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Advanced additive manufacturing in orthopedics: a comprehensive review of biomaterials, structural design, biological functions and clinical technology applications

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Large bone defects resulting from trauma, disease, or congenital aberrations present a significant clinical challenge because they often exceed the body's natural healing capacity. While conventional 3D printing has revolutionized orthopedics by providing patient-specific anatomical replicates, these constructs remain inherently static and fail to adapt to the dynamic physiological environment of a healing bone. This review provides a comprehensive analysis of the transition toward 4D additive manufacturing in orthopedics, a landmark shift that integrates the dimension of time into tissue regeneration. We evaluate the strategic landscape of stimuli-responsive smart materials such as shape memory polymers (SMPs) and functionalized hydrogels, which execute programmed morphological or functional changes in response to triggers like body heat, pH, and magnetic fields.

1. Introduction

Loss of tissue function due to defects is a common problem faced in clinical practice. In orthopedics, bone defects are a major problem that puts serious financial stress on patients. Defects might be brought about by trauma, congenital aberrations, bone disease (tumor, infection) and other factors.[1] Bone defects require immediate intervention as they affect the

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structural integrity of the bone. Larger-sized bone defects, known as critical defects, are of particular concern as they often cannot fully heal *via* the body's own repair system.[2,3] Several intervention methods have been implemented in clinical practice with the use of bone grafts being the standard method of intervention. Over 2 million bone graft procedures are required each year across the globe in defect repairs.[4,5] The source of the bone graft determines its nomenclature, with there being four main types used in orthopedics, namely, autologous, allogenic, xenogenic and synthetic bone grafts (Fig. 1).[6,7] Each of these has advantages and disadvantages in comparison to its counterparts. Autologous bone grafts are seen as the gold standard and are used in defects of critical size (>5 mm) as they exhibit the required qualities, such as biocompatibility, non-toxicity and osteoinductivity.[8,9] This process also faces various disadvantages, such as necrosis or infection at the site of graft extraction, limited quantity from the donor site, and poor integration at the recipient site.[10–12] Allogenic and xenogenic grafts also present several disadvantages ranging from rejection by the host's immune system to transmission of disease and incompatibility of blood components.[13–15] There is also concern that the processing and storage of allografts may compromise their osteoinductive and osteogenic properties.[16] To address these issues, the field has increasingly shifted towards synthetic tissue engineering strategies to bridge this gap.[17]

Synthetic bone grafts can be viewed as disadvantageous due to the major concerns of biocompatibility and sterilization. The advent of additive manufacturing (AM), or 3D printing, has marked the first revolutionary leap in this domain, allowing for the translation of patient-specific imaging into digital models for fabrication into personalized implants matching the defect.[18,19] Although 3D printed synthetics are able to meet geometrical requirements, they are still inert. The human body is a continuously evolving biological system, and an implant that fails to evolve with it remains merely a tolerated foreign body rather than a functional partner in regeneration. 3D-printed constructs are not dynamic; they fail to adapt to changes in the body's environment, such as the physiological changes in the healing environment, and they cannot actively respond to post-surgical complications, such as infection or inflammation.[20] This is a major issue in orthopedics as failure to adapt might lead to multiple revision surgeries, resulting in a financial burden to the patient. These limitations have led to further evolution in AM, which integrates the fourth dimension of time into the manufacturing process. Unlike static 3D printing, 4D technology utilizes smart stimuli-responsive materials such as shape memory polymers and hydrogels that are programmed to undergo specific structural or functional transformations when exposed to external triggers like heat, pH, or moisture. This capability allows for the creation of dynamic implants that can self-deploy through minimally invasive incisions, mechanically compress fractures as bone

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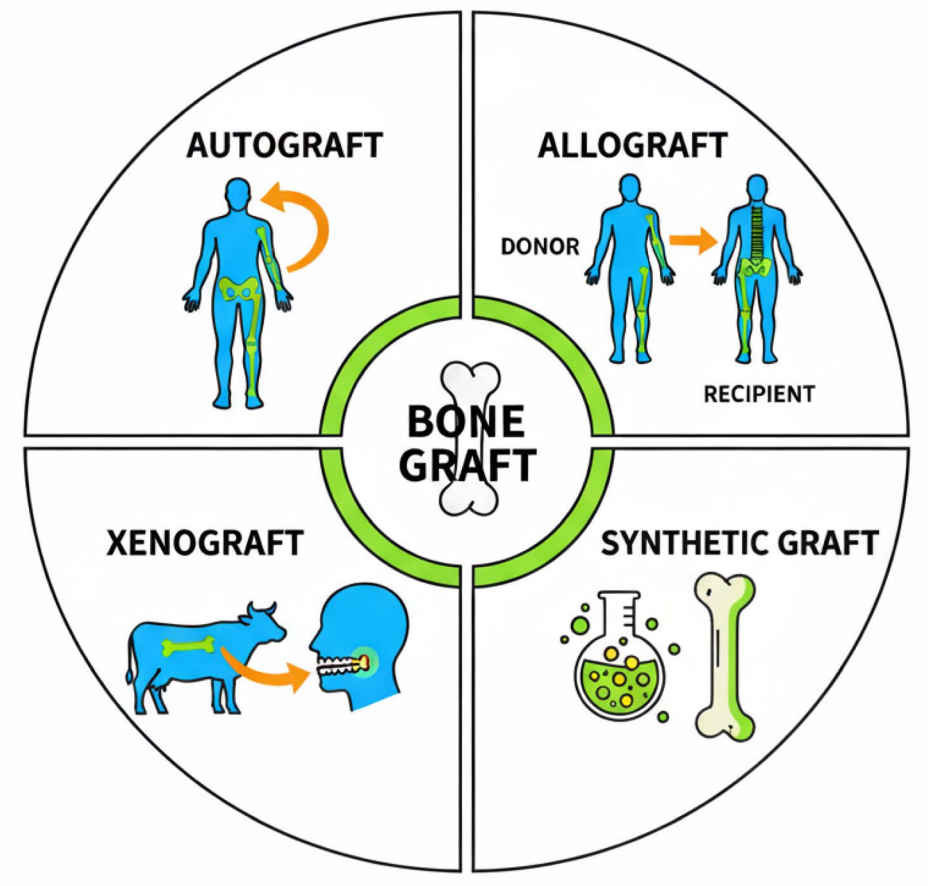

Fig. 1 Different types of bone grafts used in orthopedics and their sources.

resorbs, or release therapeutic agents on demand in response to infection signals.[21]

This review critically analyzes the evolution of AM in orthopedics from static 3D manufacturing to dynamic 4D biological systems. We move beyond the established manufacturing techniques to focus specifically on the mechanisms of stimuli-responsive biomaterials, the programming of biological functions, and the emerging clinical applications of smart orthopedic devices that actively participate in the healing cascade.

2. Advanced additive manufacturing in orthopedics

Orthopedic tissue engineering is a rapidly growing field that leverages the integration of biology, materials science, and engineering to repair or regenerate musculoskeletal tissues like bones, cartilage, tendons, and ligaments. The fundamental goal of this discipline is to program scaffolds or grafts with specific geometrical, mechanical, and morphological characteristics that improve biological function and mimic normal tissue.[22] Tissue engineering utilizes cells, biochemical signals, materials, methods, and physicochemical factors to modify scaffolds, allowing them to maintain, restore, improve, or replace biological tissue (Fig. 2).[23] The three main pillars of tissue engineering are signals, scaffolds, and cells. These three components, known as the tissue engineering triad, determine the prognosis of tissue engineering applications; any improvements in tissue engineering technology should focus on these three elements.[24,25]

Cells form the biological foundation of tissue engineering. Stem cells, particularly mesenchymal stem cells (MSCs) derived from bone marrow or adipose tissue, are widely used due to their ability to differentiate into osteoblasts, chondrocytes, and other cell types relevant to musculoskeletal repair. In addition to stem cells, mature cells such as chondrocytes and osteoblasts are also employed to ensure tissue-specific functionality. Selecting the appropriate cell type is crucial as it dictates the regenerative potential of the engineered construct. Scaffolds provide the structural framework for tissue development, mimicking the natural extracellular matrix (ECM) of musculoskeletal tissues. These scaffolds are designed to be biocompatible and biodegradable, ensuring that they support cellular attachment, proliferation, and differentiation while gradually degrading to make room for new tissue formation. Scaffolds can be made from natural materials, such as collagen and hyaluronic acid, or synthetic polymers like polylactic acid and polycaprolactone. Biochemical signals (*e.g.*, BMPs, VEGF) and mechanical stimuli (*e.g.*, compression, tension) are essential for guiding cell behavior and tissue maturation, particularly for load-bearing tissues. Bioreactors optimize this environment by

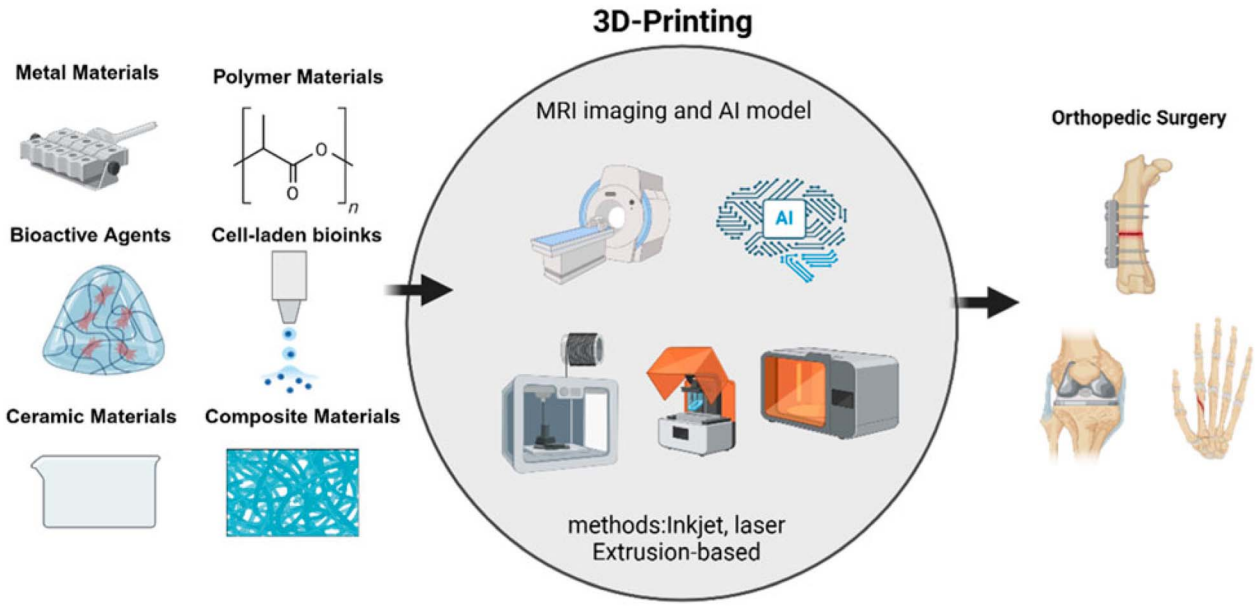

Fig. 2 Advanced additive manufacturing in orthopedics: biomaterials, structural design, biological functions, and clinical technology applications, reproduced from ref. 26, *Frontiers in Bioengineering and Biotechnology*, 2025, **13**, 1542179. Copyright 2025, under CC BY 4.0 license.

controlling nutrient delivery and providing cyclic loading to enhance functionality. The components of orthopedic tissue engineering work in synergy to create biologically pertinent solutions for musculoskeletal repair. Advances in each area continue to push the boundaries of what can be achieved, giving an improved outlook on orthopedic care outcomes.

2.1. Key elements (biomaterials, structural design and printing parameters)

The success of a tissue-engineered scaffold depends heavily on the synergy between the material used and the structural design dictated by printing parameters; this combination determines the scaffold's ability to promote cellular activities, such as adhesion, proliferation, and differentiation, while providing adequate mechanical support.[27] The selected biomaterial must be biocompatible to avoid immune rejection, possess mechanical properties that match the target tissue, and be biodegradable to allow for gradual replacement by new tissue. In 3D and 4D printing, the material must also exhibit suitable processability for the chosen fabrication technique. Orthopedic biomaterials are generally classified into natural and synthetic polymers, bioceramics, metals and composites. Natural polymers are derived from biological sources such as alginate, collagen, gelatin, and chitosan; these materials inherently mimic the extracellular matrix (ECM).[28,29] Synthetic polymers such as PLA, PCL, and PEG offer precise engineering control. Their chemistry, molecular weight, and degradation kinetics can be tuned for specific applications. High-performance thermoplastics are also prominent; for example, PEEK mimics cortical bone, while PVA is used for cartilage due to its lubricity.[30,31] Metals (*e.g.*, titanium alloys) and bioceramics remain indispensable for high-load-bearing orthopedic scenarios where polymers alone may fail.[32,33] Composite materials are achieved by combining the robust framework of synthetic polymers with the biological cues of natural materials. This allows a balance of mechanical strength with biological compatibility, eliminating the need for the binary choice of natural *vs.* synthetic. A summary of these biomaterials is given in Table 1.

The final performance of a 3D printed orthopedic scaffold does not solely depend on material selection. The fabrication parameters used exert a dominant influence in defining the scaffold's ultimate morphological, mechanical properties and biological functions. This balance between temperature, speed, and flow rate defines layer adhesion, structural integrity, and biological viability, determining how well cells can attach, proliferate, and receive nutrients. Consequently, engineering functional tissue requires looking beyond the material itself to the precise control of the printing process. Higher nozzle temperatures improve inter-layer fusion and strength, preventing delamination up to an optimal temperature. However, going beyond this optimal window can cause polymer degradation and a decrease in Young's modulus. This excessive heat can cause immediate cell necrosis or protein denaturation in bioink applications. It can also alter surface topography, potentially diminishing the surface roughness required for optimal cell adhesion.[41–43]

Understanding the hierarchy of printing parameters is crucial, as some variables exert a far greater influence than others. For example, while printing speed has a negligible effect on tensile strength, the material feed rate is the dominant factor governing scaffold density and stiffness.[41,44] Increasing infill percentage naturally reinforces the structure, while reducing layer thickness can improve ductility by enhancing inter-layer bonding. This evidences how geometric settings offer even more direct control.[44] However, optimizing these mechanical traits at times creates conflict with biological functionality,

Table 1 Comparative analysis of biomaterial classes for orthopedic additive manufacturing

Class	Examples	Core advantages	Core disadvantages	Primary role in AM
Metals	Ti_6Al_4V (titanium), CoCr (Cobalt-chrome), tantalum, 316L stainless steel	- Superior mechanical strength and fatigue resistance[32,34] - Excellent durability[34] - High osseointegration (especially porous titanium)[32,35]	- Stress shielding (stiffness mismatch with bone)[35,36] - Imaging artifacts (CT/MRI) - Potential ion release/ corrosion[34]	- Permanent load-bearing implants (hip/knee)[34] - Spinal cages and rods[32] - Custom cranial plates
Bioceramics	Hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), zirconia, bioactive glass	- High bioactivity and osteoconductivity[33,37] - Chemical composition similar to native bone mineral[33] - Non-immunogenic[34]	- High brittleness (low fracture toughness)[33,34] - Difficult to print (prone to cracking)[33] - Slow degradation (for some types like HA)[37]	- Bone graft substitutes[33] - Bioactive coatings on metal implants[37] - Non-load-bearing scaffolds
Synthetic polymers	PEEK, PLA, PCL, PLGA, PEG, PV	- Tunable degradation rates[32,38] - Easy processability and printability[32] - Radiolucent (does not interfere with X-rays)[38]	- Biologically inert (poor cell adhesion without modification)[38] - Lower mechanical strength than metals[32] - Hydrophobic surfaces[38]	- Bioresorbable screws/ plates[32] - Tissue engineering scaffolds[38] - Surgical guides and models[37] - Interbody fusion cages (PEEK)
Natural polymers	Collagen, gelatin, chitosan, alginate, silk fibroin	- Excellent biocompatibility[38,39] - Inherent bioactivity (cell recognition sites)[39] - Mimic the extracellular matrix (ECM)[39]	- Very poor mechanical strength[38,39] - High batch-to-batch variability[39] - Rapid degradation rates[38] - Potential immunogenicity	- Hydrogel matrices for cell delivery[39] - Soft tissue regeneration (cartilage/ligament)[38] - Bio-inks for 3D bioprinting[37]
Composites	PCL/HA, PLGA/TCP, carbon-fiber/PEEK	- Synergistic properties (combine the toughness of polymers with the bioactivity of ceramics)[37] - Tailored mechanical stiffness[40]	- Interfacial bonding issues between phases[40] - Complex printing parameters - Inconsistent degradation profiles	- Scaffolds requiring both structural support and bone regeneration[40] - Next-gen load-bearing implants

presenting a challenge in finding middle ground. Tissue engineering demands high porosity for cell infiltration, yet increasing void volume inevitably degrades the scaffold's compressive modulus.[45] These two properties exist in a distinct inverse relationship; increasing a scaffold's porosity significantly decreases its compressive modulus.[46] A summary of key parameter effects on scaffold mechanical and biological properties is given in Table 2.

This inverse relationship has forced researchers to shift towards computational strategies, such as artificial intelligence and machine learning (ML), to create data-driven design frameworks, as random trial and error is not sufficient to tackle this problem.[47] These computational models, including neural networks and evolutionary algorithms, can predict final scaffold properties and navigate the complex parameter space to optimize designs for specific clinical applications.[48]

2.2. 3D bioprinting classification

The ability to make patient-specific scaffolds *via* additive manufacturing lies in its fundamental principle of the layer-by-layer addition of material, guided by a digital design. The additive mechanism allows us to make complex internal architectures, such as interconnected pore networks and graded densities, which are nearly impossible to make with traditional techniques and are essential for successful tissue regeneration. This has led to a variety of AM technologies being adapted for orthopedic use, with the selection of a specific method depending on its unique material compatibilities and processing limitations.

Fused Deposition Modeling or Fused Filament Fabrication (FFF) is arguably the most common and accessible additive manufacturing technology. The process involves feeding a solid thermoplastic filament into a heated extrusion head, where it is melted and deposited onto a build platform in a precise, layer-by-layer pattern.[48] Its widespread adoption is driven by cost-effectiveness and material versatility, supporting polymers like PLA and PCL, as well as functional composites (*e.g.*, magnetic particles for cell stimulation).[60,61]

Stereolithography is a vat photopolymerization technique that was the first form of 3D printing to be commercialized. The

Table 2 Summary of the effects of key parameters on the scaffold's mechanical and biological properties

Process parameter	Primary mechanical impact	Biological impact	Summary of influence
Nozzle temperature	Inter-layer fusion, modulus: higher heat improves molecular bonding between layers, increasing overall scaffold strength[42,49]	Cell viability/surface chemistry: high heat kills cells in bio-inks; in thermoplastics, it alters surface energy/roughness, affecting cell attachment[50,51]	Must be hot enough to fuse layers for structural handling but cool enough to preserve biological agents or create favorable surface textures for adhesion[42]
Material feed rate	Young's modulus (dominant): directly controls the amount of material deposited; higher rates create thicker struts and stiffer structures[49]	Pore size/diffusion: high feed rates reduce effective pore size, limiting oxygen and nutrient diffusion to the scaffold center[49,52]	A dominant factor in stiffness; however, excessive feed rates close off porosity, preventing cell ingrowth and leading to tissue necrosis[52]
Printing speed	Build time, resolution: slower speeds generally improve dimensional accuracy and bonding[49]	Shear stress: high speeds induce shear stress, which can damage cell membranes (in bio-inks) or detach seeded cells[53,54]	Slower speeds favor both mechanical resolution and cell survival (low shear), but significantly extend the time biological materials are exposed to environmental stress[54]
Infill density (%)	Tensile/compressive strength: a direct, positive correlation; higher density equals higher load-bearing capacity[55]	Cell migration/vascularization: high density creates physical barriers that prevent cell migration and blood vessel formation[52,55]	Higher infill reinforces the structure against physical loads but inevitably degrades biological performance by limiting the space available for tissue formation[56]
Layer thickness	Ductility, layer adhesion: thinner layers (*e.g.*, 0.05 mm) improve bonding and ductility[42]	Contact guidance: layer height determines surface topography (ridges); cells often align and migrate along these grooves[57]	Thinner layers improve mechanical bonding, while specific layer heights can be selected to guide cell orientation and tissue alignment[57]
Build orientation	Anisotropy, failure mode: determines the direction of weakness; flat is usually stronger than upright[42]	Channel alignment: determines the orientation of pores relative to the host tissue, affecting how easily fluids/blood vessels flow through[58]	Orientation dictates mechanical anisotropy; biological alignment must match physiological needs (*e.g.*, aligning pores with blood flow direction)
Porosity	Compressive modulus: significant inverse relationship; higher porosity drastically reduces mechanical strength[56,59]	Cell ingrowth/metabolic exchange: essential for deep tissue colonization; allows waste removal and nutrient delivery[52,59]	The defining feature of scaffolds. Must be balanced to ensure the scaffold supports the body's weight (mechanical) while remaining open enough to sustain life (biological)[56]

basic concept behind SLA involves submerging a built platform into a vat of liquid photopolymer resin. A UV laser beam then traces specific cross-sections, selectively curing and solidifying the material layer by layer. This category of additive manufacturing also includes Digital Light Processing (DLP), which operates on a similar principle but uses a projector to cure an entire layer on the go. The high accuracy associated with SLA is what truly distinguishes it from the rest. It is this accuracy that results in high resolution, smooth surface and products that require very little post-processing. These traits make it the go-to choice for anatomical models requiring exact dimensions and intricate detailing.[26] Processes that require high precision, such as the translation of patient data, for example, CT scans, into anatomical models, are more suited to SLA rather than load-bearing implants.

Selective Laser Sintering (SLS) is a Powder Bed Fusion (PBF) technique that constructs parts *via* high-power laser heating and fusing solid powder materials. During the process, a roller spreads a thin layer of powder across the build area, the laser selectively sinters the cross-section of the design, and the platform lowers to accommodate the next layer.[62] The ability of SLS to create mechanically strong, durable components that have complex geometries is what distinguishes it from other processes. It is also this trait that makes it ideal for functional orthopedic applications like spinal cages and joint replacements.[63] The process shows broad material compatibility and includes polymers, biocompatible and bioresorbable materials like nylon, as well as metal powders. In scenarios requiring substantial load-bearing capacity, such as reconstructive maxillofacial surgery, the technology is frequently employed to process titanium alloys like Ti–6Al–4V.[63] A comparative analysis of the three AM mechanisms is shown in Table 3.

3. Evolution of additive manufacturing in orthopedics from static to dynamic

Although additive manufacturing techniques, such as FDM, SLA, and SLS, have transformed orthopedics by enabling the precise replication of complex anatomical geometries, they share an important biological limitation: the constructs they produce are inherently static and inert. Once fabricated, a titanium implant or a PCL scaffold has a fixed shape and

Table 3 Comparative analysis of FDM, SLA, and SLS for biomedical applications

Technology	Operating principle	Common biomedical materials	Key biomedical advantages	Key biomedical limitations	Ideal clinical applications
Fused deposition modeling (FDM)	Thermoplastic extrusion[48,64]	PLA, PCL, ABS, and PEEK[26,60,65]	Cost-effective, high material flexibility, simple operation	Low resolution, poor surface finish, anisotropic mechanical properties[26,48,60,66]	Educational models, prototypes, custom splints, functionalized scaffolds
Stereolithography (SLA)	Vat photopolymerization[64]	Photopolymer resins	Exceptional resolution, high accuracy, smooth surface finish	Poor mechanical strength (not load-bearing), material cytotoxicity requiring extensive post-curing[26,48,67]	High-fidelity anatomical models, pre-surgical planning, and surgical guides
Selective laser sintering (SLS)	Powder bed fusion	Nylon, PCL, and Ti–6Al–4V	High mechanical strength, complex geometry, no support structures needed[26]	Lower resolution than SLA, rough surface finish, high cost[48]	Functional load-bearing implants, spinal cages, complex lattice scaffolds[48]

predefined mechanical properties. It cannot adapt to the evolving biomechanical demands of daily patient activity, nor can it actively respond to the dynamic biological processes that occur during tissue healing. As a result, conventional 3D-printed devices largely function as passive supports rather than active participants in regeneration. To address this limitation, the field is now shifting from static manufacturing toward dynamic manufacturing, moving beyond the fabrication of form to the deliberate programming of function.

From here, the next step for AM was the introduction of the fourth dimension, time. MIT researchers, using 3D printing as the building blocks, conceptualized a technique in which smart materials are programmed to change their shape, properties, or function over time in response to a specific external stimulus[68] (Fig. 3). These materials react to specific environmental triggers, such as temperature, pH, humidity, light, or moisture, executing predetermined morphological or functional changes post-fabrication. This gave birth to 4D printing. In the context of regenerative medicine, this capability addresses a critical limitation of traditional 3D printing, namely, the static nature of the construct. The high level of biomimicry that comes with 4D printing allows for the creation of scaffolds that participate in the physiology of healing rather than simply replicating anatomy.[69]

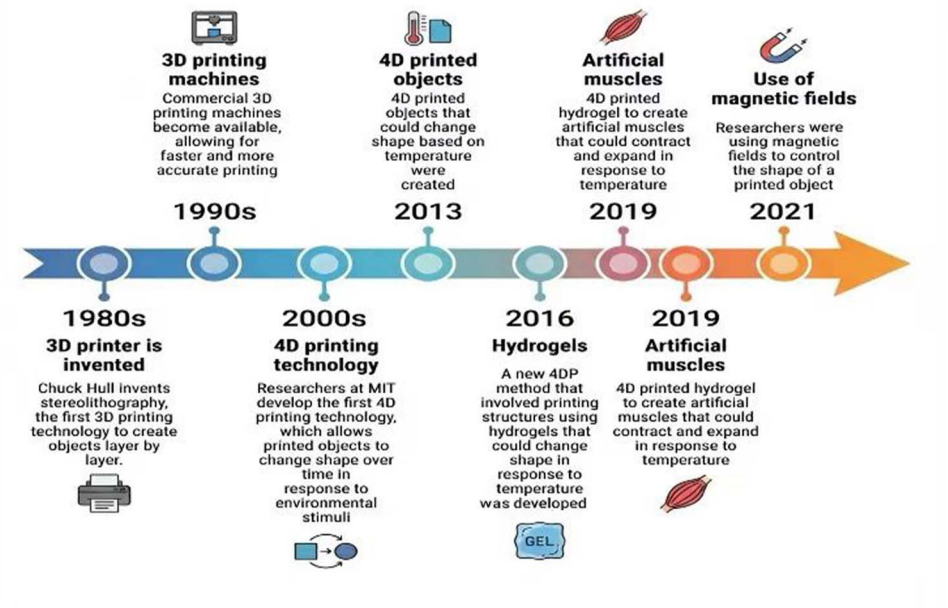

Fig. 3 Timeline infographic highlighting the key milestones of additive manufacturing from the invention of SLA to 4D printing.

4D printing does not require a new class of manufacturing hardware since the capability arises not from the printing technique itself, but from the integration of advanced printing materials, dynamic bioprinting strategies, and process innovations that enable time-dependent responses. It thus utilizes standard 3D printing technologies, such as the commonly used fused deposition modeling (FDM) and stereolithography (SLA), to process stimuli-responsive smart materials. These materials, when combined with dynamic printing methods and controlled fabrication processes, allow constructs to transform their function, or form post-printing in ways that conventional 3D scaffolds cannot. Consequently, the progression from static 3D prints to responsive 4D architectures reflects major advances in both material science and additive manufacturing design.[70]

While 3D AM focuses on matching the static anatomical geometry of the defect using inert materials (*e.g.*, titanium, PEEK), 4D AM introduces the dimension of time. By utilizing smart materials (SMPs, hydrogels) and specific stimuli (heat, pH, magnetic fields), 4D constructs can dynamically adapt their shape and function post-implantation to promote integration and healing.

4. Advances in 4D additive manufacturing in orthopedics

The transition from static 3D printing to dynamic 4D manufacturing relies fundamentally on the development of smart, stimuli-responsive biomaterials (Fig. 4) and the evolution of bioprinting technologies capable of depositing living, functional tissues.[71] While traditional orthopedic manufacturing prioritizes mechanical strength and biocompatibility, 4D systems focus on internal function.[72,73] These smart biomaterials function as the engine of the 4D system, capable of sensing environmental changes and actuating a programmed response without the need for onboard electronics or external power sources. The main driving forces of this innovation within the orthopedic field are Shape Memory Polymers (SMPs), Stimuli-Responsive Hydrogels, and Functionalized Nanocomposites.[74] The advanced bioinks enable the fabrication of biologically dynamic, living constructs through the fabrication of complex, heterogeneous tissues that mimic the native zonal architecture of bone and cartilage.[75]

4.1. Smart stimuli-responsive biomaterials

Shape Memory Polymers (SMPs) represent the most widely utilized class of materials in 4D orthopedic devices due to their ability to support significant mechanical loads while undergoing large-strain recovery.[76] The shape memory effect (SME) in SMPs does not arise from simple elastic behavior but instead originates from a deliberately engineered molecular architecture composed of two functionally distinct domains: net-points and switching segments.[77] Net-points, which may consist of permanent covalent cross-links or physically stable crystalline domains, define and preserve the permanent geometry of the device. The switching segments, typically amorphous soft chains, are responsible for freezing the temporary shape.[78]

The mechanism of action is thermodynamic. When heated above the material's transition temperature (T_{trans}), the switching segments undergo a phase transition that increases chain mobility, enabling the device to be mechanically deformed into a temporary, compact configuration.[79,80] Cooling the material below T_{trans} while maintaining the deformation restricts the mobility of the switching segments, locking the entropy-elastic energy within the polymer network. When placed inside the body, exposure to the physiological heat provides the thermal stimulus required to initiate the recovery phase. The switching segments regain mobility, releasing the stored energy and driving the implant back to its permanent, equilibrium shape.[76]

For clinical applications, the selection of T_{trans} is critical to ensure that shape recovery is triggered solely by physiological heat, thereby avoiding the need for external heating sources that could damage surrounding tissues.[81] Polyurethane (PU) and polylactic acid (PLA)-based composites are frequently employed because their glass transition temperatures (T_g) can

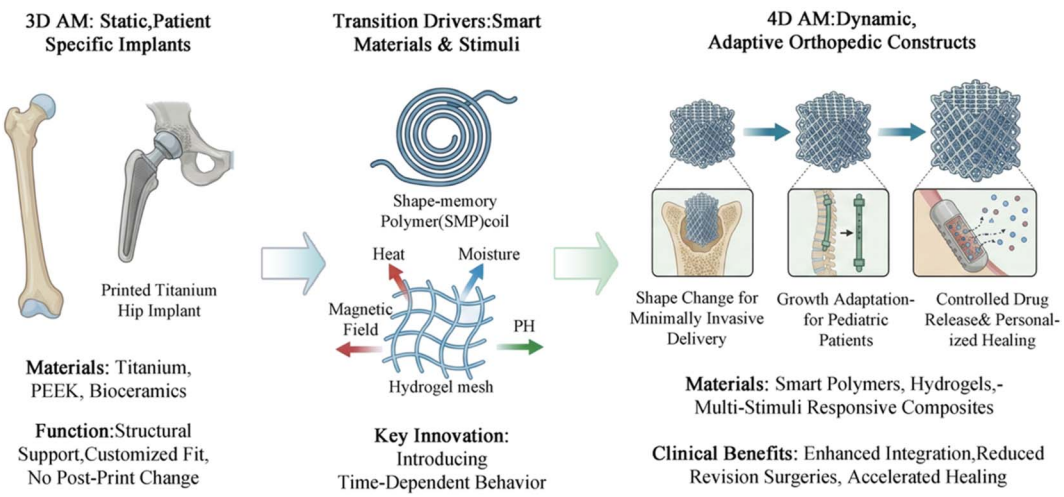

Fig. 4 Evolution from static 3D additive manufacturing (AM) to dynamic 4D manufacturing in orthopedics.

be tuned to align with human body temperature (37 °C).[82,83] This allows for the fabrication of self-deploying bone scaffolds that can be inserted through a minimally invasive incision in a compressed state and subsequently expand to fill a critical-sized defect, ensuring optimal contact with the host bone without the need for forceful manual impaction.[84]

While SMPs provide structural adaptation, stimuli-responsive hydrogels offer the chemical versatility required for on-demand therapeutic delivery.[85] These highly hydrated networks can be engineered to undergo rapid volume phase transitions (swelling or shrinking) in response to subtle physiological triggers.[86,87]

Thermal-responsive hydrogels are particularly valuable for creating injectable, in situ-forming scaffolds. These systems typically exhibit a Lower Critical Solution Temperature (LCST).[88] Below the LCST (room temperature), the polymer chains are hydrated and exist as a liquid, facilitating injection. However, upon reaching body temperature (above the LCST), the polymer chains undergo a hydrophobic transition and collapse, causing the gel to solidify instantly within the defect.[89] This sol–gel transition not only fills irregular voids perfectly but can also be utilized to squeeze out therapeutic agents in a controlled burst.[85]

pH-responsive hydrogels function through a different mechanism, primarily utilizing charge-switching protonation. In the neutral environment of healthy tissue (pH 7.4), the polymer remains stable. However, the microenvironment of bacterial biofilm or acute inflammation is characteristically acidic (pH < 6.5).[90,91] Polymers containing ionizable groups (such as carboxylic acids or amines) respond to this acidity by gaining or losing protons.[92] This ionization triggers strong electrostatic repulsions within the polymer network, causing the hydrogel to swell or degrade rapidly. This mechanism creates a closed-loop therapeutic system; the antibiotic payload is trapped within the matrix during health, but is autonomously released the moment an infection-induced pH drop is detected.[91,92]

Native bone is not merely a structural support; it is a piezoelectric tissue that generates electrical potentials under mechanical stress, a signal known to stimulate osteogenesis. Standard polymeric bioinks are electrically insulating, failing to recapitulate this critical physiological cue.[93,94] To bridge this gap, recent 4D strategies have incorporated functional nanomaterials to create conductive or magnetic-responsive composites. Conductive bioinks are synthesized by integrating carbon nanotubes, graphene oxide (GO), or gold nanoparticles into the hydrogel matrix.[95] These additives establish conductive pathways that enhance cell–cell electrical coupling and upregulate the expression of osteogenic genes (*e.g.*, RUNX2, OPN).[2,3] Furthermore, magnetic responsiveness can be achieved by embedding iron oxide nanoparticles (Fe_3O_4) into the scaffold.[96] This allows clinicians to use an external magnetic field to remotely mechanically stimulate the cells seeded within the implant (magneto-mechanotransduction) or to trigger the release of drugs from a ferrogel matrix, providing a non-invasive method to modulate the healing process post-surgery.[97]

4.1.1. Dynamic bioprinting and bioinks. The ink in bioprinting differs from the thermoplastics used in FDM. It is a hydrogel-based formulation that must satisfy the conflicting requirements of the bioprinting window; high viscosity for structural fidelity post-extrusion *versus* low shear stress for cell survival.[98,99] While natural polymers like alginate and gelatin are common due to their biocompatibility, they are biologically generic. To overcome this, the field has shifted toward Decellularized Extracellular Matrix (dECM) bioinks.[100] These materials are created by removing cellular components from animal tissues while retaining the native mixture of growth factors and structural proteins, resulting in a microenvironment that mimics the precise chemical profile of the target organ.[100,101] Recent research indicates that bioinks derived specifically from decellularized bone matrix (DBM) significantly outperform standard polymers, autonomously inducing osteogenic differentiation in stem cells without the need for exogenous growth factors like BMP-2.[102]

To address the mechanical and functional limitations of soft hydrogels, a primary concern for bone repair, researchers have developed Nanocomposite Bioinks.[103] Standard hydrogels are electrically insulating, failing to recapitulate the native piezoelectric properties of bone. Strategies now incorporate carbon nanomaterials (such as graphene oxide) or gold nanoparticles to create conductive pathways within the scaffold. This enhanced conductivity improves cell–cell electrical signaling and has been shown to upregulate key osteogenic genes, such as RUNX2 and OPN, accelerating bone formation.[94,104]

The bioprinting process is inherently traumatic for cells, making viability the defining metric of success. This mechanical challenge is defined by the wall shear stress (τ) at the wall of a cylindrical nozzle during extrusion, calculated as $\tau = 4Q\eta/\pi R3$, where Q is the flow rate, η is viscosity, and R is the nozzle radius.[105] Crucially, this formula highlights a severe design conflict, where reducing the nozzle radius (R) to improve printing resolution exponentially increases the shear stress (τ) placed on the cells, leading to membrane rupture and apoptosis.[106] Advanced strategies to counter this include the use of conical nozzles to reduce pressure drops and AI-driven optimization models to predict cell survival prior to printing.[107]

Once deposited, the bioink must be stabilized. While photocrosslinking (using UV or visible light) remains the standard, it creates a rigid, static network.[108] Alternatively, chemical or enzymatic methods offer different crosslinking routes. For instance, using thrombin to crosslink fibrin-based inks mimics the body's natural clotting cascade. While this yields a soft, highly biocompatible construct, its lack of mechanical strength generally limits it to cartilage or non-load-bearing void filling.[109] Emerging 4D approaches utilize dynamic crosslinking chemistries, such as Schiff base formation or boronate ester bonds. Unlike permanent covalent bonds, these dynamic crosslinks are reversible, endowing the hydrogel with self-healing capabilities. This allows cells to locally degrade and remodel the matrix, which is a critical requirement for cell migration and tissue maturation, thus creating a scaffold that is not a permanent cage, but a remodelable niche.[110,111]

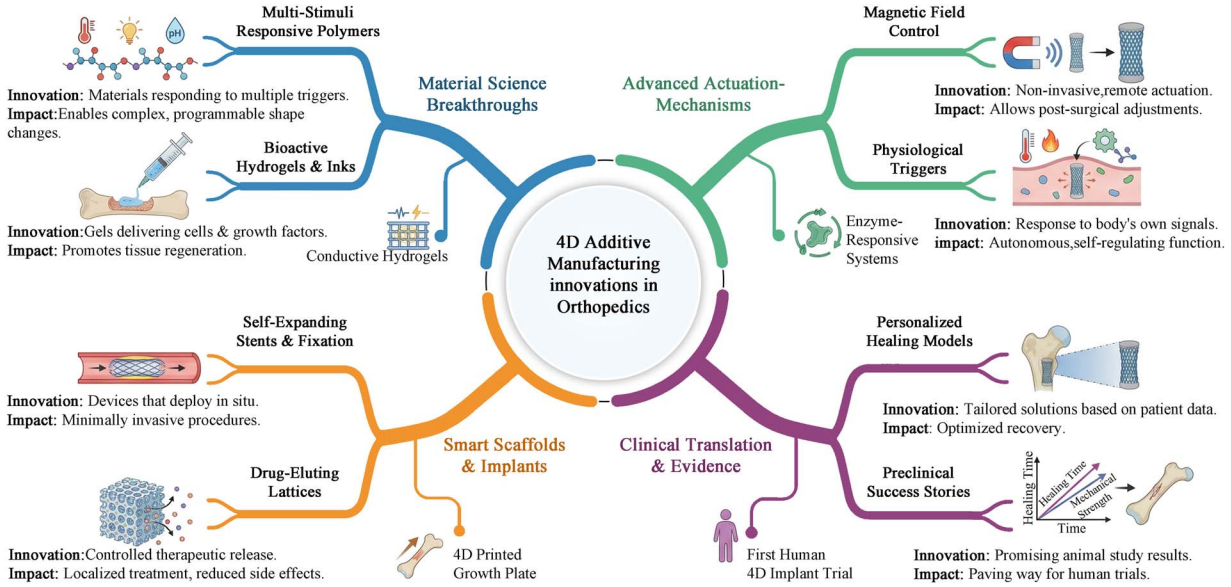

Fig. 5 Comprehensive landscape of 4D-additive-manufacturing innovations in orthopedics. The field relies on the synergistic integration of four key pillars: (1) material science breakthroughs (developing multi-stimuli-responsive bioinks), (2) advanced actuation mechanisms (utilizing physiological triggers like body heat or external controls like magnetic fields), (3) smart scaffolds and implants (creating devices for minimally invasive delivery and drug elution), and (4) clinical translation (progressing from preclinical models to personalized human therapies).

5. Clinical frontiers: current applications of 4D printing in orthopedics

The translation of additive manufacturing from research laboratories to clinical practice has fundamentally altered orthopedic surgery, initially by enabling the creation of patient-specific static implants. However, the frontier has now shifted toward smart dynamic systems designed to solve the persistent failures of static devices, surgical trauma, implant loosening, stress shielding, and infection (Fig. 5). If 3D printing solved the anatomical challenge, 4D printing aims to solve the biological one. The goal is no longer to fabricate passive supports, but to engineer active, biomimetic devices capable of adapting to the extracellular microenvironment.[112] This transforms the implant from a tolerated foreign body into an intelligent partner in the healing cascade.[113]

5.1. Dynamic scaffolds for adaptive bone reconstruction

A primary application of 4D printing in orthopedics is the development of dynamic scaffolds for bone reconstruction.[114] These devices utilize the properties of smart materials, most commonly Shape Memory Polymers (SMPs). These can include biodegradable materials such as polyurethane (PU) or polylactic acid (PLA) composites, which are engineered to possess a shape memory effect.[114] The fabrication process involves 3D printing the scaffold in its final, desired shape, one that perfectly matches the bone defect. This scaffold is then programmed into a temporary, compressed, or smaller shape. This temporary shape is stable until the material is exposed to its specific activation stimulus.[114] The 4D scaffolding concept directly addresses a significant clinical paradox in orthopedic trauma. Large, critical-size bone defects, particularly those with irregular geometries, require the most precise, custom-fit implants to ensure proper healing.[112] However, implanting such a large, complex, and rigid implant typically requires a large, traumatic open surgery, which increases the risk of complications and morbidity. 4D printing provides an elegant solution. The programmed scaffold, in its temporarily compressed state, can be delivered to the defect site through a small incision, facilitating a minimally invasive surgical (MIS) procedure. Once *in vivo*, the scaffold is exposed to its trigger, most commonly the body's own temperature (approximately 37 °C), thus activating its shape memory effect. The scaffold expands from its compressed form, restoring itself to its original, ideal shape. This self-deployment allows the implant to automatically match the edges of bone defects with a precision that would be difficult to achieve manually.[114] A study by Hu *et al.* developed a shape memory polyurethane/hydroxyapatite (SMPU/HA) foam. This scaffold was implanted in its compressed state, which reduced implantation trauma, and then adaptively expanded in animal models to perfectly conform to the defect edges, subsequently promoting vascularization and accelerating bone reconstruction.[115] This approach is ideal for the personalized regeneration of complex, irregular defects.[114] This concept of dynamic adaptation is being extended to one of the most challenging areas of musculoskeletal repair, osteochondral tissue engineering. Osteochondral defects, which involve damage to both the articular cartilage and the underlying subchondral bone, are notoriously difficult to treat due to the tissue's complex, layered (zonal) architecture.

While 3D bioprinting can fabricate static, biomimetic scaffolds with multiple layers of materials and cells, 4D bioprinting

aims to add a dynamic component.[116] Researchers are exploring 4D-bioprinted constructs that can change their structure over time, potentially adapting to tissue growth, applying mechanical micro-stimuli to differentiating stem cells, or transforming from a simple structure into the complex functional architecture required for a joint surface.[117]

5.2. 4D-enabled dynamic implants

In the realm of fracture fixation, 4D printing is being used to create intelligent implants that address a primary cause of surgical failure: loss of compression. Traditional fixation devices, such as static metal plates and screws, hold bone fragments together rigidly. However, as the bone begins to heal, it naturally remodels and settles (a process called subsidence). This can create a micro-gap between the bone and the static implant, leading to a loss of the compressive force that is critical for primary bone healing. Using 4D manufacturing principles, these devices, including shape memory staples, screws, and intramedullary devices, are engineered to exist in a state that, upon implantation, exerts continuous and active dynamic compression across the fracture line.[45]

This technology transforms the implant from a passive splint into an active healing engine. It becomes a biomechanical device that intelligently manages the force environment at the fracture site over time.

5.3. 4D printing for on-demand drug delivery

Perhaps the most versatile application of 4D printing is in transforming implants from structural supports into smart therapeutic delivery systems.[118] A significant challenge in bone regeneration is the delivery of biologic agents, such as growth factors or anti-inflammatories. Traditionally, a surgeon might soak a 3D-printed scaffold or bone cement in a drug.[119] This method is highly uncontrolled, resulting in a massive initial burst release where the majority of the drug is washed away within hours, followed by a long period of sub-therapeutic dosing.[120]

4D printing is being used to create specific carriers for accurate drug release.[121] These systems are designed to be stimuli-responsive, allowing for the on-demand, localized, and temporally-controlled release of therapeutics.[122] The ultimate goal of 4D drug delivery is not just to release a drug, but to orchestrate the biological cascade of healing. Bone healing is a multi-phase process (inflammation, proliferation, and remodeling), each requiring a different set of cellular signals. 4D implants can be designed to release different drugs at different times to match these distinct biological phases.[112]

This controlled release is governed by the implant's response to specific stimuli. Thermal-responsiveness is the most common stimulus, whereby body temperature can be used to trigger drug release from an SMP scaffold. A 2024 study described a near-infrared (NIR) light-responsive 4D scaffold that could adaptively release growth factors according to body temperature and the process of fracture healing.[112] Magnetic responsiveness is also utilized; 4D-printed magnetic-responsive hydrogels (ferrogels) can be loaded with drugs. When a clinician applies a specific external magnetic field, the hydrogel deforms, squeezing out and releasing its therapeutic payload (*e.g.*, growth factors or cytokines) on-demand.[123] Researchers are also developing multifunctional microsphere systems that respond to ultrasound, allowing for on-demand release of growth factors to reverse the microenvironment of bone damage.[124] Bio-piezoelectric smart scaffolds can generate small electrical currents when mechanically stimulated (*e.g.*, by the patient walking). This electrical cue is known to promote osteogenesis and could also be harnessed as a trigger for on-demand drug release.[112]

5.4. Infection-responsive antimicrobial 4D implants

One of the most devastating complications in orthopedic surgery is implant-associated infection.[45] These infections are difficult to eradicate, often require multiple revision surgeries, and are a major source of patient morbidity. Traditional treatments rely on high-dose systemic antibiotics, which have poor permeability at the implant site, or pre-loading the implant with antibiotics.[125] This prophylactic approach is inefficient, releasing drugs even when no infection is present and contributing to the global crisis of antibiotic resistance.[126]

4D printing offers a groundbreaking alternative by creating an autonomous diagnostic and therapeutic system. The implant itself becomes a smart device that can sense the earliest biochemical signs of an infection and respond by releasing a targeted antimicrobial payload precisely when and where it is needed.[45,126]

The key mechanism for this is pH-sensing. The colonization of bacteria and the formation of a biofilm create an acidic microenvironment, causing a local drop in pH. 4D implants can be fabricated with pH-responsive polymers, hydrogels, or smart zwitterionic coatings that are engineered to be on-demand.[45,126] This creates an "if-then" therapeutic loop: if the surrounding tissue is at a normal, healthy pH, the coating remains inactive and may simply provide an anti-adhesive surface;[127] however, if bacteria colonize and the local pH drops, the acidic environment triggers a change in the material (*e.g.*, hydrolyzing acid-sensitive bonds), initiating the immediate, localized release of a high-concentration antimicrobial payload (such as antibiotics or antimicrobial peptides) (Fig. 6).[45,126]

5.5. Advanced multi-stage systems

Recent research has demonstrated systems that are even more sophisticated, managing multiple phases of infection and healing. A 2024 study detailed a pH-responsive PEEK implant with a bilayer core–shell structure designed for just this purpose.[128]

(1) Infection phase: when infection causes a local drop in pH, the implant's outer shell is triggered to release an antimicrobial peptide (KR12) to kill the bacteria and inhibit the biofilm.

(2) Inflammation phase: the material also helps to modulate the body's immune response, promoting the conversion of pro-inflammatory (M1) macrophages to pro-healing (M2) phenotypes.

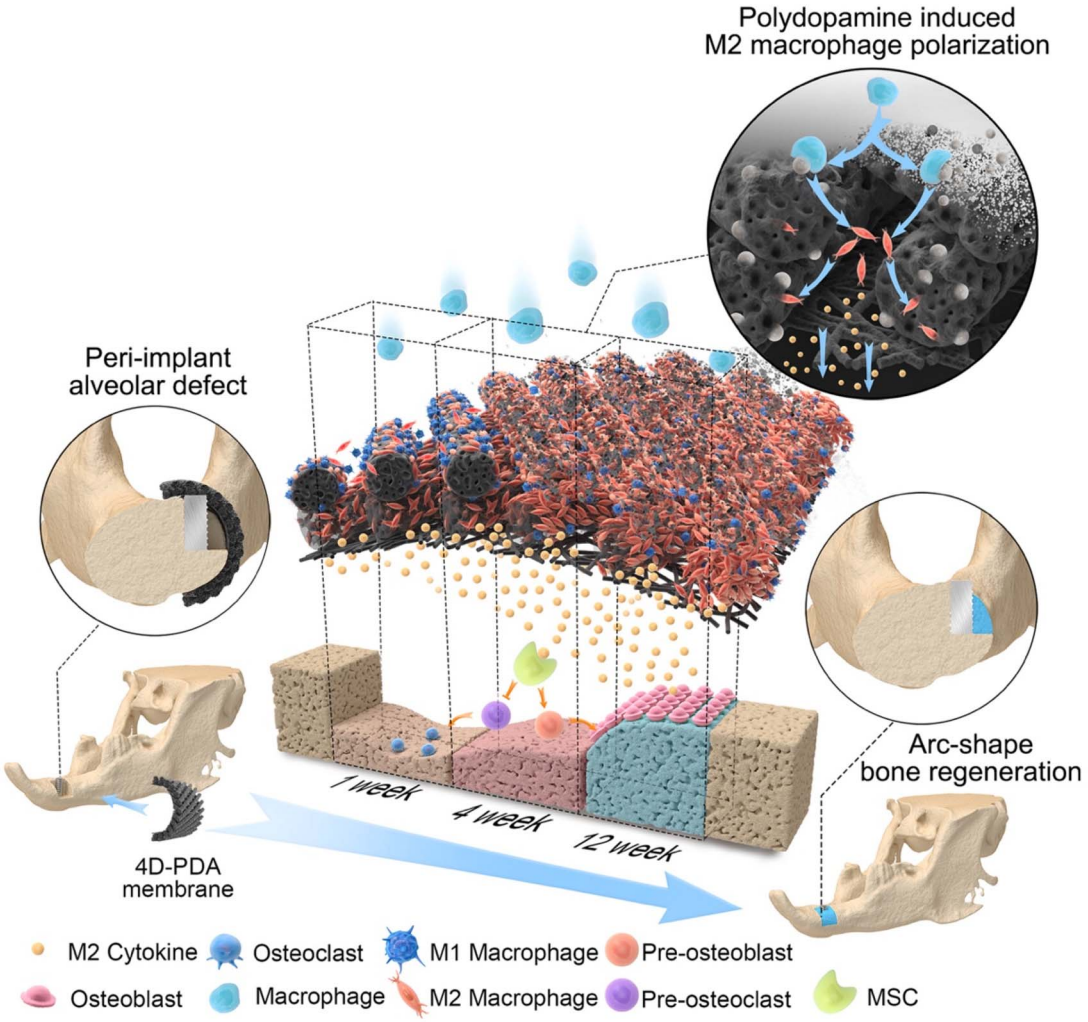

Fig. 6 Schematic illustrating the early and durable enrichment of M2 macrophages above a bone defect, mediated by a 4D hierarchically channeled elastomeric membrane. The system leverages stimulus-responsive 4D morphing to achieve precise physiological adaptation and specific-shape bone healing; reproduced from ref. 129 with permission from Elsevier (*Biomaterials*, 2021, **276**, 120998). Copyright 2021.

(3) Regeneration phase: once the infection is managed, the implant's inner core begins to release an osteogenic peptide (OGP) to actively promote new bone growth and osseointegration.

This single 4D implant functions as a complete seek-and-destroy-and-rebuild system, autonomously managing the distinct and sequential challenges of infection, inflammation, and bone regeneration (Table 4).

6. Challenges and future outlook

6.1. Translational verification; biomechanical and clinical assessment

The most immediate barrier to clinical adoption is the lack of standardized assessment protocols for dynamic implants. To demonstrate practical utility, 4D constructs must undergo a rigorous two-stage verification process. First, biomechanical validation must go beyond static testing.[2] While standard protocols like ISO 14801 (fatigue) and ASTM F2077 (spinal fusion) provide a baseline, 4D smart scaffolds require Dynamic Mechanical Analysis (DMA) to verify that their shape-change capability does not compromise structural integrity.[141] Key performance metrics must include matching the compressive modulus of the host bone (10–20 GPa for cortical bone) to prevent stress shielding, and verifying the recovery ratio of shape-memory polymers under physiological load. Post-surgical efficacy must be quantified using standardized clinical indicators. Radiographic success is defined by the visibility of the bridging trabecular bone and the absence of radiolucent lines. Functional recovery must be tracked using validated metrics such as the Visual Analog Scale (VAS) for pain and the Oswestry Disability Index (ODI) for spinal function.[142] Demonstrating a statistically significant improvement in these specific indicators compared to autologous grafting is the essential threshold for proving the clinical utility of 4D technologies.

6.2. The regulatory paradox

The most significant barrier to commercialization is the lack of a clear regulatory pathway.[3] Current frameworks, such as the

Table 4 Summary of 4D printing applications in orthopedics

Application area	4D mechanism/smart material	Intended clinical function and significance	Key examples
Bone reconstruction	Thermal-responsive shape memory polymer (SMP) (*e.g.*, PU, PLA composites)	Minimally invasive implantation and defect conformance The compressed scaffold is implanted *via* MIS. It expands *in vivo* (*via* body heat) to perfectly match complex, irregular bone defects. Reduces surgical trauma, improves fit	4D-printed SMPs for irregular defects[130] SMPU/hydroxyapatite foam[131] SMPs for MIS and irregular defect conformance[132]
Personalized implants (dynamic fixation)	Shape memory alloy (SMA) (*e.g.*, nitinol)	Active and continuous fracture compression Solves the primary failure mode of static fixation (loss of compression). The SMA implant (screw, staple) actively maintains compressive force as the bone heals and settles, promoting union	Dynamic compression bone staples[133] Dynamic compression screws and intramedullary devices[134]
Smart drug delivery	Stimuli-responsive scaffolds/hydrogels (*e.g.*, magnetic, thermal, ultrasound, and piezoelectric materials)	On-demand and temporally orchestrated therapeutics Replaces burst release with controlled release of growth factors (*e.g.*, BMPs) or anti-inflammatories. Allows for on-demand release or phased release to match biological healing stages	Temperature-responsive scaffolds for drug delivery[135] NIR-responsive 4D scaffold for growth factor release[136] Magnetic-responsive hydrogels (ferrogels) for drug release[137] Tunable-release kinetics *via* DLP printing[138]
Antimicrobial/ antibacterial	pH-responsive polymers and coatings	Autonomous infection diagnosis and treatment Smart implant senses the acidic (low pH) microenvironment of a bacterial infection. This triggers the on-demand release of antibiotics/antimicrobials, preventing biofilm formation and resistance	pH-responsive drug delivery systems[139] Smart zwitterionic coatings[140] Dual-layer, pH-responsive PEEK implant (releases KR12 peptide)[128]

FDA's 510(k) or the EU's MDR, are largely predicated on the testing of static devices with fixed dimensions and stable material properties. A 4D implant that changes its geometry *in vivo* presents a regulatory paradox; which state does one validate? A device might pass mechanical testing in its compressed delivery state but fail in its expanded functional state, or *vice versa*. Furthermore, dynamic drug-eluting implants often straddle the line between medical devices and pharmaceutical products, requiring complex combination product designations. Regulatory bodies will need to establish new standards for dynamic equivalence before these innovations can reach patients.

6.3. Quality assurance and fatigue

Standardizing quality assurance for 4D manufacturing is equally challenging. Unlike static 3D printing, where dimensional accuracy is the primary metric, 4D printing introduces time-dependent variables such as stimulus sensitivity and recovery fidelity. Manufacturers must validate that a shape-memory scaffold will expand to the exact predicted dimensions every time, regardless of slight variations in the patient's body temperature or pH.

6.4. The vascularization bottleneck

While 4D printing addresses the issue of fit and fixation, it has not yet overcome the fundamental biological limitation of tissue engineering: vascularization. Large-scale bone defects require a rapid blood supply to support cell survival deep within the scaffold. Current 4D constructs, despite their smart capabilities, are largely avascular upon implantation. If the rate of shape recovery or drug release outpaces the rate of angiogenesis, the core of the implant may become necrotic. Future research must prioritize the development of 4D angiogenic system scaffolds that not only expand to fill the defect but also sequentially release angiogenic factors (like VEGF) to pull blood vessels into the deep matrix.

7. Conclusion

The convergence of advanced additive manufacturing and stimuli-responsive materials has ushered in a transformative era in musculoskeletal repair. This review has traced the evolution of the field from the foundational principles of static 3D printing to the emerging dynamic capabilities of 4D manufacturing.

The advent of 4D printing represents the next conceptual leap, imbuing scaffolds with the dimension of time. By utilizing smart, stimuli-responsive materials, we can now design implants that are not static but are active participants in the healing process. The potential for scaffolds that can dynamically modulate their mechanical properties to prevent stress shielding, deliver therapeutic agents on demand in response to physiological cues, and self-deploy through minimally invasive approaches promises to solve some of the most persistent challenges in orthopedic medicine. Concurrently, the development of sophisticated antibacterial strategies from drug-eluting coatings to contact-killing nanoparticles is turning implants from passive substrates into active defenders against infection, a critical step in ensuring long-term surgical success.

Conflicts of interest

The authors declare that they have no competing interests.

Data availability

No datasets were generated or analysed during the current study.

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