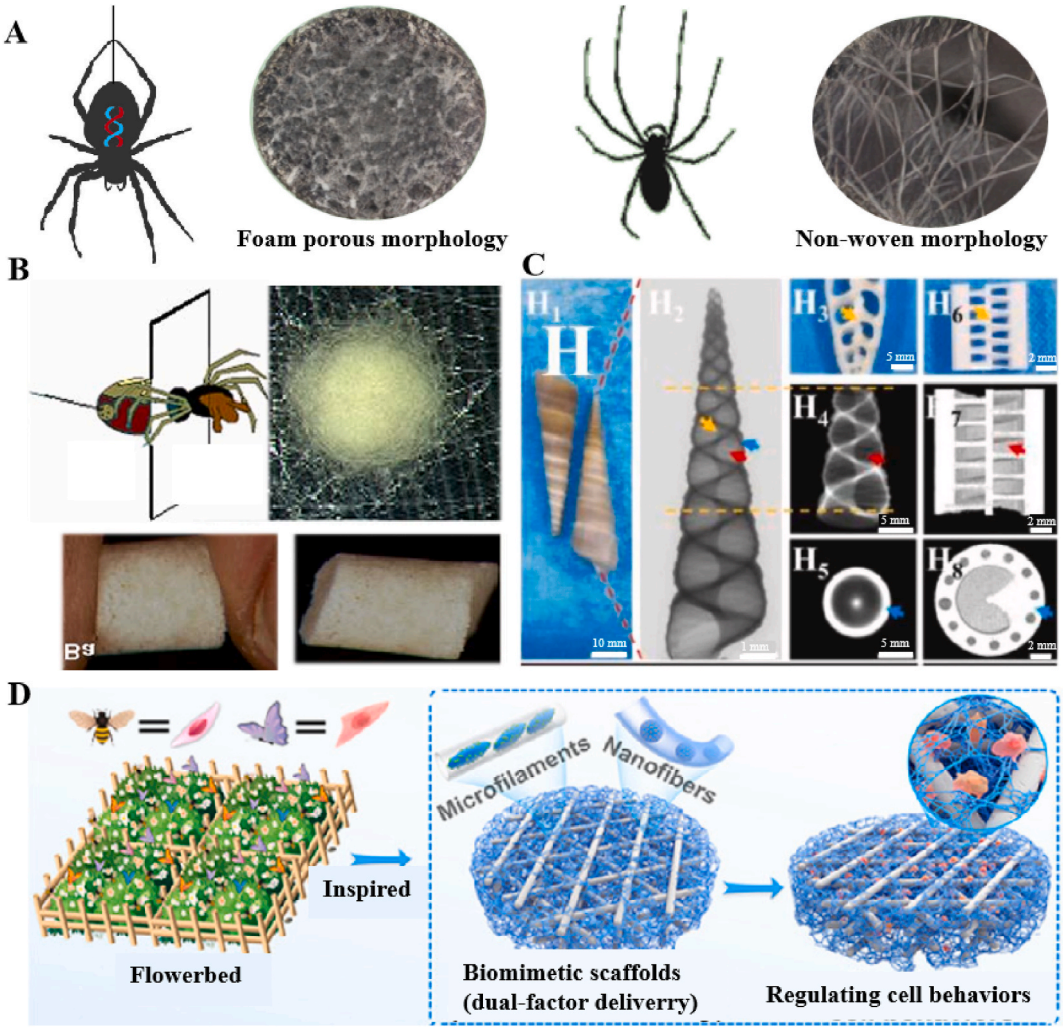

Fig. 4. Nature-inspired porous structures. A) Spider silk-inspired scaffold. Reproduced with permission [42]. Copyright 2020, MDPI. B) Silkworm-inspired scaffolds. Reproduced with permission [43]. Copyright 2008, Springer Link. C) Conch-like-inspired scaffolds. Reproduced with permission [44]. Copyright 2022, Elsevier. D) Flowerbed-inspired biomimetic scaffold. Reproduced with permission [45]. Copyright 2023, American Chemical Society.

structural designs to augment cellular behavior and enable bone regeneration. These biomimetic structural designs not only replicate the multilevel microporous architecture of bone tissue, thereby providing favorable conditions to support cellular processes and nutrient exchange, but also optimize the mechanical properties, enhance the integration of implants with the host bone tissue, and further advance bone regeneration.

Further research has explored scaffolds crafted from silk fibroin (Fig. 4A) and *Bombyx mori* cocoon materials (Fig. 4B), which due to their porosity and adjustable microstructure, enhance the attachment and proliferation of chondrocytes and promote the synthesis of the extracellular matrix [42,43].

The conch-like (CL) scaffold [44] emulates the growth pattern and physiological characteristics observed in snails, where cells navigate a stair-like path. Its helically arranged porous structures serve to guide and support the directional growth of bone cells. Compared to the conventional scaffold, the CL scaffold demonstrates superior mechanical performance, material transport capabilities, and stimulation of osteogenic differentiation *in vitro*, attributable to its unique structural features. This performance disparity not only signifies progress beyond traditional bone scaffolds but also signifies a deeper comprehension and application of porous structures (Fig. 4C). Zhou et al. [45] drew inspiration from a "flower bed" to engineer an innovative bone tissue scaffold using 3D printing technology (Fig. 4D). The scaffold's design borrows from the bioactive nanofibers found in plant structures within a flower bed, which mimic the process of plants dispersing "pollen" by releasing bioactive substances to attract nearby cells and encourage dynamic material exchange within the bone microenvironment. By adjusting the density of these nanofibers, the porous structure of the scaffold can be readily adapted to accommodate various stages of bone cell growth and meet biomechanical demands.

Cacti exhibit uniquely evolved structures reminiscent of both the porous composition of bone and the fibrous architecture of cactus fibers, showcasing significant diversity among various species [46,47]. Neto et al. [48] have underscored the potential of marine skeletons' porous structure as a bone graft material, obviating the need for additional mineralogical alterations. These porous formations bear closer anatomical and physiochemical resemblance to cortical bone and, when combined with cells and/or growth factors, can effectively stimulate bone growth [49]. Subramaniam Puvaneswary et al. [50] conducted a comparative analysis of the morphology, osteogenic differentiation, and growth potential of bone grafts (BG) and coral-like structure grafts (CG) utilizing rabbit mesenchymal stem cells (rMSCs) *in vitro*. Their findings indicate that coral-like structure grafts exhibited relatively superior performance in promoting rMSCs' osteogenic differentiation, with scanning electron microscope (SEM) images revealing interconnected pores, yielding an overall total porosity exceeding 92 %.

Through extensive research and comprehension of the porous

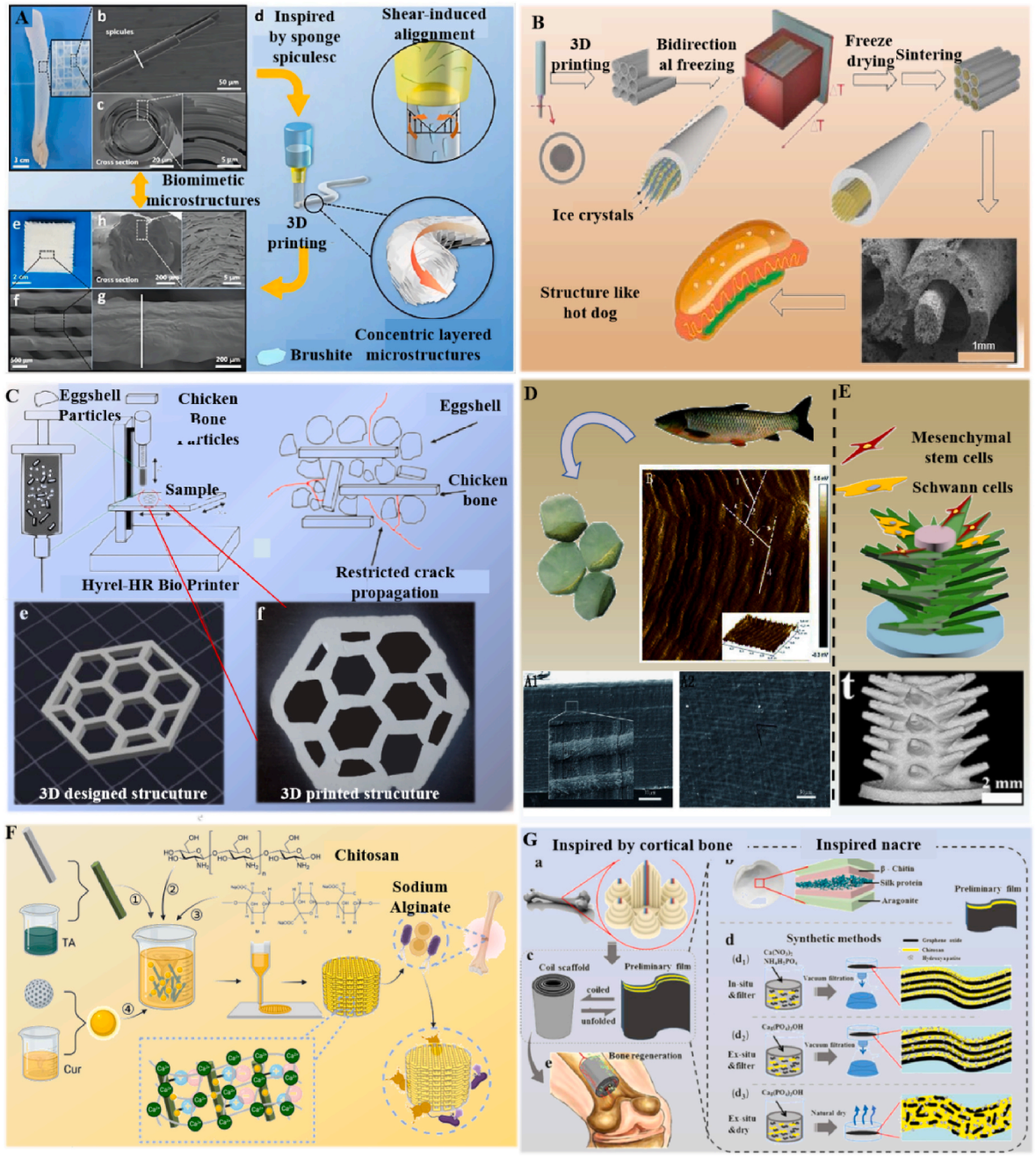

Fig. 5. Nature-inspired layered structures. A) Skeleton of the Euplectella aspergillum natural sponge, a cage-like structure composed of thousands of spicules (illustration). Reproduced with permission [60]. Copyright 2022, Institute of Physics. B) Fabrication and morphology of hot dog-like scaffolds (HD-AKT). Reproduced with permission [61]. Copyright 2019, Wiley. C) CAD models for the design of eggshell and chicken bone and 3D printed structure. Reproduced with permission [62]. Copyright 2022, Elsevier. D) The layered structure of fish scale matrix. Reproduced with permission [63]. Copyright 2020, Royal Society of Chemistry. E) 3D printing of bioinspired tree-like bioceramic scaffolds with different divergence angles. Reproduced with permission [66]. Copyright 2022, Elsevier. F) Inspired by the adhesion mechanism of mussels, HA@TA powder was prepared by adhering TA to HA surface. TA was then used as a "bridge" connecting HA and CS, compounded with SA through electrostatic interaction and doped with DMON@Cur nanoparticles of different mass fractions to produce curcumin-loaded HA@TA-CS/SA scaffolders by 3D printing. Reproduced with permission [67]. Copyright 2023, Frontier. G) Inspired by nacre, we prepared the preliminary films with a “mortar and brick” layered structure. Reproduced with permission [69]. Copyright 2021, Elsevier.

framework of bones [29], we can create scaffolds using 3D bioprinting technology that are more closely aligned with human biological characteristics. The complex patterns found in nature provide a unique perspective and limitless inspiration for the innovative design of porous bone scaffolds. By employing 3D bioprinting techniques, we aim to more precisely mimic the natural process of bone growth and support tissue regeneration. This approach not only enhances the functional integration of the scaffolds but also opens new pathways for advancements in regenerative medicine [51,52].

The intricate multi-level microporous structures inspired by nature are crucial in the design of artificial bones for optimal osteogenesis. These biomimetic frameworks facilitate nutrient transport, waste removal, and cellular behavior, while simultaneously enhancing mechanical properties to promote implant integration and bone regeneration. By drawing on natural models such as the lotus seedpod, honeycomb, and butterfly wings, researchers have created innovative

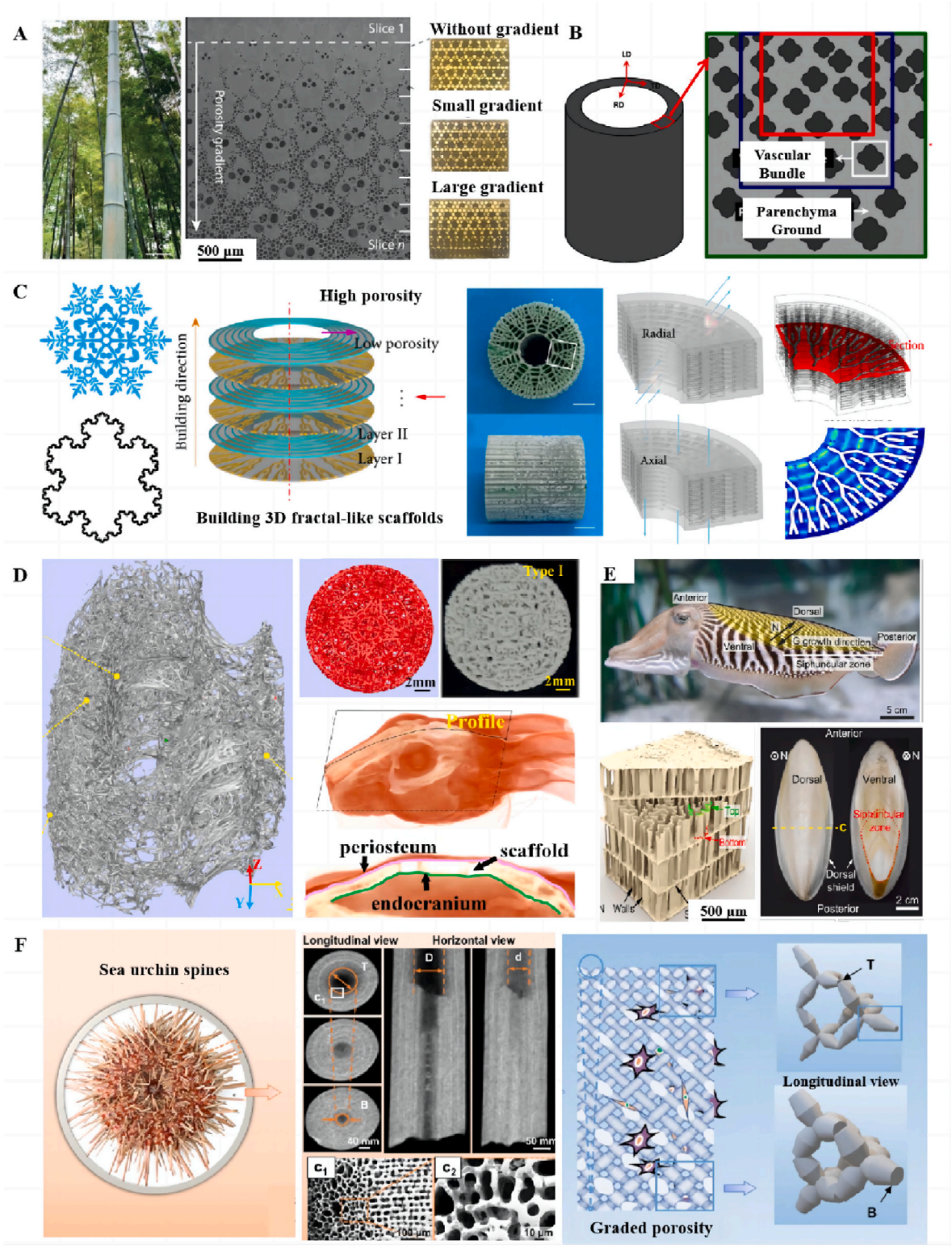

Fig. 6. Nature-inspired gradient distribution structures. A) SEM image reveals the bamboo's composition of densified vascular bundles and porous parenchyma cells. Reproduced with permission [71]. Copyright 2023, Wiley. B) Functional gradient (FG) hierarchical structure of bamboo. Reproduced with permission [72]. Copyright 2015, Elsevier. C) Schematic illustrations for designing fractal-like Koch snowflake scaffolds. Reproduced with permission [74]. Copyright 2021, Science Partner Journa. D) Micro-CT imaging of the loofah showcasing its high porosity and interconnected structure. Reproduced with permission [76]. Copyright 2021, Elsevier. E) Analysis of the wavy gradient morphology in cuttlefish bone microstructure. Reproduced with permission [77]. Copyright 2022, National Acad Sciences. F) Examination of sea urchin spines' needle-like appearance and internal architecture with graded porosity. Reproduced with permission. [78].Copyright 2023, Elsevier.

scaffolds that closely replicate the microenvironment of bone tissue, thereby providing an ideal platform for cell attachment, growth, and extracellular matrix synthesis. These advancements in scaffold design not only mimic the complex architecture of bone but also improve mechanical performance and create a favorable microenvironment for osteocytes, significantly advancing the fields of bone tissue engineering.

2.1.2. Hierarchical structures

Bone primarily consists of inorganic salts, with hydroxyapatite serving as the predominant component, imparting hardness and strength to the bone tissue. Additionally, bone comprises a substantial portion of organic matter, such as collagen and proteoglycans, which confer flexibility and elasticity upon the bone structure [53,54]. This distinctive combination of material properties enables the formation of hierarchical structures, allowing bones to possess both adequate hardness and flexibility, thereby accommodating various physiological activities and environmental changes [55,56]. The hierarchical structure of bone, comprising cortical and cancellous bone, is essential for its mechanical strength and biological functionality. Cortical bone, with its densely packed lamellae and trabeculae aligned along stress directions, provides rigidity and toughness, while cancellous bone offers elasticity and adaptability, facilitating growth and repair [57–59].

Inspired by these natural hierarchical structures, researchers have developed biomimetic scaffolds for bone tissue engineering. For instance, Yang et al. [60] designed a scaffold mimicking the needle-like spicules of marine sponges using 3D printing technology (Fig. 5A). This scaffold, comprising needle-like flexible layer structures, demonstrated superior flexibility and toughness compared to conventional biomimetic scaffolds, and exhibited enhanced osteogenic and neurogenic activities *in vitro* and *in vivo* compared to traditional β-tricalcium phosphate (β-TCP) scaffolds. Notably, the amalgamation of bread and sausage to create a hot dog is a well-known culinary creation. Drawing inspiration from everyday structural arrangements, such as the hot dog, researchers have developed scaffolds that mimic the nutrient storage and layered transport characteristics of bone tissue [61] (Fig. 5B). Das et al. [62] created robust hierarchical structures inspired by chicken bones and eggshells, demonstrating potential for orthopedic applications (Fig. 5C). The layered microarchitecture of grass carp scales, with its excellent mechanical properties, has also inspired scaffold designs [63] (Fig. 5D). The structural diversity of plant leaves, characterized by their hierarchical organization of varying inter-leaf spacing and divergence angles, serves as an effective blueprint for designing scaffolds that promote efficient material exchange and cellular interactions [64,65]. This hierarchical arrangement inspired Zhang et al. [66]to develop dendritic scaffold structures that mimic the architectural features of plant leaf axes, fostering both osteogenic and neurogenic differentiation (Fig. 5E). By replicating the graded and layered organization of plant leaves, these scaffolds enhance cell proliferation and differentiation, demonstrating how hierarchical structures can be leveraged to optimize bone tissue regeneration. Inspired by the adhesive mechanism of mussels, Ji et al. [67] designed and 3D-printed a novel multilayer bone repair scaffold (Fig. 5F). This special layered structure is often used to improve the toughness and strength of materials [68]. The scaffold exhibits excellent mechanical properties, including compressive strength (≈95 MPa), bending strength (≈161 MPa), and toughness (≈1.1 MJ/m^3), and possesses potential angiogenic and osteogenic capabilities. Wu et al. [69] also developed a hierarchical scaffold inspired by shell nacre and cortical bone, combining graphene oxide (GO), chitosan (CS), and hydroxyapatite (HA) for vascularized bone regeneration (Fig. 5G). These designs emphasize the importance of biocompatibility and structural optimization to guide tissue growth and regeneration.

2.1.3. Gradient designs

The porosity gradient in natural bone decreases gradually from the inner trabecular bone to the outer cortical bone [58], showing a continuous variation [70]. The adult skeletal system comprises two key regions, where significant gradient changes occur in both porosity and structure. Firstly, the internal region comprises trabecular bone, also known as cancellous bone, with a porosity of approximately 90 %. Trabecular bone consists of numerous interconnected bone trabeculae, forming a unique porous structure filled with blood and lymphatic fluid. Secondly, the external region consists of cortical bone, with a relatively lower porosity usually not exceeding 10 %. Inspired by the honeycomb structure of bamboo, Mao et al. [71] used 3D printing technology to create structures with a porosity gradient (Fig. 6A). The performance of the biomimetic scaffolds resembling the bamboo honeycomb structure can be significantly optimized by the magnitude and continuity of the porosity gradient. When the porosity gradient is appropriately increased and continuously maintained, the designed scaffolds show a significant improvement in maximum bending load and energy absorption capacity. The maximum bending load can increase by up to 40 %, and the energy absorption capacity can increase by up to 110 %. These results underscore the critical importance of a well-designed porosity gradient in enhancing the mechanical performance of scaffolds. Moreover, the concentric layered arrangement structure of natural bamboo [72], which shows a radial gradient distribution from the center to the outer layer, mimics the natural model of porosity gradient changes in trabecular and cortical bones (Fig. 6B). This structure illustrates not only the importance of gradient structures in biomaterials but also how mechanical properties of artificial materials can be optimized through biomimetic design. Thus, the porosity gradient distribution structure of bamboo honeycomb serves as an effective template for biomimetic material design, enabling the creation of materials with outstanding mechanical performance and structural adaptability.

The high elasticity modulus of 3D-printed scaffolds ensures stability and durability under repetitive loads, making them suitable for load-bearing applications such as spinal fusion and long bone repair [73]. The iterative Koch snowflake model from fractal mathematics [74] achieves a highly accurate representation of the complex internal structure of bone tissue by simulating its gradient porosity (Fig. 6C). This model utilizes fractal geometry principles to generate bone scaffold structures with multiple scales and porosities through iterative refinement. This gradient structural design not only provides sufficient mechanical strength but also promotes cell growth and angiogenesis, which are beneficial for bone tissue regeneration and repair. Inspired by the silk-spinning process that produces tough cocoons, a structure assembled from gradients of silk fibroin and HA was fabricated using 3D printing technology. This design aims to mimic the complex structure of inorganic minerals and organic matrices found in natural bone tissue, aiming to enhance bone regeneration [75].

The natural loofah fiber scaffolds, characterized by high porosity and connectivity [76], are inspired by the inherent arrangement of loofah fibers, ensuring robustness alongside excellent biocompatibility and mechanical properties (Fig. 6D). The 3D-printed porous bone scaffolds possess suitable pore sizes, intricate internal structures, and optimal porosities. Analysis of their osteogenic capacity reveals a bone volume/tissue volume (BV/TV) of 33 %, indicating promising osteogenic potential. Yang et al. [77] meticulously scrutinized the distinctive chamber structure of squid bone, termed the "wall-partition" microstructure, which exhibits an optimized wave gradient design in its vertical walls (Fig. 6E). This structural feature endows squid bone with high rigidity and strength, making it well-suited for applications in bone tissue engineering. Drawing inspiration from the microstructure of natural sea urchin spines, Zhang et al. [78] engineered a biomimetic particle scaffold with a customizable multi-level structure. This scaffold showcases a hierarchical pore distribution and adequate mechanical strength, significantly enhancing cell seeding efficiency, permeability, and impact resistance, while effectively fostering *in vivo* osteogenesis (Fig. 6F).

The transition from the high porosity of trabecular bone to the lower porosity of cortical bone is replicated in biomaterials to improve mechanical performance and structural adaptability. In optimizing

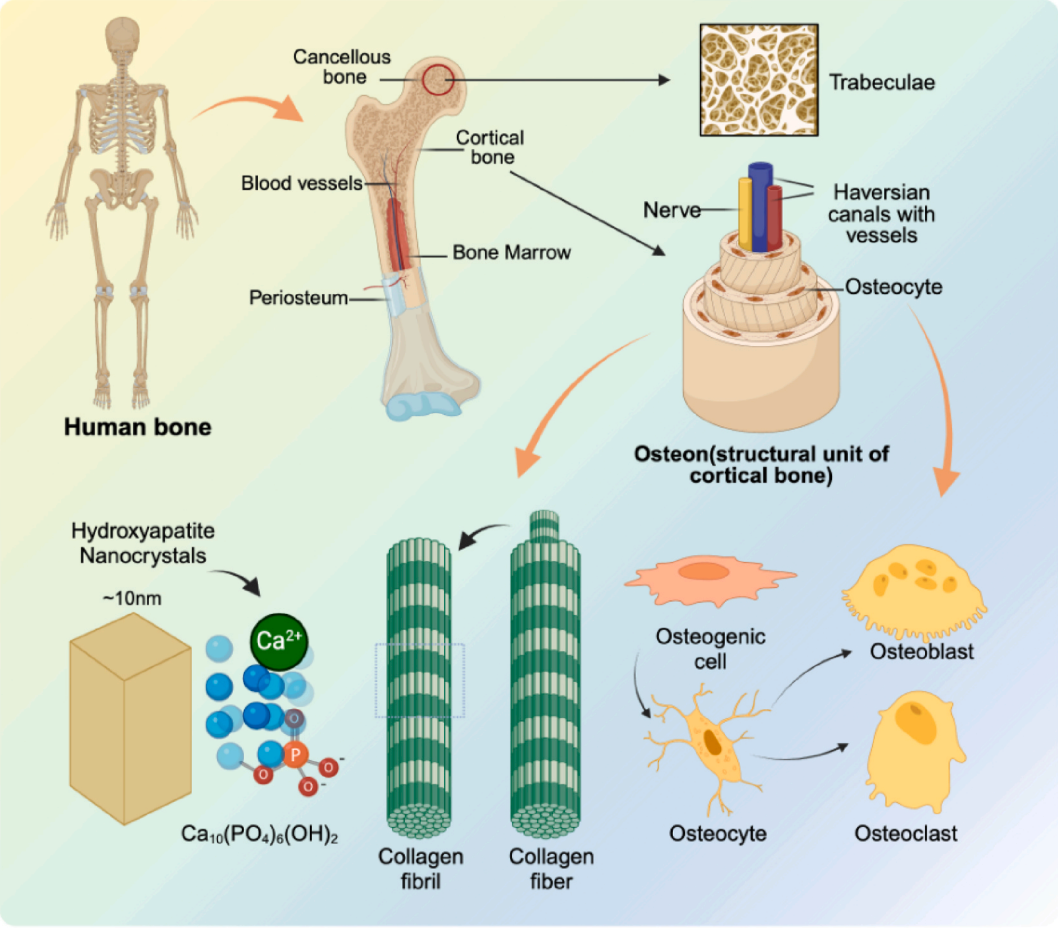

Fig. 7. Hierarchical structure of human bone, from macroscopic features (cortical and cancellous bone, periosteum, and bone marrow) to microscopic components (trabeculae, osteons, HA nanocrystals, and collagen fibers), and the roles of key bone cells (osteogenic cells, osteoblasts, osteocytes, and osteoclasts).

biomimetic constructs for bone tissue engineering, gradient distribution structures inspired by natural bone porosity are essential design principles [79]. These findings highlight the necessity of gradient structures in biomaterial design, as they not only enhance mechanical properties but also facilitate osteogenic processes. This emphasizes the considerable potential of nature-inspired designs in developing next-generation bone scaffolds.

2.1.4. *Other structure*

Indeed, other biomimetic structures have demonstrated exceptional performance in bone tissue engineering. Utilizing electrostatic flocking technology, bidirectionally interlocking biomimetic interfaces have been developed. These consist of two electrostatically flocked substrates that mechanically and reversibly interlock, offering superior compressive and shear resistances. These properties are particularly crucial in the biomechanical environment of simulated bone tissue [80], essential for mimicking bone behavior under physiological loads to ensure stability and durability. Inspired by the macroscopic structure of succulents, Wang et al. [81] have shown the capability to finely adjust scaffold morphology by modifying the size, shape, and arrangement of succulent leaves. This design effectively controls cell distribution, improves cellular interactions, and enhances bone regeneration. Taking cues from the hollow structure of chestnuts [82], tuning the hollow HA microsphere structures offers benefits in attracting calcium ions and modulating inflammatory responses to support bone regeneration and remodeling. Despite significant advancements in biomimetic bone structure design, challenges persist. Key challenges include accurately simulating the intricate structures and functions found *in vivo* and effectively managing the biodegradation of scaffolds and the bone tissue regeneration process, necessitating additional research [83–85].

In conclusion, the utilization of biomimetics in 3D bioprinting design has introduced a innovative approach to bone tissue regeneration [86]. By delving into comprehensive research and comprehension of natural biological structures, we can engineer artificial bone structures that better align with human requirements, offering enhanced therapeutic possibilities for bone tissue regeneration. Furthermore, further exploration is essential in the realms of biocompatibility, mechanical properties, and the controlled release of bioactive substances in 3D bioprinted structures to achieve optimal therapeutic results.

2.2. *Mimicking bone architecture for bone constructs design*

In the fields of bone tissue engineering and regenerative medicine, not only can natural structures inspire the design of novel bone scaffold structures, but the intrinsic architecture of bone itself also warrants thorough exploration and application in bone constructs. It is crucial to understand and replicate both the macroscopic and microscopic structures of bone tissue. The development of biomimetic simulation structures represents a distinctive engineering optimization that has found widespread application in the realms of 3D bioprinting design and bone tissue regeneration [87].

Both microstructural attributes and macroscopic configurations play indispensable roles in the functionality of bone tissue. The inherent microstructure of trabeculae serves as a wellspring of inspiration and guidance for structural design [88]. Constructing biomimetic structures that emulate the shape and texture of natural bone can significantly

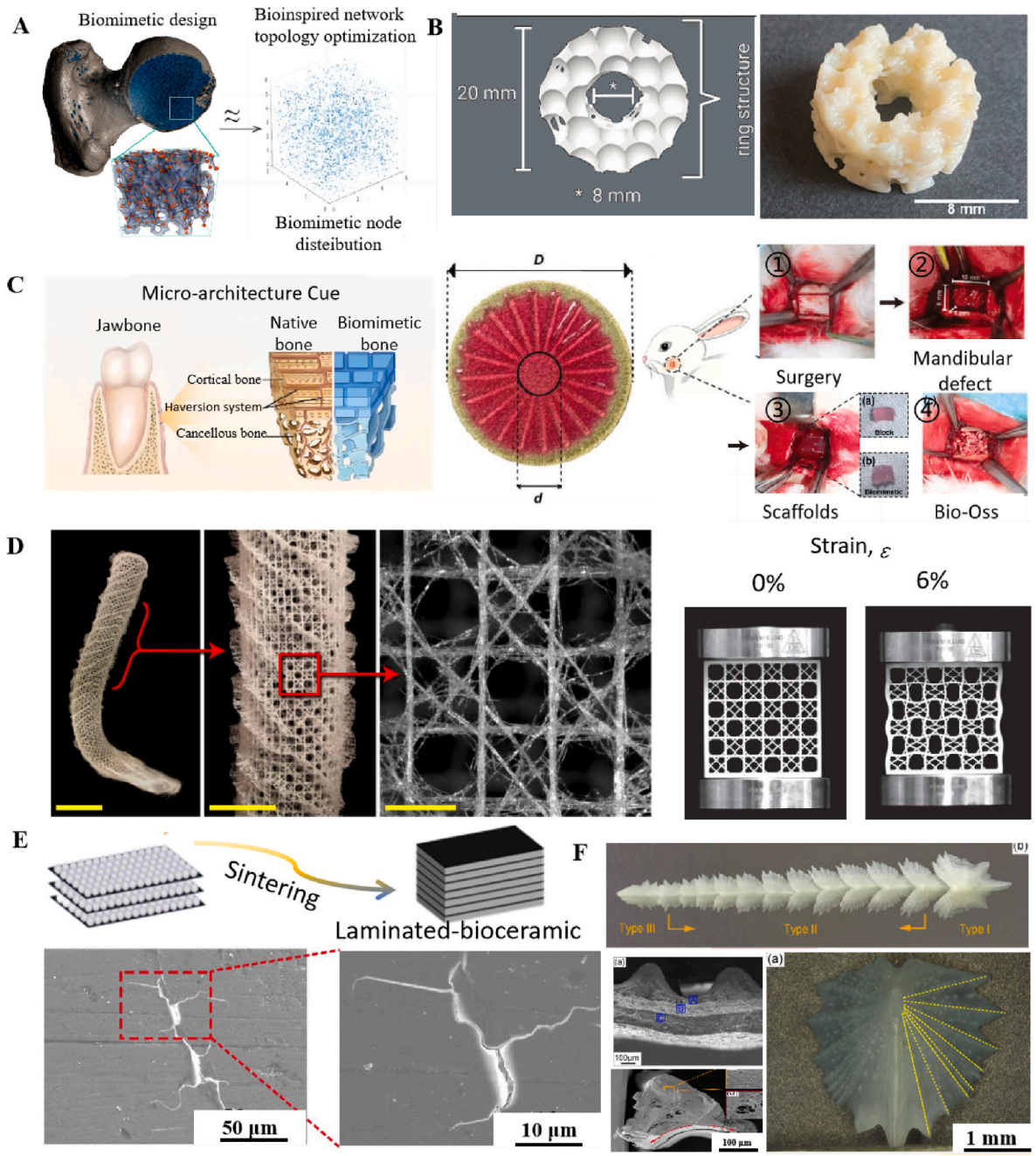

Fig. 8. Simulation of microstructure of cancellous and cortical bone. A) Trabecular bone bioinspired design with network optimization. Reproduced with permission [97]. Copyright 2021, Elsevier. B) Ring-shaped scaffold mimicking a spongiform structure. Reproduced with permission [98]. Copyright 2023, Frontiers. C) The biomimetic scaffold was designed according to the natural structure of the jaw. Reproduced with permission [99]. Copyright 2023, Wiley. D) Inspired by deep-sea glass sponges. Reproduced with permission [102]. Copyright 2021, Springer Nature. E) Bioinspired laminated bioceramics's crack deflection and crack branching. The L-M/CS-8 had the better mechanical properties than traditional $CaSiO_3$ bioceramics and exhibited similar modulus and strength with cortical bone. Reproduced with permission [108]. Copyright 2022, MDPI. F) Structural characteristics of bone plates. Reproduced with permission [109]. Copyright 2019, Wiley.

enhance the efficacy of bone defect repair. Leveraging 3D printing technology, researchers can precisely replicate these intricate structures to facilitate the growth and regeneration of new bone tissue. Furthermore, endeavors to devise biomimetic periosteum, vascularized scaffold structures, and interfaces mimicking the bone-cartilage transition aim to emulate the natural processes of bone growth and repair, thereby augmenting the success rate and effectiveness of bone tissue regeneration. Through the adoption of these biomimetic structural designs, one can envisage a proliferation of breakthroughs and advancements in the realms of bone tissue engineering and regenerative medicine.

2.2.1. *Structural features of bone*

Bone is a remarkable and complex tissue that serves as the foundation of the skeletal system. Bone comprises both cancellous and cortical bone. Cancellous bone, situated internally, possesses a sponge-like structure, primarily tasked with bearing pressure and absorbing shocks [89]. Trabeculae constitute the principal component of cancellous bone [90], organized within a three-dimensional network, thereby augmenting the bone's compressive strength [91]. Furthermore, cancellous bone harbors Haversian canals, vascular channels that interconnect with bone tissue through Haversian canals and trabecular tunnels, supplying essential nutrients and oxygen to the bone while

facilitating the elimination of metabolic waste [92]. Cortical bone forms the bone's outer layer, characterized by high hardness and toughness, serving a supportive and protective function [93]. Lamellae, integral to cortical bone, consist of densely packed osteocytes and collagen fibers, contributing to the bone's hardness [94]. Bone cells are responsible for the formation, repair, and remodeling of bone tissue. The marrow cavity, situated at the bone's core, houses marrow and participates in blood production and immune responses [95]. Fig. 7 displays a detailed presentation of the bone structure, elucidating the intricate interplay between the microarchitecture and the functional significance of each constituent element. This detailed analysis is paramount for comprehending the biomechanical characteristics and the dynamic mechanisms underlying bone tissue homeostasis.

2.2.2. Simulating trabecular microarchitecture

Trabeculae are interwoven fine beam-like structures within bone, particularly abundant in cancellous bone [96]. These trabeculae form the internal network structure of bone tissue, providing strength, stability, and contributing to the lightweighting of bone tissue.

Ammar et al. [97] drew inspiration from constructive regression-a natural process of network connection optimization occurring in early bone development-and achieved structures with low metabolic cost and high functional efficiency through iterative pruning of connections (Fig. 8A). 3D-printed scaffolds, inspired by the structure of bone sponges (Fig. 8B), featured irregular and interconnected porous structures with a porosity of 35.2 %. These implants, designed as annular structures, exhibited compressive strengths within the range of natural cancellous bone [98].

Shi et al. [99] developed an organic-inorganic nanoink containing ultra-small calcium phosphate oligomers and bone morphogenetic protein 2 (BMP-2) for craniofacial bone repair grafts. This nanoink comprised a cortical layer with a Haversian system and a cancellous layer featuring a triphasic minimal surface macrostructure, loaded with factors conducive to regenerating new bone, exhibiting a gradient density of biologically active substances (Fig. 8C). The graft exhibited promising osteogenic and angiogenic potential *in vitro* and effectively promoted new bone formation with original morphology in a rat cranial defect model. Its natural architecture facilitated load dispersion, ensuring long-term stability and making it a promising solution for craniofacial bone regeneration. Zhou et al. [100] designed scaffold cross-sections mirroring the hierarchical structure of new bone formation from bottom-up, manifesting an irregular honeycomb-like microstructure akin to that of natural bone tissue. This biomimetic artificial bone scaffold possessed trabecular characteristics and a porous structure. Recent studies on 3D-printed biomimetic scaffolds for meniscus reconstruction demonstrate their potential to replicate native tissue anisotropy and address personalized medical needs [101].

The cancellous skeletal system, constituting a microstructure of bone tissue, typically consists of numerous small beams or columns arranged in a specific configuration to maximize strength and stiffness while retaining a lightweight structure. Empirical evidence has demonstrated that structural insights drawn from the cancellous skeletal system can be harnessed to achieve geometrically optimized square lattices (Fig. 8D), averting overall structural buckling, which holds significant importance in bone tissue engineering applications [102]. Inspired by the trabecular structure, Mario et al. [103] employed 3D printing technology to fabricate scaffolds with a microstructured design. They validated that by emulating the layered structure of natural bone, these scaffolds not only provided an appropriate biocompatible environment but also enhanced their bioactivity. Furthermore, Li et al. [104] have corroborated that the mechanical properties of the cancellous lattices in Euplectella aspergillum (a deep-sea glass sponge) surpass those of cancellous structures under various loading conditions.

By emulating the internal network of trabeculae, 3D-printed constructs featuring irregular and interconnected porous structures have been developed, closely resembling the mechanical properties of natural cancellous bone. These biomimetic approaches not only optimize load distribution and biocompatibility but also enhance bioactivity, underscoring the potential of trabecular-inspired designs in advancing bone tissue engineering.

2.2.3. Cortical bone simulation

The remarkable mechanical resilience of bone stems from its intricate layered composition in cortical bone. This structure not only empowers bone to withstand fracturing under diverse physiological stresses but also establishes an adaptable and self-repairing framework for damage resistance [105–107]. Such a framework stands as a pivotal source of inspiration for biomaterial design, showcasing the effective adaptation of biological systems to dynamic environments and the innate regenerative abilities of living organisms. Building upon this inspiration, Huang et al. [108], engineered a biomimetic structure, termed layered MXene/calcium silicate (L-M/CS), mirroring the toughness of natural materials with multilevel laminates. This innovative biomimetic ceramic exhibited remarkable properties closely resembling those of cortical bone, boasting a significantly heightened center point toughness of 2.23 MPa and a robust flexural strength of 145 MPa, thus offering a fresh perspective for the design and manufacturing of biomaterials (Fig. 8E). Additionally, a bionic osteoplate featuring a multilayer microstructure, modeled after the Chinese sturgeon, showcased exceptional mechanical prowess, including high specific tensile strength (Fig. 8F), thus presenting a novel blueprint for the bionic design of lightweight, high-strength bulletproof vests [109]. The mechanical resilience of cortical bone, resulting from its layered composition, is foundational for biomaterial design and inspires the creation of biomimetic structures that can withstand various stresses and promote self-repair.

2.2.4. Morphological adaptations in biomimetic structures

The morphology of synthetic bone scaffolds often mirrors the anatomical structure of the bone defect site, enabling precise and personalized repair [110–112]. Given the variability in defect size and shape, biomimetic designs-such as gradient structures and hierarchical architectures-are essential for achieving optimal mechanical performance and biological functionality [113]. For instance, Durgalakshmi et al. [114] developed a biomimetic periosteum mimicking the layered structure of natural bone matrix, which exhibited excellent mechanical properties and biocompatibility for targeting bone diseases. Similarly, Aleksandra et al. [115] designed multi-striped and gradient structures to emulate the bone-cartilage interface, demonstrating the potential of 3D bioprinting for complex tissue regeneration. Inspired by natural bone tissue, hierarchical vascularized structures composed of angiogenesis and osteogenesis modules have been engineered to promote bone regeneration [116]. Zhang et al. [117] fabricated biomimetic wave-like elastic structures for costal cartilage implants, precisely tuning their mechanical properties by adjusting design parameters. These designs not only enhance mechanical stability but also facilitate cell encapsulation and growth factor delivery, critical for successful bone repair. Growth plates, located in the cartilaginous regions of immature long bones, have also inspired biomimetic scaffold designs. Wang et al. [118] fabricated poly(ε-caprolactone) (PCL) scaffolds with varying pore sizes to mimic the anatomical structure of growth plates *In vitro* experiments revealed that stratified scaffolds could induce organized patterns in cartilage cells, similar to those found in natural growth plates.

Advancements in bone tissue engineering are increasingly focused on replicating both the macroscopic and microscopic structures of natural bone tissue. By leveraging 3D bioprinting technology, researchers can precisely mimic the intricate architecture of bone, enhancing the success rate and efficacy of bone repair [119]. Biomimetic structural design not only fosters a biocompatible environment but also enhances bioactivity, offering novel solutions for bone tissue engineering applications.

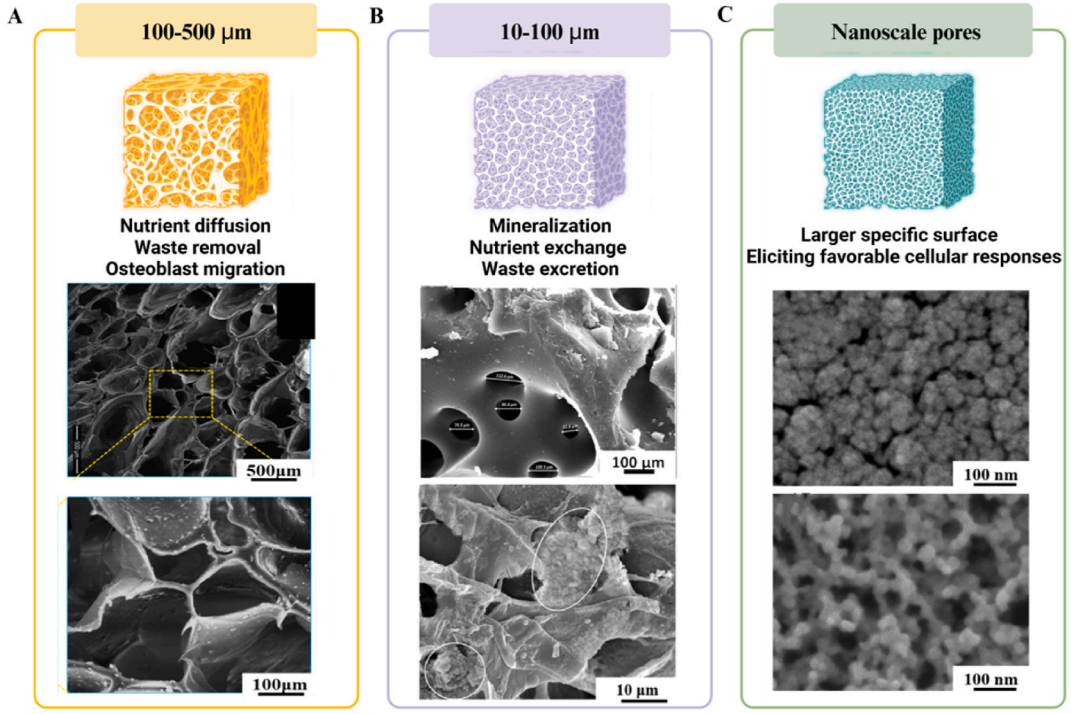

Fig. 9. SEM images with different pore sizes. A) 100–500 μm pore size. Reproduced with permission [121]. Copyright 2020, Elsevier. B) 10–100 μm pore size for mineralization. Reproduced with permission [125]. Copyright 2020, Elsevier Copyright 2022, ACS. C) Nanoscale pore. Reproduced with permission [126]. Copyright 2021, Elsevier.

3. Key structural parameters for bone constructs design

3.1. Pore size

Pore size is a critical factor in the design of 3D printed structures for bone tissue engineering. Smaller pores (~100–500 μm) support cell attachment and proliferation, while larger pores (>500 μm) enhance vascularization and bone ingrowth. These variations directly influence the biophysical and biochemical environment within the scaffold, ultimately impacting bone tissue formation and growth [120]. Studies have shown that a porous network comprising pores sized between 100 and 500 μm offers channels for nutrient diffusion and waste removal, facilitates osteoblast migration and bone tissue regeneration (Fig. 9A), and provides a certain level of mechanical integrity [121,122]. Hence, this pore size range is widely adopted in the design of 3D printed structures. The pore size of 40–100 μm is conducive to the growth of mineralized tissues [123,124], while pores of size ~100 μm are consistent with the growth of capillaries, promoting the exchange of nutrients and the excretion of waste products [125] (Fig. 9B). Nanoscale pores can provide a larger specific surface area and more active targets (Fig. 9C), which assist in cell nucleation and protein adsorption, thereby eliciting favorable cellular responses [126]. Research indicates that 3D interconnected porous multilevel nanostructured carbon demonstrates superior properties, with its macroporous/mesoporous structure optimizing mass transfer pathways and significantly enhancing material selectivity [127,128]. Nanobiostructures have also emerged as a focal point in bone tissue research due to their size-dependent properties, offering unique advantages [129]. Excessively large pores can compromise mechanical strength, while small pores may hinder cell infiltration and nutrient transport. Therefore, a balance must be struck between biological functionality and mechanical integrity.

In a study on 3D printed porous scaffolds (3DPP), Hong et al. [130] compared three scaffold types with varying pore sizes (3DPP-1: 150–200 μm, 3DPP-2: 250–300 μm, and 3DPP-3: 300–350 μm). Utilizing micro-computed tomography for analysis, they observed bone regeneration on the microscopic porous structures of all scaffolds. The 3DPP-3 scaffolds, with approximately 350 μm pores, exhibited the highest percentage of bone formation volume, while the 3DPP-1 group demonstrated significantly superior compression force of 273 ± 20.8 Kgf. This discovery holds significant implications for dentistry and orthopedics, indicating that larger pore sizes better promote bone regeneration while providing adequate structural support. Similarly, at the same porosity, Cheng et al. [131] fabricated open-pore magnesium scaffolds with pore sizes of 250 μm and 400 μm, respectively. They noted that by adjusting pore size alone, the mechanical properties of the scaffolds could be tailored within the range of human cancellous bone without compromising their porous structure. Scaffolds with larger pores exhibited enhanced formation of mature bone, attributed to improved oxygen and nutrient delivery, sustained osteoblast activity, and upregulation of osteoblastic polypeptide (OPN) and type I collagen, directly influencing bone mass increase.

Optimizing pore size in bone scaffold design not only regulates structural strength but also facilitates nutrient transport, waste removal, and uniform cell distribution [132], promoting seamless integration with surrounding bone tissue and ultimately achieving structural and functional restoration of bone defects.

3.2. Porosity

Porosity stands as a critical parameter in porous structure design, directly influencing both the biological functionality and mechanical characteristics of bone tissue engineering scaffolds. It denotes the total volume of voids within a porous material relative to the volume of the solid material. This ratio is influenced not only by pore size and strut dimensions but also by overall porous structure characteristics [133]. Optimal porosity is essential for bone tissue regeneration, providing sufficient space for cell proliferation and ensuring adequate load-bearing capacity [122,134].

Cell growth scaffolds typically require around 80 % porosity to stimulate cell activity and tissue growth. Increasing porosity generally

Table 1
Structural and biological properties of 3D-printed bone scaffolds.

Structural Classification	Structural Parameters	Fabrication Technique	Biological Outcomes	**Structural Design Inspiration**	Reference
Porous architectures	**Porosity:** 68 %; **Pore Size:** 100–500 μm	3D Printing/Gel Microspheres	Enhanced angiogenesis, bone repair in rat femoral defects	Lotus seedpod-inspired design	[32]
Porous architectures	**Elastic moduli:** 1.6–3 GPa; **Pore Size:** 200–400 μm	3D Printing/Finite Element Analysis	Mechanical properties matched human cancellous bone	Honeycomb design	[35]
Porous architectures	**Helical porous structures**; **Pore Size**: 100–300 μm; **Mechanical Property**; High torsional strength and flexibility	3D Printing	Superior mechanical performance and osteogenic differentiation *in vitro*	Conch-Like Scaffolds	[44]
Porous architectures	**Gradient Porosity**; **Pore Size**: 50–300 μm; **Gradient connectivity; Stiffness:** 0.5–2 GPa	3D Printing	Dynamic cell-material exchange, promoted bone cell growth	Plant pollen release mechanism	[45]
Hierarchical structures	**Pore Size:** 150–300 μm; **Porosity:** 50–70 %	3D Printing	Enhanced osteogenic and neurogenic activities *in vitro* and *in vivo*	Marine sponge spicules	[60]
Hierarchical structures	**Pore Size:** 100–400 μm; **Gradient porosity**	3D Printing	Promoted osteogenic and neurogenic differentiation	Plant leaf architecture	[66]
Hierarchical structures	**Pore Size:** 200–500 μm; **Porosity:** 60–80 %; **High compressive strength** ~95 MPa	3D Printing	Excellent mechanical properties (compressive strength: ≈95 MPa); angiogenic and osteogenic capabilities	Mussel-inspired design	[67]
Gradient designs	**Gradient porosity; Pore Size**: 100–500 μm; **Enhanced bending and energy absorption**	3D Printing	Improved bending load (up to 40 %) and energy absorption capacity (up to 110 %)	Bamboo's radial gradient distribution	[72]
Gradient designs	**Hierarchical pore distribution; Pore Size**: 50–300 μm; **High interconnectivity; High impact resistance and permeability**	3D Printing	Enhanced cell seeding efficiency, permeability, and impact resistance; promoted *in vivo* osteogenesis	Sea urchin spines	[78]

enhances cellular response, facilitating cell migration and proliferation within the scaffold, thereby promoting bone tissue formation and maturation [135,136]. Wang et al. [137] observed more mature osteoblast differentiation within the pore spaces of high-porosity scaffolds (>70 % porosity) compared to low-porosity counterparts (<70 % porosity). Additionally, high porosity influences scaffold mechanical properties, with the Young's modulus typically decreasing as porosity increases, aligning the mechanical properties more closely with those of natural bone [138]. Hence, when employing 3D printing technology, bionic and complex structural designs must consider the effects of porosity on cell behavior and mechanical properties to achieve optimal bone tissue regeneration.

3.3. Connectivity

Connectivity refers to the interconnection of closed loops (holes) within porous materials [139], playing a pivotal role in their mechanical and transport properties [140]. Moreover, highly interconnected pore networks have been shown to enhance angiogenesis by promoting endothelial cell migration and capillary formation, while also supporting immune modulation through improved cytokine diffusion [141]. While connectivity has minimal impact on the morphological variables of normal cancellous bone, bone stiffness typically decreases with increasing connectivity [142]. However, in porous composite structures like bone and sea ice, quantifying connectivity is essential for understanding their mechanical and electromagnetic characteristics. This decrease in bone stiffness results from the presence of additional channels in the cancellous bone structure, affecting the bone's elastic modulus and compressive strength [143,144].

In bone tissue engineering, connectivity influences bone tissue growth within the implant and angiogenesis, thereby affecting the bone healing process [145]. Excessive connectivity in porous materials may lead to uneven bone tissue growth into the material, affecting skeletal stability. Conversely, insufficient connectivity may impede nutrient transport and metabolic waste elimination, impacting bone tissue health. Otsuki et al. [146] conducted a 3D interconnectivity analysis of porous titanium implants with varying pore sizes and porosities, finding that the degree of porosity differentiation was closely linked to the narrowness of pore throats, potentially hindering inward bone tissue growth. Excessive connectivity can lead to uneven bone tissue growth, while insufficient connectivity may hinder nutrient transport. Therefore, optimizing connectivity is essential for achieving uniform tissue regeneration.

3.4. Mechanical property

The mechanical properties of scaffolds, such as elasticity modulus and compressive strength, are critical for ensuring stability and durability under physiological loads. Zhang et al. [147] successfully engineered scaffolds with tailored mechanical properties by precisely controlling the porous Ti_6Al_4V scaffold's mimetic structure through selective laser melting (SLM). They discovered the scaffolds with a high elasticity modulus (7–30 GPa) are suitable for load-bearing applications, while those with lower modulus (0.05–0.5 GPa) are more appropriate for non-load-bearing regions. This is because the low modulus scaffolds more closely mimic the compliance of soft tissue, allowing them to better absorb and dampen minor deformations caused by physiological movements, thus promoting the natural healing process of bone tissue. For non-load-bearing areas, 3D printed soft scaffolds are more suitable because of their lower elasticity modulus and compressive strength. These scaffolds can effectively replicate the non-weight-bearing conditions *in vivo*, offering structural support to facilitate cell infiltration and neovascularization [148,149]. The reduced stiffness allows the scaffolds to better absorb and dampen minor deformations resulting from physiological movements in non-weight-bearing regions, thereby supporting the natural healing process of bone tissue [150].

To meet these performance criteria, 3D printing technology serves as a valuable manufacturing tool. By precisely controlling the printing process, scaffolds with diverse mechanical properties can be tailored to meet the specific physiological demands of individual regions (Table 1). Furthermore, the capability of 3D printing to create intricate biomimetic structures, mirroring the natural bone tissue structure on a microscopic level, enhances the biocompatibility and mechanical characteristics of the scaffolds.

4. Advanced fabrication technologies for constructs design

4.1. The role of 3D printing

3D printing is a groundbreaking additive manufacturing technology that translates digital models into solid structures with intricate designs through meticulous control of the layer-by-layer stacking of biomaterials [151,152]. This technology shows immense promise in applications such as tissue engineering, drug release systems, and cell

Table 2
Comprehensive comparative analysis of 3D printing technologies for biomimetic scaffold.

Printing Method	Strengths	Limitations	Application Areas
Extrusion Printing	Cost-effective Easy to use Suitable for a wide range of biomaterials (e.g., hydrogels, ceramics)	Lower precision speed Limited accuracy Limited resolution for fine details	Fabrication of large, porous scaffolds [98] Production of fractal porous scaffolds with controlled gradients [57] Osteoinductive scaffolds for bone regeneration [74, 157]
Inkjet Printing	High printing speed and precise droplet control Suitable for printing cells and bioactive molecules Enables multi-material printing	Relatively high cost Limited to low-viscosity bio-inks Challenges in maintaining cell viability during printing	Fabrication of small, intricate scaffolds [99] Drug delivery systems and cell-laden constructs [160]
Laser Bioprinting	High resolution and precision for fine details Minimal cell damage due to non-contact printing Suitable for printing delicate biomaterials and cells	High equipment and operational costs Limited scalability for large-scale production Requires specialized expertise and equipment	Fabrication of complex, geometrically controlled scaffolds [163,165] Printing of cell-laden constructs with high cell viability [164] High-precision structures for bone-cartilage interfaces [165]

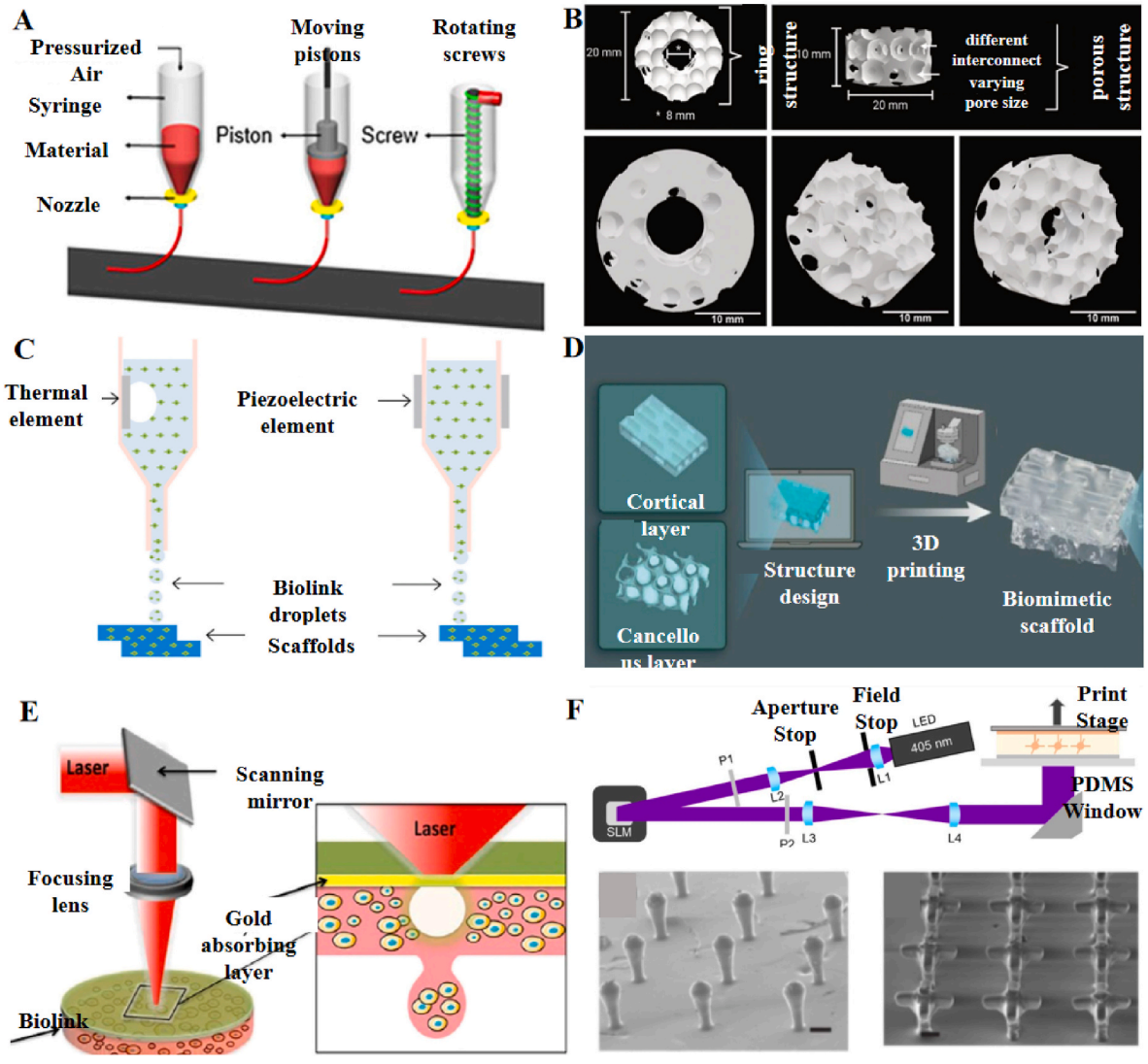

Fig. 10. Illustrative examples and fundamental principles of 3D printing technologies. A) Extrusion-based bio-printing methods, involving pressurized air, moving pistons, and rotating screws. Reproduced with permission [154]. Copyright 2017, Wiley. B) Different views and angles of the spongiosa-inspired 3D model. Reproduced with permission [98]. Copyright 2023, Frontiers. C) Schematic diagram of inkjet 3D bioprinting. Reproduced with permission [159]. Copyright 2020, Frontiers. D) The biomimetic graft were designed and printed by the projection-based 3D printer. Reproduced with permission [99]. Copyright 2023, Wiley. E) Schematic representation of laser assisted 3D bioprinting. Reproduced with permission [159]. Copyright 2020, Frontiers. F) Laser 3D bioprinting diagram: arrays (left) and branched crypt (right). Reproduced with permission [164]. Copyright 2020, IOP.

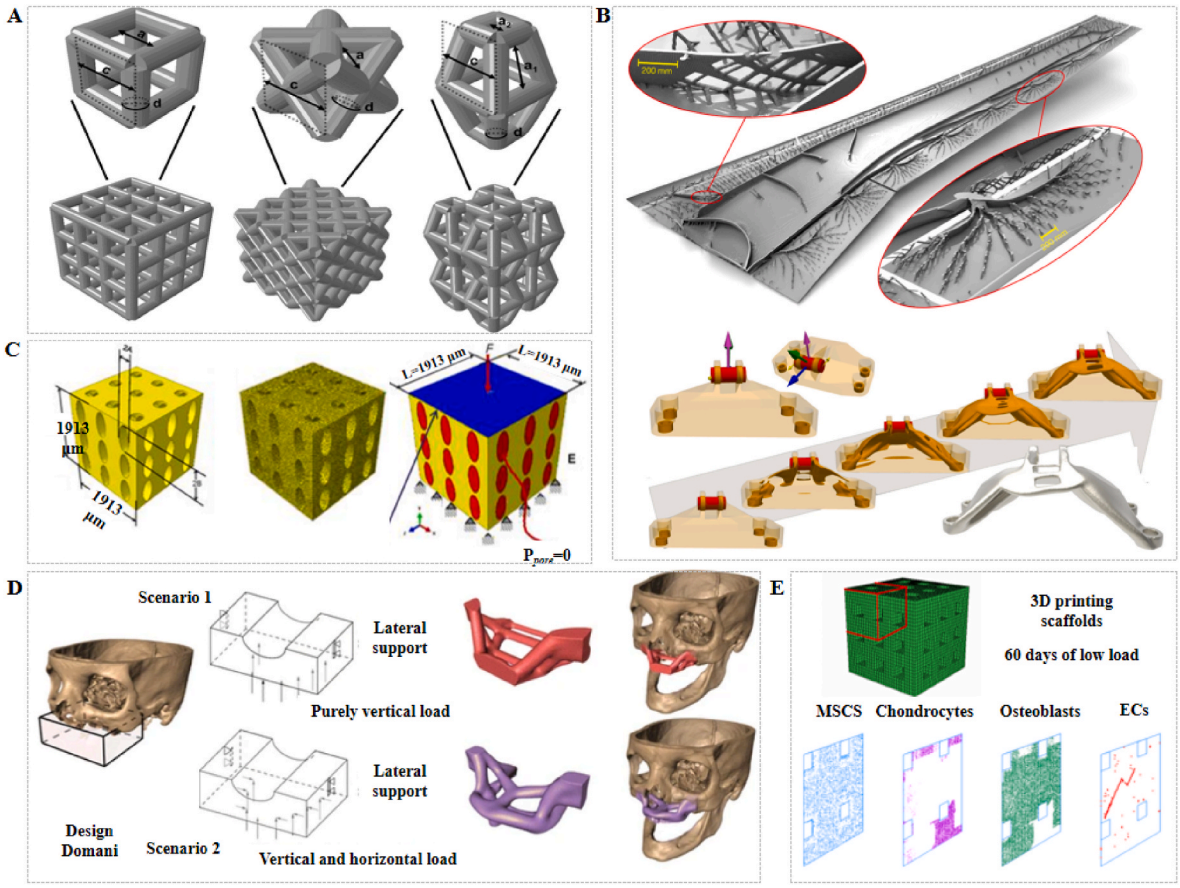

Fig. 11. CAD design for 3D printing. A) Design of parametric models for three different strut diameters, basic cell sizes and hole diameters using an optimization approach. Reproduced with permission [174]. Copyright 2014, Elsevier. B) The optimization algorithm used to design the morphogenesis of the jet engine support. Below is, after 400 topology optimization steps, the results of applying the giga-voxel morphogenesis process to aircraft wing design. Reproduced with permission [176]. Copyright 2017, Nature. C) In the case of elliptical pores, the CAD model, finite element mesh, the boundary and loading conditions on the model. Reproduced with permission [175]. Copyright 2016, PMC. D) Design and insertion simulation of 3D-printed implants post bilateral subtotal maxillectomy, optimized through topology. Reproduced with permission [177]. Copyright 2015, Springer Link. E) Predicting cell distribution in printable scaffolds using computer simulation (color). Reproduced with permission [178]. Copyright 2009, The Royal Society. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

culture [153]. Central to the efficacy of 3D bioprinting is its unique manufacturing process, which allows for the precise deposition of biomaterials layer by layer at specific locations. This is based on pre-designed digital models and utilizes techniques such as extrusion, inkjet, or laser printing to craft three-dimensional structures (Table 2)

Extrusion printing operates on a pneumatic or mechanical mechanism that extrudes materials or cells through a nozzle to build layers in adherence to a digital model [154–156] (Fig. 10A). In contrast, Julie et al. [98] succeeded in producing osteoinductive scaffolds with sponge-inspired structures using extrusion-based 3D printing technology (Fig. 10B). Extrusion printing offers advantages in terms of ease of use and cost-efficiency; however, it is characterized by relatively lower precision and speed [157,158].

Inkjet printing involves spraying ink onto paper or other media to form a pattern by controlling the ink jet's amount and position. This printing technology operates through two main methods: continuous inkjet printing and on-demand inkjet printing. In continuous inkjet printing, bio-ink is pressurized and ejected from the nozzle in a steady stream of droplets. These droplets are then directed onto the target substrate using an electric field. Conversely, on-demand inkjet printing, similar to continuous inkjet printing, generates droplets only when necessary. This mode achieves droplet formation by applying pulses of pressure instead of continuous pressure [159] (Fig. 10C). Shi et al. [99] developed an organic-inorganic nano-ink for 3D printing bionic layered craniofacial bone grafts (Fig. 10D). Thermal inkjet printers are known for their fast printing speed, easy control, and broad applicability; however, they come with a relatively high cost [160].

Laser bioprinting employs a laser beam to precisely manipulate biomaterials, constructing them layer by layer according to a digital model (Fig. 10E). This technique relies on the high energy and precise control of the laser beam, allowing for fine manipulation by focusing the beam on specific biomaterial parts [161]. Danilevicius et al. utilized femtosecond lasers to design and fabricate complex, geometrically controllable 3D printed scaffolds. Laser bioprinting technology finds diverse applications, given its high resolution and precision in printing active cells and biological tissues with minimal cell damage [162,163]. Carberry et al. [164] used laser printing to accurately produce structures that copy the crypt architecture of intestinal tissue (Fig. 10F). Nonetheless, the technology faces limitations, notably the high equipment cost of high-precision lasers [165], which may restrict its adoption in commercialization and large-scale applications. Regardless, as technology advances and costs decrease, the future application of laser bioprinting technology remains promising.

Printing parameters, such as pore size, porosity, resolution, and structural complexity, directly influence the biocompatibility, mechanical properties, and biological functionality of bone scaffolds [166]. Optimizing pore size enhances cell migration, nutrient transport, and bone tissue formation, while porosity and interconnectivity impact mechanical strength and osteointegration. However, variations in printing parameters can lead to inconsistencies in scaffold architecture,

affecting reproducibility and clinical reliability. Small deviations in printing resolution, layer thickness, or material viscosity can alter mechanical stability, degradation rates, and cellular interactions, potentially compromising scaffold performance. Therefore, establishing standardized printing protocols, real-time monitoring systems, and post-fabrication quality assessments is essential for ensuring scaffold consistency and regulatory compliance in clinical applications. These optimizations not only enhance bone repair and regeneration but also support personalized medicine, enabling the fabrication of patient-specific scaffolds that meet diverse clinical needs and drive successful clinical translation.

In conclusion, the significance of 3D bioprinting technology lies in its ability to facilitate the intricate design construction of complex 3D structures through precise fabrication, opening up new possibilities in fields like tissue engineering [167]. By adjusting design parameters such as pore size, porosity, and connectivity, scaffolds can be customized to meet specific clinical requirements, such as addressing severe rib fractures or promoting high vascularization for critical-sized bone defects [168,169]. The promising future of 3D bioprinting technology is further enhanced by ongoing technological advancements and cost reductions.

4.2. Integration of computational tools

4.2.1. Computer-aided design (CAD)

CAD utilizes computer-based modeling to optimize implant properties such as stiffness, permeability, and porosity [170,171], aiming to achieve the most effective structural design mode [172]. It enables the creation and modification of 3D models with specialized software and is commonly integrated with finite element analysis for designing intricate structures crucial in bone tissue engineering [173]. Wieding et al. [174] showcased the potential of additive manufacturing in treating substantial segmental bone defects by refining the geometric parameters of open porous titanium scaffolds to emulate the elastic properties of human cortical bone. This study underlined the efficacy of numerical optimization tools in reducing material usage while maintaining biomechanical scaffold properties (Fig. 11A). The advent of computer-aided design has sparked considerable interest among researchers in the field of personalized regenerative medicine. A recent study [175] introduced an algorithm that integrates CAD technology, parametric finite element analysis, numerical optimization, and computational mechanics tuning to predict and enhance scaffold microstructures for improved bone regeneration (Fig. 11B).

Notably, topology optimization, a computer-aided method, offers unrestricted design flexibility, enabling all scaffold parameters to be incorporated into the optimization framework objective function [176] (Fig. 11C). Sutradhar et al. [177] employed CAD in bone replacement design, utilizing topology optimization to create an optimized shape for areas of bone loss. The validated model was then produced using an FDM 3D printer with ABSplus TM-P430 thermoplastic, affirming the mechanical feasibility of the customized bone replacement shape (Fig. 11D). Furthermore, applying computer-aided design in tissue engineering offers a comprehensive method for the evaluation and screening of biomaterials, surpassing the conventional trial-and-error approach in new biomaterial research, which relies heavily on experimental methods [178] (Fig. 11E).

CAD has transformed bone tissue engineering by optimizing implant properties through advanced modeling and finite element analysis, facilitating the creation of complex structures that closely mimic natural bone. Despite its transformative impact on bone tissue engineering, CAD faces several limitations, including computational complexity in optimizing scaffold designs, limitations in translating intricate designs into physical constructs due to 3D printing constraints, and reliance on idealized models that may not fully capture real-world biological variability. These challenges highlight the need for more adaptive and computationally efficient design tools to better bridge the gap between theoretical models and practical applications.

4.2.2. Artificial intelligence (AI)

The integration of AI-assisted 3D printing technology in bone tissue engineering structural design is primarily focused on design optimization, material selection, bionic modeling, personalized medicine, and machine learning along with self-optimization [179]. AI enhances scaffold performance by predicting mechanical properties, refining pore architecture to improve cell infiltration, and enabling the generation of personalized structures based on patient-specific data. These advancements contribute to more effective bone tissue regeneration by ensuring optimal structural and biological functionality of the scaffold. An essential application of AI-driven optimization, particularly using genetic algorithm-aided artificial neural network (ANN) techniques, is observed in the development and material characterization of 3D-printed hand exoskeletons to enhance the tensile strength of their components [180]. Through computer-aided design and ANN optimization, a bone scaffold structurally resembling healthy human bone matrix in terms of strength, elasticity, and porosity was successfully fabricated using 3D bioprinting. Its potential as a fracture repair implant was validated through *in vitro* release kinetics studies and the formation of pseudobone in a butterfly fracture model [181]. Peng et al. [182] introduced a machine learning (ML) cycle combining the finite element method (FEM) and 3D neural networks to efficiently optimize the multi-property aspects of 3D-printed building materials. This methodology was implemented in orthopedic implant design, leading to the creation of microscale heterostructures with biocompatible elastic modulus and enhanced strength. Furthermore, by adapting machine learning designs architecturally, this approach not only boosts experimental load-bearing capacity but also reveals the potential for machine-human collaboration in addressing irregularly shaped, macroscale animal bone defects. The incorporation of artificial intelligence in the 3D printing process enhances predictive capabilities, parameter adjustment, and control, thereby minimizing error risks [183–185]. The ongoing advancements in AI technology significantly bolster bone tissue engineering, improving the accuracy and efficiency of skeletal repair and reconstruction, ultimately enhancing personalized medical outcomes for patients.

Integrating AI into 3D printing and bone tissue engineering presents significant potential, particularly in design optimization, parameter tuning, and predictive modeling. However, challenges remain, including the reliance on large datasets, unpredictability in biological responses, and the lack of interpretability in AI-generated designs. Addressing these issues requires improved data collection, interdisciplinary collaboration, and the development of explainable AI models to ensure clinical reliability and regulatory acceptance. Moreover, standardized manufacturing processes and quality control systems are crucial to ensuring reproducibility and clinical efficiency. AI-driven fabrication must be complemented by automated monitoring techniques, validation protocols, and real-time error detection to minimize variability in scaffold production and meet clinical safety standards. Implementing these strategies will help bridge the gap between AI-generated scaffold designs and their successful clinical application.

5. Applications of structural design

5.1. Promoting angiogenesis

Angiogenesis frequently accompanies bone formation, with pore size and porosity identified as key influencing factors [186–188]. In a study by Frank et al. [189], biphasic calcium phosphate particle scaffolds with pore sizes exceeding 140 μm demonstrated increased capillary density during live microscopy compared to scaffolds with smaller pores. Research by Artel et al. [190] revealed that larger pore sizes (160–270 μm) supported rapid generation of sprouting vessels in scaffolds, with vascularization efficiency improving as pore size increased. Scaffolds with suitable pore size and porosity create a porous structure mimicking natural bone, while porous branching structures offer enhanced surface

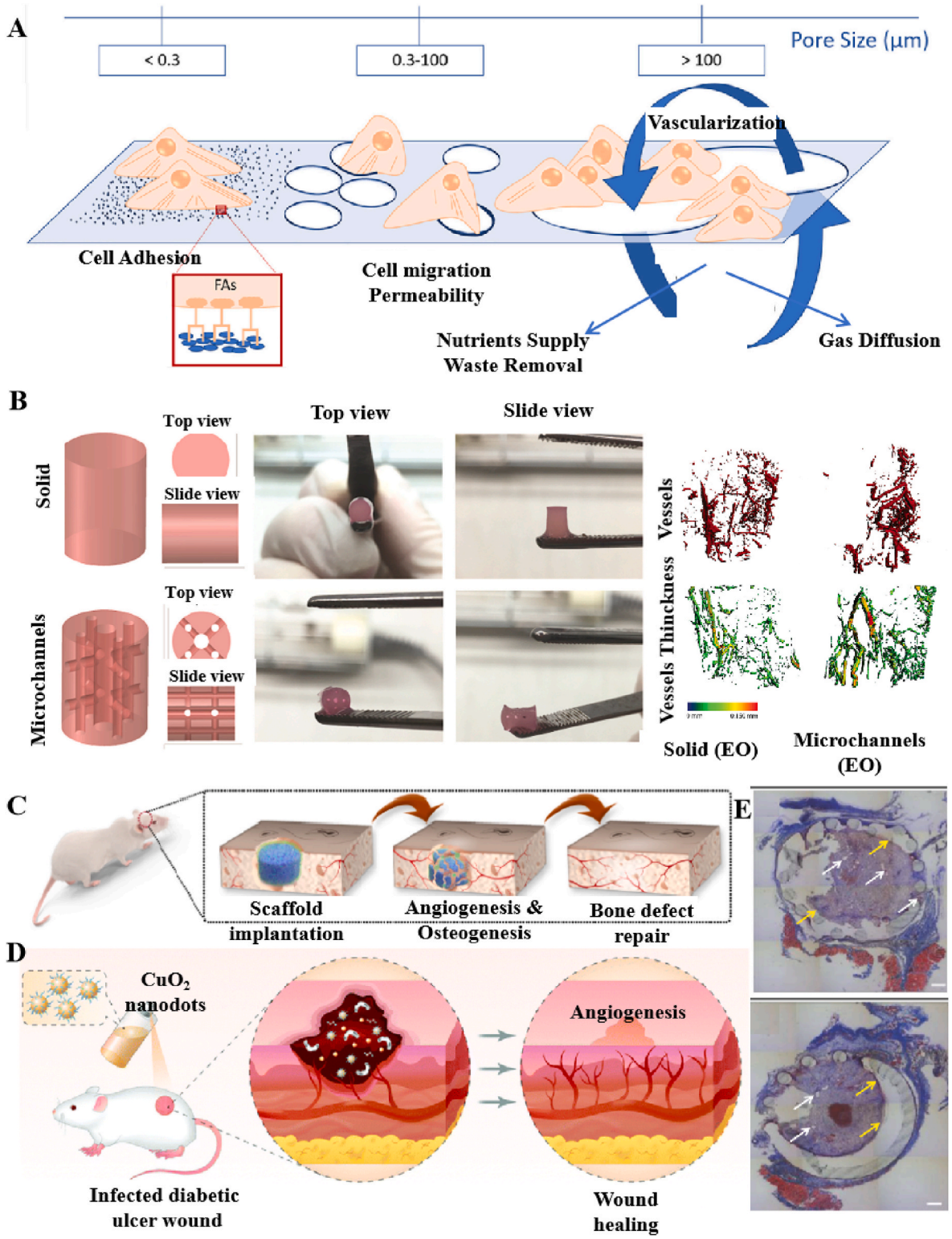

Fig. 12. Applications of structural design on angiogenesis. A) The porous surface affects cell behavior promoting angiogenesis. Reproduced with permission [191]. Copyright 2019,Wiley. B) Structural design demonstrating interconnected microchannel network and 3D reconstructions illustrating vessel formation, along with corresponding 3D morphometric reconstructions of vessel diameters in the defects. Reproduced with permission [192]. Copyright 2018, Elsevier. C) Schematic representation of repairing rat calvarial defects with scaffold implantation. Reproduced with permission [198]. Copyright 2023, Elsevier. D) Schematic representation of CuO_2 nanodots promoting angiogenesis and wound healing. Reproduced with permission [199]. Copyright 2021, The Royal Society of Chemistry. E) Masson's trichrome staining technique was employed for imaging. The top image features a scaffold with a thick wall, measuring 400 μm in pore size and boasting a porosity of 38 %. Conversely, the bottom image presents a scaffold with larger pores, sized at 800 μm, and a porosity of 25 %. Both images reveal the presence of vessels and collagen fibers within the scaffold's columns. The yellow arrow signifies a moderate inflammatory cell response at the interface of the polypropylene fiber, while the white arrow indicates the direction of the blood vessels. Reproduced with permission [193]. Copyright 2011, Wiley. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

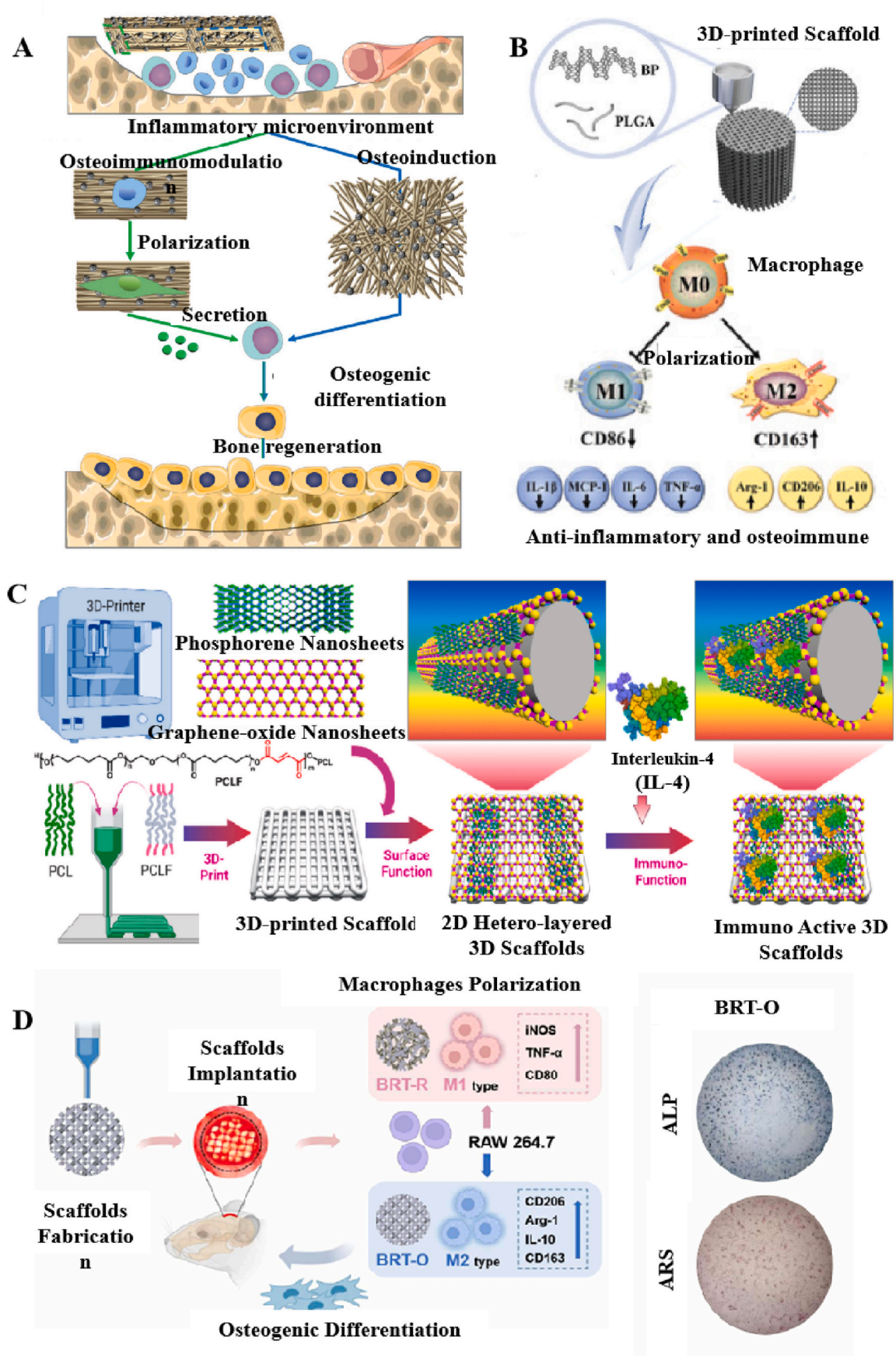

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Fig. 13. Applications of structural design on immunoregulation. A) The regenerative mechanism of socket augmentation involves the activation of anisotropic nanofiber architecture and CAP-mediated modulation of bone immunity, as well as the facilitation of anisotropic nanofiber morphology and CAP-induced bone formation. Reproduced with permission [205]. Copyright 2021, Wiley. B) Schematic illustration of PLGA/BP scaffolds fabricated by 3D printing and proposed mechanism of osteoimmune environment induced by BP degradation to accelerate bone regeneration. Reproduced with permission [206]. Copyright 2023, Wiley. C) A schematic illustration of the creation of a 3D-printed scaffold with immunological activity via an extrusion-based 3D printer, subsequent to which a 2D material is applied to its surface and loaded with cytokines. Reproduced with permission [208]. Copyright 2023, Elsevier. D) Mechanism of osteo-immunomodulation by 3D-printed BRT-O scaffolds for bone tissue engineering. And ALP staining for alkaline phosphatase activities and ARS images for calcium deposits of the BMSCs. Reproduced with permission [211]. Copyright 2023, PMC.

area and channels facilitating new substance diffusion within vessels, further supporting angiogenesis [191] (Fig. 12A). Daly et al. [192] utilized 3D printing with mesenchymal stem cell (MSC)-loaded GelMA hydrogel to produce cartilage templates featuring interconnected microchannel networks, promoting endochondral bone regeneration and guiding blood vessel formation (Fig. 12B). To study inward vessel growth, Martha et al. [193] utilized a computer model, analyzing the impact of parameter adjustments on stent vascularization rates and depth (Fig. 12E). Varying porosities (25 % and 50 %) and pore diameters (200, 400, and 800 μm) besides wall thicknesses (100 and 500 μm) were considered. The study highlighted that scaffolds with larger porosity exhibited increased angiogenic indices with rising porosity, while under constant wall thickness and porosity conditions, angiogenic parameters like maximum invasion depth (MID), successful germination rate (ROSS), invasion depth (AID), and total blood vessel length (TBVL) typically decreased. Computer simulations indicated reduced vascularization with increasing wall thickness. Thus, parameters such as pore size and porosity are critical in shaping vascular networks in bone tissue engineering [125,194,195].

The influence of nanotopography design on biological processes, including cell adhesion, proliferation, and differentiation, is crucial for bone regeneration and angiogenesis [196,197]. Zhou et al. [198] engineered polyelectrolyte-modified biomimetic scaffolds with a nanofibrous structure, significantly enhancing cellular proliferation and new microvessel formation *in vitro* rat cranial defects (Fig. 12C). Zhang et al. [199] conducted a study on copper peroxide nanodots (CuO_2) stimulating high expression of HIF-1α and VEGF (Fig. 12D). Comparative analysis between nanoconvexed dots (NCDots) and nanoconvexed pits (NCpits) demonstrated superior osteogenic and pro-angiogenic capabilities of NCDot microarrays over NCPit chips, fostering an appropriate immune microenvironment [200]. Emulating the natural extracellular matrix, the nanoscale scaffolds offer an ideal setting for cell adhesion, proliferation, and differentiation, yielding benefits superior to traditional therapies [200–202].

5.2. Immunomodulation

Scaffolds engineered for bone regeneration can facilitate immunomodulation through cell behavior regulation [203,204]. Through optimizing scaffold structural design, precise regulation of cell behavior is achievable, fostering an immune microenvironment supportive of bone tissue regeneration in a 3D context [205] (Fig. 13A). Lai et al. [206] developed a multifunctional biomimetic porous scaffold composed of degradable polymer composite black phosphorus (BP) using low-temperature deposition 3D printing technology (Fig. 13B). This scaffold not only delivered specific chemical signals but also mimicked the 3D structure of human bone tissues, offering a platform for cell attachment and growth. By modulating macrophage polarization, these scaffolds influenced the immune microenvironment effectively, promoting bone defect repair. Wu et al. [207] successfully engineered scaffolds for bone regeneration that can facilitate immunomodulation by regulating cell behavior. Through optimizing scaffold structural design, precise regulation of cell behavior is achievable, fostering an immune microenvironment supportive of bone tissue regeneration in a 3D context [208] (Fig. 13C). Chen et al. developed a 3D-printed, stone-cottage-inspired microsphere-patterned scaffold that enhances bone regeneration by promoting cell recruitment and modulating immune responses through surface microtopography regulation [209].

Furthermore, by controlling pore size and connectivity [210], precise regulation of cell growth and migration within the scaffolds can be achieved, subsequently enhancing immunomodulation. For instance, the structured BRT-O scaffolds derived from Bredigite (BRT) bioceramics released a substantial concentration of ionic products due to their uniform morphology and consistent porosity, thereby stimulating new bone formation and M2-type macrophage infiltration in a critical-sized bone defect rat model. This scaffold also upregulated osteogenesis-related markers' expression in the skull defects [211] (Fig. 13D). Hence, well-designed scaffold structures can effectively regulate cellular behavior and immune responses to establish an optimal microenvironment for bone regeneration [212,213].

Structurally engineered bone regeneration scaffolds provide vital biomechanical support and immunomodulatory mechanisms for repairing bone defects by modulating cell behavior and influencing the immune microenvironment.

5.3. Improving osseointegration

Osteointegration is a complex biological process *in vivo*, involving intricate spatio-temporal interactions encompassing immune response, angiogenesis, and osteogenesis (Fig. 15). The process of osteointegration refers to the intricate interplay between bone tissue and the structural and functional aspects of an implant's surface, representing a continuous and dynamic exchange that evolves within a temporal and spatial matrix [214] (Fig. 14A). During this process, biomolecules and cytokines interact to facilitate bone tissue repair and regeneration.

The immune response is pivotal in osseointegration, aiding in pathogen clearance and tissue recovery, fostering a favorable milieu for new blood vessel and osteoblast growth [218–220]. Angiogenesis is essential for bone tissue by providing the necessary oxygen and nutrients to osteoblasts, promoting tissue growth and repair [221,222]. Zhang et al. [215] developed bionic layered scaffolds utilizing artificial DFO@PCL nanoparticles, manganese carbonyl nanosheets, gelatin methacryloyl hydrogel, and poly(propylene glycolide)/HA matrix (Fig. 14B). The biomimetic scaffold markedly ameliorates bone tissue regeneration and angiogenesis through the strategic modulation of the immune response and the fostering of equilibrium in bone metabolic processes. In bone development, mesenchymal stem cells actively pursue differentiation into osteoblastic lineage cells [216] (Fig. 14C). Osteoblasts are indispensable for bone regeneration, secreting bone matrix proteins such as collagen and osteocalcin that stimulate bone formation and mineralization [223]. In bone tissue engineering, the method of promoting bone defect repair by co-regulating bone regeneration, angiogenesis and immune regulation is receiving more and more attention [224–226]. 3D printing technology was employed to craft these scaffolds with a gradient structure akin to cortical and cancellous bone tissue [217] (Fig. 14D). Upon implantation, the scaffolds triggered vascular neovascularization by decreasing inflammation via M2 macrophage phenotype activation, concurrently enhancing vascular endothelial growth factor secretion. Extensive *in vitro* and *in vivo* experimental evidence showcased the scaffold's proficiency in immunomodulation, angiogenesis promotion, and bone regeneration, presenting a novel and effective strategy for addressing bone defects. Liu et al. [213] engineered composite PCL scaffolds with a specific structure using 3D printing technology, capable of modulating immune responses through M2

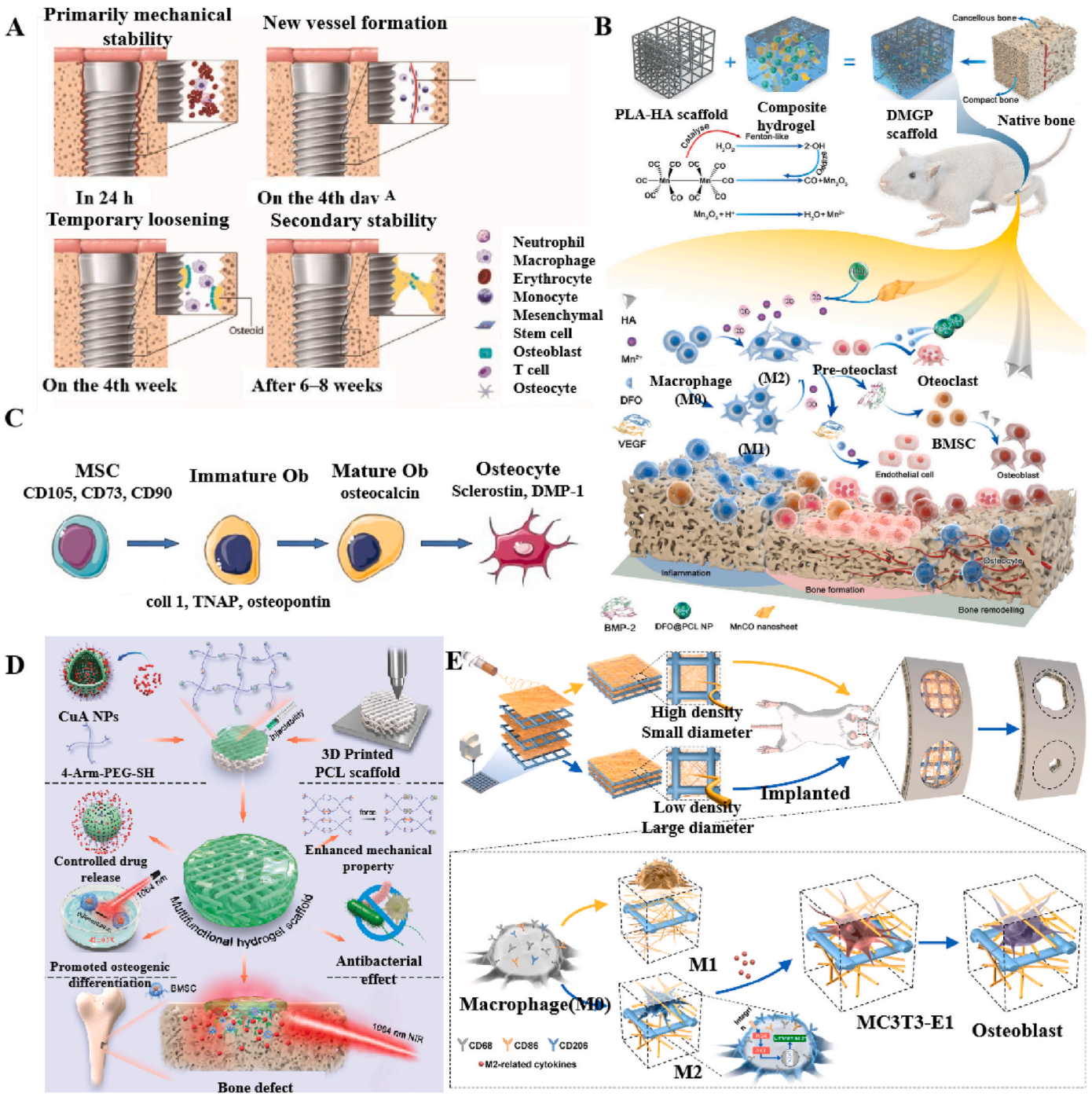

Fig. 14. Applications of structural design on osseointegration. A) The process of osseointegration over time. Reproduced with permission [214]. Copyright 2022, MDPI. B) Illustration of a biomimetic hierarchical scaffold regulating osteoimmunity for enhanced bone regeneration. The DMGP scaffold was composed of DFO@PCL nanoparticles, MnCO nanosheets, GelMA hydrogel, and a PLA/HA matrix. Reproduced with permission [215]. Copyright 2022, Wiley. C) Process in osteoblast differentiation form mesenchymal stem cells. Reproduced with permission [216]. Copyright 2013, Baishideng Publishing Group Co. D) Schematic representation of the synthesis of the multifunctional CuS nanoparticle-PEG composite hydrogel-coated 3D-printed polycaprolactone scaffold (CuS-PEG-PCL scaffold) featuring a soft-hard hybrid structure for bone tissue engineering. Reproduced with permission [217]. Copyright 2022, Wiley. E) The 3D-printed electrospun fibrous scaffolds polarized macrophages toward the M2 phenotype via PI3K/AKT signaling and enhanced bone regeneration. Reproduced with permission [213]. Copyright 2021, Elsevier.

macrophage polarization, thereby favoring osteogenesis, angiogenesis, and accelerating new bone formation (Fig. 14E).

The biomimetic scaffolds reviewed exhibit promising preclinical results in bone regeneration, angiogenesis, and immunomodulation. Recent advancements in 3D bioprinting have demonstrated the potential to fabricate patient-specific tissues and living cell systems, such as vascular networks, organs, and skeletal structures, which are critical for addressing complex bone defects [169]. For instance, 3D bioprinting platforms have been successfully used to create bone grafts with precise shapes tailored to critically sized defects, significantly improving bone healing outcomes. The integration of 3D medical imaging data with biomimetic design strategies has enabled the development of scaffolds that meet the specific size and shape requirements of individual patients, further enhancing their clinical applicability [227]. However,

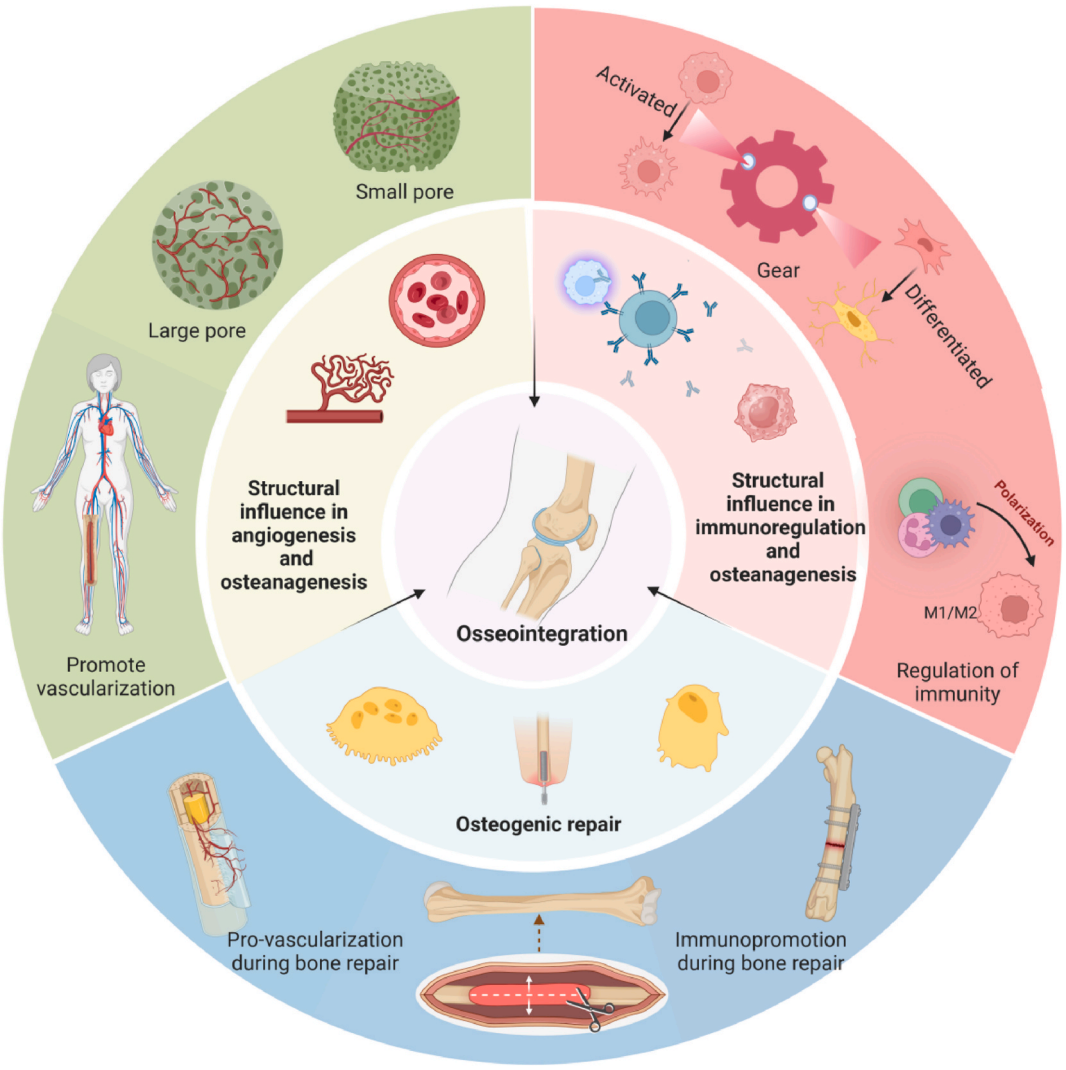

Fig. 15. Integrated structural strategies in bone scaffolds, highlighting their roles in promoting vascularization, immune regulation, and osseointegration for enhanced bone regeneration.

challenges such as long-term biocompatibility, large-scale manufacturing consistency, and regulatory approval remain. Future efforts should prioritize patient-specific design optimization, leveraging 3D printing and AI tools, and rigorous clinical validation. Overcoming these hurdles could transform bone tissue engineering, enabling personalized bone defect repair and enhancing clinical outcomes.

6. Conclusion and perspective

Bone tissue engineering structure design, a rapidly evolving field, holds promise for revolutionizing personalized medicine and advancing regenerative medicine. By optimizing key parameters like porosity, pore size, connectivity, and mechanical properties, and drawing inspiration from nature complex architectures, we can engineer scaffolds that closely mimic the structural and functional complexities of native bone, thereby enhancing their mechanical performance and biocompatibility. Understanding the intricate relationship between structural design and scaffold performance is crucial for successful bone regeneration. For instance, inadequate pore size or poor interconnectivity can hinder cell migration, nutrient transport, and vascularization, ultimately compromising the scaffold's ability to promote bone repair. Furthermore, this review highlights the integration of advanced technologies, such as AI and CAD, to propose optimization strategies that align with the multifunctional requirements of native bone, offering a novel perspective on patient-specific scaffold design. By addressing the critical but often underexplored role of scaffold structural design, this review provides a systematic evaluation that bridges the gap in the literature and offers insights for future scaffold optimization.

Despite significant advancements, the field still grapples with substantial challenges that hinder clinical translation. High production costs, coupled with stringent regulatory approvals and the imperative for consistent reproducibility in manufacturing personalized scaffolds, present formidable hurdles. Overcoming these obstacles necessitates extensive research and development efforts aimed at creating cost-effective materials, refining fabrication processes, establishing standardized testing protocols, and integrating AI-driven optimization tools to ensure compliance and efficacy in clinical settings. Looking ahead, the continued refinement of 3D printing technologies, coupled with advancements in CAD and AI, holds the potential to revolutionize scaffold fabrication and significantly enhance the precision, efficiency, and accessibility of bone tissue engineering. These innovations will be critical in driving the field towards large-scale clinical implementation, overcoming existing barriers, and fostering interdisciplinary collaboration. By addressing these challenges and leveraging the full potential of structural design, the next generation of bone tissue engineering scaffolds could transform personalized medicine, improve the clinical success rate of bone defect treatments, and contribute to better patient outcomes.

CRediT authorship contribution statement

Dan Huang: Writing – original draft. **Zuhao Li:** Writing – original draft. **Guangfeng Li:** Writing – original draft. **Fengjin Zhou:** Writing – review & editing. **Guangchao Wang:** Writing – review & editing. **Xiaoxiang Ren:** Writing – review & editing. **Jiacan Su:** Writing – review & editing, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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