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Intelligent 3D bioprinting platforms for complex bone-tissue interfaces: Mechanisms, biofabrication, and regenerative applications

Running title: Intelligent 3D bioprinting for bone interfaces

Table S1. Standardized evaluation framework for 3D bioprinting technologies applied to complex bone–tissue interface regeneration

Interface type	Printing modality	Bioink/material composition	Cell type	Gradient design strategy	Key biological outcome	Mechanical outcome	Major limitation
Bone–cartilage	Extrusion-based printing	Me-HA/HAp	Human ADMSCs	Biphasic bone-like and cartilage-like regions	HAp and hypoxia modulated chondrogenesis and reduced hypertrophy	Enabled region-specific osteochondral construct formation	Biological maturation still relies on exogenous cues
Bone–cartilage	Extrusion-based printing + MEW	P-CL-MA	Equine ACPCs	Fiber-reinforced osteochondral interface	Improved hydrogel–ceramic adhesion and interface repair potential	Increased mechanical integrity	Full tissue-level maturation remains limited
Bone–cartilage	Aspiration-assisted bioprinting	Alginate-CaCl2	Human ADSC spheroids	Scaffold-free layered assembly	Supported osteochondral interface formation	Not primarily designed as a load-bearing construct	Spheroid handling and long-term robustness are challenging

Bone–cartilage	Extrusion-based 3D printing	PLA, PLGA, RGD-γ-alginate	Porcine BMSCs / chondrocytes	Biphasic fiber-reinforced template	Regenerated subchondral bone and articular cartilage in vivo	Provided structural support for defect repair	Mechanical performance depends on polymer reinforcement
Bone–cartilage	Extrusion-based bioprinting	PLA / Alginate	Human C28/I2 cells	Multizonal gradient scaffold	Supported hierarchical osteochondral regeneration	Improved shape fidelity and regional organization	Lower bioactivity than cell-rich hydrogel systems
Bone–cartilage	Embedded bioprinting	GelMA / α-TCP	Human ADSCs	One-pot hierarchical multiphasic printing	Enabled fabrication of osteochondral constructs	Produced structurally stable multiphasic constructs	Embedded printing increases fabrication complexity
Bone–cartilage	DLP	Col II MA / HAMA / HAp	Rat BMSCs	Graded bioinks	Promoted region-specific differentiation for osteochondral repair	Improved graded scaffold fidelity	Photopolymerization requires careful cytocompatibility control
Bone–vessel	FDM	PLA / nHA	Human hMSCs	Interconnected microvascular channels	Enhanced osteogenesis and HUVEC growth	Added mechanical support via thermoplastic framework	No direct cell encapsulation during printing
Bone–vessel	Direct-writing bioprinting	GelMA / VEGF / Silicate nanoplatelets	Human hMSCs	Perfusable lumen architecture	Promoted osteogenesis and vascularization	Enabled perfusable constructs	Vascular maturity and perfusion stability remain limited
Bone–vessel	Extrusion-based bioprinting	PCL / CS / PDACS	Human WJMSCs + HUVECs	Spatially separated osteogenic and vasculogenic regions	Promoted coupled osteogenesis and angiogenesis	Improved scaffold stability	Balancing stiffness and cell compatibility remains difficult
Bone–vessel	Coaxial extrusion-based bioprinting	GelMA / Alginate / Gelatin / HAp	HUVECs + MC3T3-E1	Core-shell osteon-like design	Enhanced vascularization and osteogenesis	Better mimicked hierarchical osteon structure	High nozzle-control complexity

Bone–vessel	Dual-ink 3D printing	CaP / Alginate / GelMA	HUVECs	Fibers + microchannel architecture	Supported vascularization and pericyte-like differentiation	Improved hierarchical organization	Complex dual-ink control required
Bone–nerve	Extrusion bioprinting	OPF / Gelatin / PEGDA / Irgacure 2959	MC3T3-E1 + PC12	Bone–nerve co-patterning	Supported viability and proliferation of both cell types	Printable hydrogel with acceptable mechanics	Interface complexity is still limited
Bone–nerve	Air extrusion-based bioprinting	GelMA / AlgMA / Laponite / NGF	BMSCs + Schwann cells / DRG neurons	Ossification-center-mimetic design	Promoted neurovascular network-mediated osteogenesis	Reinforced construct integrity	High biological complexity increases fabrication sensitivity
Bone–nerve	Additive-lathe 3D bioprinting	GelMA / PEGDA	MSC-laden bilayer conduit	Bilayer conduit architecture	Balanced bone/nerve repair requirements	Improved mechanical strength and biocompatibility	Best suited for conduit-like structures
Bone–tendon	Multi-head tissue/organ building system	PCL / PLGA / β-TCP	MSCs	Tendon-to-bone sleeve-like design	Enhanced tendon-to-bone healing in ACL reconstruction	Improved structural support	Fabrication system is complex
Bone–tendon	Extrusion-based 3D printing	PLGA / COL-I	Endogenous progenitor cells	Spatiotemporal growth factor delivery	Promoted integrative tendon-to-bone healing	Supported interface repair	Depends on host cell recruitment
Bone–tendon	Microfluidic-based 3D bioprinting	PLGA / RGD-alginate / Fibrinogen	hUCMSCs	Layer-specific growth factor guidance	Supported rotator cuff enthesis regeneration	Enabled layered interface formation	Biofabrication complexity is high
Bone–tendon	Extrusion-based 3D bioprinting	PCL / PLGA / HA / dECM	hBMSCs	Structure-, composition-, and mechanics-graded scaffold	Promoted tendon-to-bone healing via regional differentiation	Improved graded mechanical properties	dECM variability and reproducibility remain concerns

Bone–immune	Dual-channel bioprinting	GelMA / HAMA / Alginate / GO	BMSCs + BMMs	Dual-channel co-encapsulation	Promoted early immune regulation and osteogenic induction	Improved scaffold biofunctionality	Immune timing is difficult to optimize
Bone–immune	Pneumatic extrusion 3D printing	PCL / PEG / HA	RAW 264.7-related immune context	Pore-size optimization	Reduced foreign body response and promoted M2 polarization	Larger pores improved regeneration	Pore-size effects may not generalize across defects
Bone–immune	Extrusion-based printing	GelMA / Lap / Apt19s	rBMSCs + BMDMs	Functionalized osteoimmunomodulatory scaffold	Promoted BMSC recruitment and osteogenesis	Improved repair potential	Mechanistic validation still needed
Bone–immune	Extrusion-based 3D bioprinting	GelMA / LUT / ZIF-8	RAW 264.7-related immune context + rBMSCs	Sustained dual-function release	Promoted bone repair through osteoimmunomodulation	Enhanced scaffold functionality	Release/degradation balance remains unresolved

Abbreviations: ACL: Anterior cruciate ligament; ACPCs: Articular cartilage progenitor cells; ADMSCs: Adipose-derived mesenchymal stem cells; ADSC: Adipose-derived stem cells; ADSCs: Adipose-derived stem cells; AlgMA: Alginate methacrylate; Apt19s: Aptamer 19s; BMDMs: Bone marrow-derived macrophages; BMMs: Bone marrow macrophages; BMSCs: Bone marrow mesenchymal stem cells; CaP: Calcium phosphate; COL-I: Collagen type I; CS: Chitosan; DLP: Digital light processing; dECM: Decellularized extracellular matrix; DRG: Dorsal root ganglion; FDM: Fused deposition modeling; GelMA: Gelatin methacryloyl; GO: Graphene oxide; HA: Hyaluronic acid; HAMA: Hyaluronic acid methacrylate; HAp: Hydroxyapatite; hBMSCs: Human bone marrow mesenchymal stem cells; hMSCs: Human mesenchymal stem cells; HUVEC: Human umbilical vein endothelial cell; HUVECs: Human umbilical vein endothelial cells; Lap: Laponite; LUT: Luteolin; Me-HA: Methacrylated hyaluronic acid; MEW: Melt electrowriting; MSCs: Mesenchymal stem cells; NGF: Nerve growth factor; nHA: Nano-α-TCP: Alpha-tricalcium phosphate; β-TCP: Beta-tricalcium phosphate; VEGF: Vascular endothelial growth factor; WJMSCs: Wharton's jelly mesenchymal stem cells; ZIF-8: Zeolitic imidazolate framework-8

Table 2. Representative gradient-design strategies used in 3D bioprinting for bone–tissue interface regeneration

Gradient design strategy	Typical 3D bioprinting approach / construct	Representative study	Key biological function	Interface relevance	Major limitation
Material composition gradient	Multi-material extrusion, coaxial printing, or DLP-based graded constructs	Biphasic or multilayer osteochondral, tendon-to-bone, and vascularized bone scaffolds using combinations of hydrogel and mineralized phases, such as GelMA/alginate, collagen/HA, or PCL/HA-based systems	Recapitulates native compositional transitions between soft and hard tissues; supports region-specific cell differentiation	Particularly important for bone–cartilage and bone–tendon interfaces, where abrupt changes in matrix composition must be avoided	Material gradients are often discretized rather than truly continuous; reproducibility and long-term interfacial remodeling remain challenging
Stiffness gradient	Gradient crosslinking, multi-material printing, dECM-coated graded scaffolds, or core-shell architectures	DLP-printed collagen-based gradient osteochondral scaffold ; dECM-coated graded tendon-to-bone scaffold ; core-shell gradient enthesis scaffolds	Provides mechanical cues that direct chondrogenic, osteogenic, or fibrocartilaginous differentiation depending on local modulus	Critical for osteochondral and enthesis repair, where mechanical mismatch is a major cause of failure	Mechanical gradients may evolve during degradation, creating mismatch between scaffold softening and tissue maturation
Mineral content gradient	Spatially graded incorporation of HAp, β-TCP, CaP, nHA, or piezoelectric/mineral fillers	Osteochondral and tendon-to-bone constructs containing HAp, β-TCP, CaP, or nHA	Promotes osteogenic differentiation in mineral-rich regions while preserving softer domains for cartilage or tendon formation	Especially relevant for bone-facing regions in osteochondral and enthesis constructs	Excess mineral loading can reduce printability, increase brittleness, and impair cell spreading in softer compartments
Porosity gradient	Controlled pore-size design, hierarchical microchannels, osteon-mimetic channel architecture, or multi-axial printing	Pore-size-modulated PCL/PEG/HA scaffolds ; osteon-mimetic microchannel scaffolds; microchannel-based vascularized bone constructs	Regulates cell infiltration, vascular ingrowth, nutrient diffusion, and immune cell recruitment	Highly relevant to vascularized bone regeneration and immune-regulated bone repair	Too-small pores hinder vascularization; too-large pores weaken mechanical integrity and may reduce surface area for cell attachment

Cell-density gradient	Multi-nozzle deposition, bicellular or multicellular layered printing, spheroid assembly, or co-culture patterning	Spatially differentiated ADMSC constructs; anisotropic bicellular hydrogels; multicellular tendon-to-bone or neuro-bone constructs	Mimics native cellular heterogeneity and supports spatially specific lineage commitment and paracrine signaling	Important across nearly all bone–tissue interfaces, particularly where multiple cell phenotypes must be organized spatially	Maintaining viability and phenotype during and after printing is difficult; high-density constructs are often limited by diffusion
Growth-factor concentration gradient	Layer-specific loading of microspheres, gradient bead distribution, or controlled release systems	Layer-specific growth factor-loaded microspheres for enthesis healing ; gradient BMP-2-loaded microbeads; spatiotemporal GF delivery in tendon-to-bone repair	Provides instructive cues for spatially controlled differentiation and tissue zonation	Particularly valuable for tendon-to-bone and osteochondral interfaces, where distinct zones require different signals	Release kinetics are difficult to match with tissue remodeling; burst release and signal loss remain concerns

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