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Holistic insights of 6D printing in healthcare

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A B S T R A C T

Additive manufacturing has recently demonstrated significant progress in healthcare. Six-dimensional (6D) printing is an emerging field that holds great promise through the rapid, layer-by-layer creation of complex objects capable of changing over time in response to external stimuli, resulting in dynamic and adaptable products. 6D printing represents a superimposition of 4D and 5D printing, combining the stimuli-responsiveness of 4D printing with the structural robustness of 5D printing. It uniquely enables autonomous, adaptive drug delivery systems by utilizing smart materials such as shape-memory alloys, responsive polymers, and hydrogels that react to environmental triggers. This review explores the evolution, mechanisms, significance, and innovations of 6D printing, which has made notable strides toward patient-centered medical approaches. Future developments in 6D printing may involve the use of material panels that adapt to stimuli varying over time under physiological conditions, offering new possibilities for advanced medical applications and solutions.

1. Introduction

1.1. Evolution in printing technology from 1D to 6D printing

The evolution from one-dimensional (1D) to six-dimensional (6D) printing as depicted in Fig. 1 reflects a progressive advancement in additive manufacturing, characterized by increasing control over spatial geometry and material behaviour. Although rarely implemented independently, 1D printing conceptually represents linear material deposition along a single axis, serving as the foundational principle for early-stage prototyping and micro-pattern fabrication.[1] Two-dimensional (2D) printing expanded this concept by enabling the planar deposition of inks and substrates, thereby establishing the foundation for conventional inkjet- and laser-based printing techniques widely adopted for documentation and circuit fabrication. Beyond these applications, the same planar deposition strategies were instrumental in the early development of biosensors, including printed electrodes, glucose test strips, and DNA microarrays, where functional inks and biomolecules were precisely deposited onto flat substrates to create sensitive and reproducible sensing platforms.[2] The development of Three-dimensional (3D) printing, or additive manufacturing, marked a significant shift by introducing volumetric layer-by-layer fabrication. This advancement enabled the production of structurally complex and functionally diverse objects, fostering innovation across biomedical, aerospace, and consumer manufacturing sectors.[3] Four-dimensional (4D) printing built upon this capability by incorporating time as a functional dimension facilitating the use of smart materials that respond to external stimuli such as temperature, light, pH, or magnetic fields. This enabled the development of dynamic systems, including self-folding devices, shape-memory implants, and programmable textiles.[4] Further progression to 5D printing introduced fabrication across five axes (three spatial plus two rotational), allowing optimal deposition angles and enhanced structural integrity. This geometric freedom improves part strength, especially in load-bearing applications such as orthopedic implants and aerospace components.[5] 6D printing, the latest advancement, integrates the programmable material properties of 4D printing with the multi-axis deposition strategy of Five-dimensional (5D) printing. This hybrid approach enables the fabrication of constructs that are both geometrically sophisticated and stimuli-responsive capable of real-time interaction with environmental and physiological cues. It is especially transformative in biomedical contexts, where 6D systems support the creation of adaptive prosthetics, smart drug delivery platforms, and bioactive tissue scaffolds tailored to patient-specific anatomy and pathology.[1,6] This dimensional progression illustrates a clear technological shift from passive object construction to the development of intelligent, responsive, and personalized systems positioning 6D printing at the

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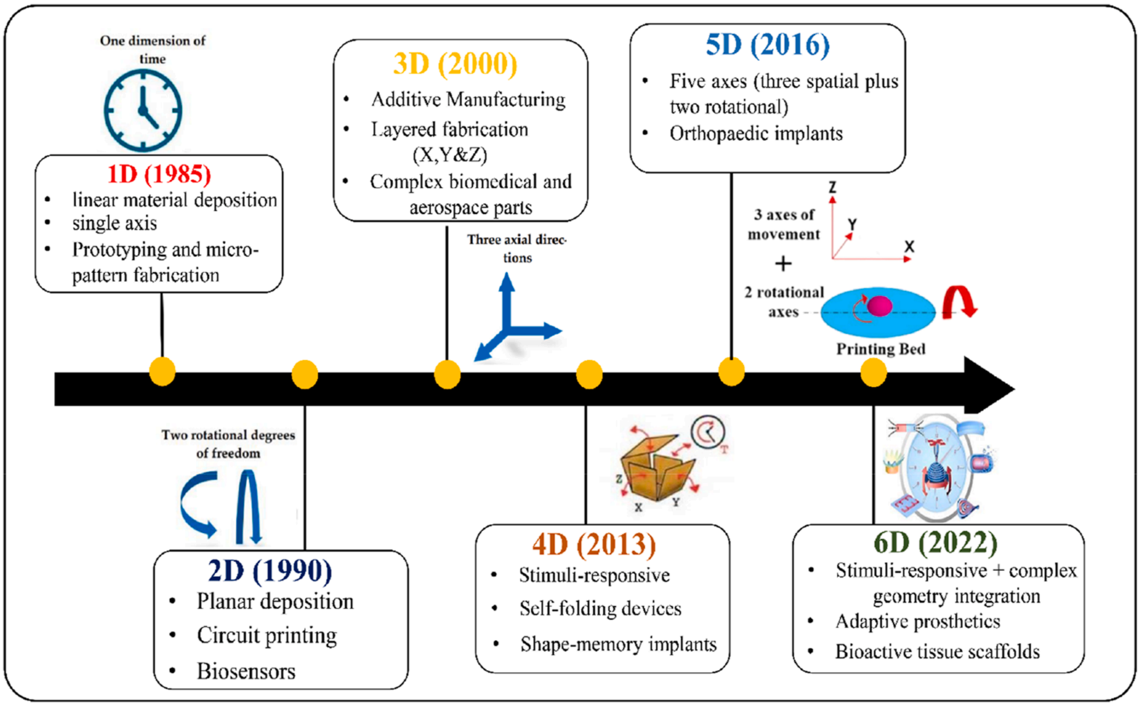

Fig. 1. ***Timeline of printing evolution from 1D to 6D.*** This scheme outlines key advancements from linear deposition (1D) to intelligent, sensor-integrated systems (6D). Applications include biosensors (2D), additive manufacturing (3D), shape-responsive devices (4D), complex curvature printing (5D), and adaptive biomedical platforms such as smart drug delivery systems and tissue scaffolds (6D). Icons were adapted from open-access sources; the design is *self-drawn.*[7–14]

forefront of integrative pharmaceutical and clinical manufacturing.

While 4D printing introduced time-responsive transformations using smart materials, its adaptive capacity remains fundamentally passive triggered only by predefined stimuli. In contrast, 6D printing surpasses 4D printing by integrating real-time feedback control, predictive machine learning algorithms, and sensor-actuated behavior, enabling truly autonomous systems. A 6D printed object can detect environmental cues, analyse them, and actively reconfigure its mechanical, chemical, or structural properties in situ. This shift from stimulus-reactive to context-aware and decision-making constructs marks a major advancement in intelligent manufacturing. Unlike 4D systems that operate in open-loop modes, 6D printing employs closed-loop adaptive control, leading to self-regulating drug delivery, responsive implants, and patient-specific biomedical tools that evolve with physiological needs.

1.2. Defining 6D printing: A self-adaptive manufacturing paradigm

6D printing represents a transformative advancement in additive manufacturing, defined by its integration of spatial freedom, stimuli-responsiveness, and intelligent system adaptability. Unlike traditional 3D printing, which constructs static geometries layer by layer, 6D printing operates across six distinct dimensions: three spatial axes as depicted in Fig. 2, the temporal evolution of structure (4th dimension), active material behaviour (5th dimension), and real-time feedback-controlled intelligence (6th). This sixth dimension is realized through embedded sensors, machine learning algorithms, and IoT-enabled systems, allowing printed objects to sense, interpret, and autonomously respond to environmental inputs[15,16] As a result, 6D-printed systems can adapt their form and function dynamically, enabling personalized, context-aware performance.[17]

Technically, 6D printing utilizes six-axis robotic arms to deposit material on non-planar and multidirectional surfaces with high precision, and this mechanical flexibility can be coupled with stimuli-responsive materials, such as shape-memory polymers (SMPs) that undergo transformation at a pre-set activation temperature, hydrogels that

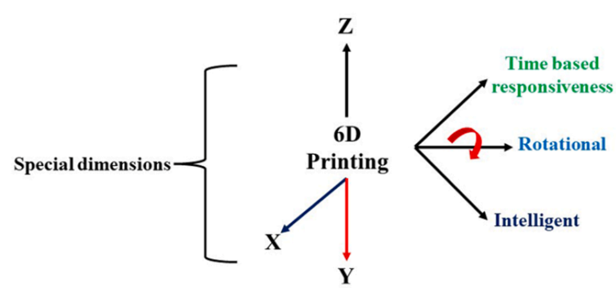

Fig. 2. ***Visual representation of the six dimensions in 6D printing technology.*** The diagram illustrates the six distinct dimensions that define 6D printing. The X, Y, and Z axes (grouped under the curly bracket) represent the three spatial dimensions used in traditional 3D printing. 4D printing adds the time dimension, enabling materials to change shape or function in response to external stimuli. 5D printing introduces rotational freedom through additional degrees of orientation, allowing fabrication on curved or angled surfaces. Finally, 6D printing incorporates intelligent adaptation via sensor feedback and AI-driven control systems, enabling real-time reprogramming of material behavior. Together, these six dimensions enable the fabrication of smart, personalized, and autonomous biomedical devices such as adaptive implants, scaffolds, and drug delivery platforms.

swell in aqueous environments, and bioactive composites that modulate biochemical activity.[18,19] These materials are engineered to undergo controlled deformation, porosity change, or property alteration in response to physical, chemical, or biological stimuli such as pH, temperature, or mechanical stress. Crucially, these dynamic transformations are not passive but are regulated by embedded microcontrollers, nano sensors, and Artificial Intelligence (AI) driven actuators that interpret environmental signals in real time and initiate appropriate responses.[1]

Unlike 4D printing which introduces time-based shape change or 5D printing, which enhances geometric freedom via multi-axis deposition, 6D printing synergizes both concepts with digital intelligence and adaptive behaviour. For example, a 6D-printed orthopedic implant can modify its stiffness or drug release profile in response to inflammatory cytokines, or a printed biomedical scaffold may modulate its mechanical properties and porosity based on cellular feedback during tissue regeneration.[18,20]

6D printing holds significant potential in biomedical applications. Adaptive scaffolds can dynamically adjust their microarchitecture, stiffness, and biochemical release rates in response to physiological cues improving integration and promoting precise, staged tissue regeneration.[21] 6D-printed drug delivery systems are similarly enhanced: incorporating biosensors and microfluidic channels, they can trigger targeted drug release upon detecting changes in pH, temperature, or biomarker concentrations.[20] These features enable localized, personalized therapies with reduced systemic toxicity.

Moreover, 6D printing is augmented by AI and Internet of Things (IoT) integration, where machine learning algorithms predict material behaviour under variable conditions and optimize design iteratively. This ensures not only responsive behaviour but anticipatory adaptation, whereby the printed structure evolves in anticipation of environmental change, enhancing reliability and efficiency in high-stakes domains such as surgery, aerospace, and defence. [15,17]

In surgical applications, real-time adaptable tools and implants engineered via 6D printing can alter their geometry, surface properties, or stiffness intraoperatively in response to biological or mechanical cues. Such intelligent responsiveness enables unprecedented precision, personalized interventions, and faster patient recovery. To avoid conflation with other advanced manufacturing paradigms, a comparative framework distinguishing 6D from 3D, 4D, and 5D printing is essential, as each encompasses a unique combination of spatial, temporal, and functional dimensions [1] presented in Table 1.

2. Mechanisms of 6D printing

Time and Space Manipulation 6D printing technology represents a significant evolution from traditional additive manufacturing methods by integrating time and space manipulation into printed structures, enabling them to respond dynamically to environmental stimuli. The dimension of time in 6D printing refers to the capacity of materials to adapt or transform over a predefined period. These adaptations could be triggered by external factors like temperature, light, or mechanical stress, making them ideal for applications where functionality needs to change over time, such as in biomedical devices that adjust as a patient's physiological state evolves. Space manipulation involves the ability of materials to respond to spatial environmental conditions, such as pressure, magnetic fields, or proximity to other objects. This spatial awareness allows structures to interact with their surroundings in real time, facilitating the creation of adaptive medical implants, smart textiles, or aerospace components that change their mechanical properties when exposed to stress or environmental changes. Combining both temporal and spatial responses, 6D printing can produce highly functional, context aware materials capable of multifaceted transformations.[22–24]

2.1. Materials used in 6D printing

6D printing requires materials that exhibit spatiotemporal responsiveness, enabling structures to adapt their shape, function, or mechanical properties over time or in response to localized environmental stimuli. This functionality depends on the integration of advanced smart materials, each offering a unique form of stimulus sensitivity. The primary material classes suitable for 6D printing Table 2 include smart polymers, hydrogels, nanomaterials, shape-memory alloys (SMAs), piezoelectric materials, biodegradable polymers, and composite or hybrid materials.

2.1.1. Smart polymers

Smart polymers are stimuli-responsive materials that undergo reversible changes in physical or chemical properties in response to specific environmental cues such as temperature, pH, magnetic fields, or light.[25] For instance, poly(N-isopropylacrylamide) (PNIPAAm) exhibits a coil-to-globule transition above its lower critical solution temperature (LCST) of approximately 32 °C, making it highly applicable in biomedical settings.[26] These transitions can lead to shape memory, phase switching, or changes in solubility, providing temporal adaptability essential for 6D printed structures.

Examples: PNIPAAm, polyelectrolyte gels.

Applications: Drug delivery systems, micro actuators, soft robotics.

2.1.2. Hydrogels

Hydrogels are a subclass of smart polymers, composed of hydrophilic, crosslinked polymer networks that can absorb water up to several hundred times their dry weight.[27] They respond to stimuli such as pH, ionic strength, or temperature by undergoing volumetric swelling or shrinking. In 6D printing, hydrogels enable gradual, time-driven structural transitions, making them ideal for applications requiring moisture-activated or biochemically-triggered transformations.

Examples: Polyvinyl alcohol (PVA), polyethylene glycol (PEG)-based hydrogels.

Applications: Tissue scaffolds, responsive wound dressings, injectable drug reservoirs.

2.1.3. Nanomaterials (nanoparticles, nanotubes, nanowires)

Nanomaterials possess exceptionally high surface area-to-volume ratios, along with enhanced mechanical, thermal, and electrical properties.[28] Their nanoscale dimensions enable remote manipulation via light, heat, or magnetic fields, making them useful as functional reinforcements in 6D printing. For example, carbon nanotubes (CNTs) provide mechanical strength and electrical conductivity, while gold nanoparticles can be used for localized photothermal activation.

Example: Carbon nanotubes, gold nano particle, silver nanowires.

Applications: Flexible electronics, biosensors, reinforced smart composites.

2.1.4. Shape-memory alloys (SMAs)

Shape-memory alloys (SMAs) are metals capable of returning to their original shape after deformation upon exposure to a specific temperature, based on solid-state phase transformation between martensite and austenite phases.[29] This transformation enables them to perform repeatable mechanical movements. For example, Nitinol (Ni-Ti) exhibits strain recovery of up to 8% and excellent fatigue resistance, making it ideal for time-dependent actuation in 6D-printed components.[30]

Example: Nitinol.

Applications: Aerospace actuators, self-expanding stents, morphing structures.

2.1.5. Piezoelectric materials

Piezoelectric materials convert mechanical stress into electrical charge, and vice versa, allowing printed structures to act as self-powered sensors or actuators.[16] Their dual capability is crucial for real-time, embedded feedback systems. Lead zirconate titanate (PZT), for instance, exhibits a high piezoelectric coefficient ($d_{33} > 500$ pC/N), enabling effective force sensing and actuation in responsive 6D-printed surfaces.

Example: PZT, Zinc oxide, Barium titanate.

Applications: Pressure sensors, haptic interfaces, energy-harvesting devices.

2.1.6. Biodegradable polymers

Biodegradable polymers are designed to decompose within biological or environmental systems through hydrolysis or enzymatic cleavage of ester linkages.[31] This property enables temporal disappearance or functional change, an essential trait in many biomedical applications. For example, polycaprolactone (PCL) degrades slowly over months, while polyglycolic acid (PGA) degrades more rapidly *in vivo*, allowing

Table 1
Comparative evolution of printing technologies from 1D to 6D: Functional dimensions, capabilities, and biomedical readiness.

Feature/Dimension	1D Printing	2D Printing	3D Printing	4D Printing	5D Printing	6D Printing
Spatial axes [15]	Linear (X)	Planar (X, Y)	Volumetric (X, Y, Z)	XYZ + Time	Multi-axis (5D)	6-axis with adaptivity
Temporal dynamics[16,17]	None	None	None	Passive shape/time change	None	Predictive adaptive response
Smart materials [18]	Not applicable	Inks, toners	Polylactic Acid (PLA), Acrylonitrile Butadiene Styrene (ABS), resins	SMPs, hydrogels	Engineering polymers	Multifunctional composites
Material programming [7,10]	None	None	Static properties	Pre-programmed	Not programmable	Reprogrammable & stimulus-responsive
Sensor integration[19]	None	None	Minimal (hybrids)	Basic environmental sensors	Rarely used	Full suite (strain, thermal, biosensors)
AI/Machine learning (ML) integration[20]	None	None	None	None	None	AI for prediction, design, optimization
Feedback control [16,20]	None	None	Manual	Open-loop	Geometry-based	Closed-loop adaptive control
Application focus [15,18,19]	Micro-interconnects	Document/text printing	Prototypes, implants	Wearables, smart textiles	Aerospace, complex geometry	Tissue scaffolds, adaptive tools
Example use case[21]	Nanowire writing	Newspaper printing	3D bone models	Shape-shifting patch	Curved turbine blades	Bone implant adjusting stiffness
Fabrication technique [17,20]	1D printheads	2D raster scan	Layered Fused Deposition Modelling (FDM)/ Stereolithography (SLA)	Extrusion + stimuli	CNC-based multi-axis	Robotic extrusion + AI + sensors
Hardware architecture [18,21]	Line print unit	2-axis printer	3-axis system	4-axis printer with smart material feed	5-axis head and pathing	6- Degrees of Freedom (DOF) arm + embedded microcontrollers
Innovation focus [16,19]	Micro precision	Surface fidelity	Volumetric freedom	Stimuli-induced change	Curved geometry printing	Self-aware intelligent manufacturing
Limitations [16,17,21]	Only linear output	Flat, static prints	No functional change	Slow actuation	Expensive kinematics	High cost, regulatory unknowns
System requirements [18]	Basic driver	Print head & medium	3-axis controller	Actuator + smart material	Multi-axis kinematics	Sensor network + edge AI + robotic control
Commercial maturity [20,21]	Fully deployed	Mature tech	Mature tech	Translational R&D	Advanced prototyping	Research/prototype stage
Ethical/Regulatory issues [15,17]	None	None	Material safety	Biocompatibility	Mechanical certification	AI ethics, U.S. Food and Drug Administration (FDA)/European Medicines Agency (EMA) compliance
Printing resolution[19,20]	N/A	≥300 dpi	100–200 μm	Variable (100–500 μm)	50–150 μm	≤100 μm
Post-processing needs [15,16,21]	None	Drying/lamination	Support removal, curing	Heat or pH triggering	Polishing, machining	Testing, calibration
Energy efficiency[1]	High	Moderate	Moderate	Variable	Low to Moderate	Low (sensor + AI load)
technology Readiness level (TRL)[17,20]	9	9	8–9	5–6	4–6	2–4
AI capabilities[18]	None	None	None	None	None	Predictive modeling, generative design, anomaly detection
Learning mode (AI) [16,18,20]	N/A	N/A	N/A	N/A	N/A	Supervised & Reinforcement Learning
Ethical risks[21]	None	None	Material waste	Biocompatibility	Environmental waste	Data privacy, misuse, regulation gaps

Table 2
Comparative analysis of material categories for 6D printing.

Material class	Stimuli response	Response mechanism	Representative materials	Key property (quantified)	6D functional role
Smart polymers [33,34]	Temp, pH, light	Coil-to-globule, ionization	PNIPAAm, polyelectrolyte gels	LCST ~32 °C (PNIPAAm)	Time-dependent actuation
Hydrogels [35,36]	Water, pH, ions	Swelling/deswelling	PEG, PVA	Water uptake >500 × weight	Volume modulation
Nanomaterials [37,38]	Light, magnetic field	Electromagnetic or thermal activation	CNTs, Gold Nanoparticles (AuNPs)	Thermal conductivity >3000 W/m·K (CNTs)	Spatial signal responsiveness
Shape-memory alloys [39,40]	Heat, stress	Martensitic-austenitic transformation	Nitinol	Shape recovery strain ~8%, activation ~70 °C	Shape adaptation over time
Piezoelectric material [41,42]	Mechanical stress	Charge generation/deformation	PZT, ZnO, Barium titanate ($BaTiO_3$)	d_{33} ~500 pC/N (PZT)	Real-time sensing & feedback
Biodegradable polymers [43,44]	Enzymes, water	Hydrolytic or enzymatic degradation	PLA, PCL, PGA	Degradation time: Weeks–Months	Temporary bio integration
Hybrid composites [45,46]	Multi-stimuli	Synergistic multi-material response	CNT-hydrogel composites	Multifunctional; properties combined	Spatiotemporal multifunctionality

programmed functionality based on application needs.

Example: Polylactic Acid (PLA), PCL, PGA.

Applications: Resorbable sutures, drug-eluting implants, bio-absorbable devices.

2.1.7. Composite and hybrid materials

Composite and hybrid materials combine two or more functional material classes (e.g., polymers, metals, and nanomaterials) to achieve multifunctional, synergistic behaviour.[32] This integration allows for simultaneous stimulus detection, actuation, and structural adaptation, critical for complex 6D tasks. A CNT hydrogel composite, for example, can detect mechanical strain (via CNT conductivity) and respond volumetrically to hydration (via hydrogel swelling), achieving spatiotemporal responsiveness in one system.

Example: CNT-reinforced polymers, hydrogel metal hybrids.

Application: Smart textiles, adaptive prosthetics, self-healing coatings.

2.2. Technological principles (software and tools) of 6D printing

Design and Fabrication Processes 6D printing therefore is the next step beyond the 4D printing since it can change its reactive mode when and where it is subjected to spatial and temporal signals. Technological and sophisticated methods and approaches are used in manufacturing as well as the designing and modelling of this smart material. The 6D printing manufacturers and researchers have to work closely with the software tools, design perspectives, and fabrication approaches to enable objects created through the technology to be manipulated through time and space.

The design and simulation of 6D-printed objects require highly specialized software capable of modelling dynamic, multi-material, and stimulus-responsive behaviour. These tools are critical in ensuring that the printed objects can react predictably and efficiently to both temporal and spatial changes in their environment.[30] Key softwares and tools used in the 6D printing process involved CAD (Computer-Aided Design), Finite Element Analysis (FEA) and Multi-Physics Simulations, Design Software and Material Slicing Software.

2.2.1. CAD (Computer-Aided Design) software

As mentioned before, it is Additive Manufacturing (AM) whereby the material being used is deposited layer by layer and bonded together to make a solid part as per the design of the CAD model along with form and loading behaviour; design models also have to accept the material behaviour, which is time-dependent or position-dependent material. While 4D printing utilizes stimuli-responsive materials such as shape-memory alloys to enable time-based transformations, 6D printing expands this concept by integrating advanced CAD systems with multi-material design and real-time adaptive control. Unlike 4D printing, which typically involves pre-programmed responses to stimuli, 6D printing incorporates spatial feedback mechanisms, AI algorithms, and embedded sensors to allow objects to dynamically adapt their structure based on environmental changes.[16,31,32]

2.2.2. Finite element analysis (FEA) and multi-physics simulations

In order to human-like replicate the mechanical, thermal, and chemical behaviour of 6D printed structures, software such as ANSYS, COMSOL Multiphysics, and Abacus are used. These programs help engineers estimate how certain postures of used materials will perform to warrant the final printed work. For control of mechanical properties of the end part like strength, elasticity, and deformation, Finite Element Analysis or FEA is required for 6D printed objects and multi physics for having interaction with heat, pressure, magnetic field, etc.[47]

2.2.3. Design software for 6D printing

Design software in 6D printing plays a critical role in modeling not only structural geometry but also programmable behaviour that responds to environmental cues. These platforms, such as Self-CAD and n-Topology, are optimized for multi-material integration, spatial-temporal transformation, and real-time adaptability. Users can define stimulus-specific behavior at the voxel or region level such as thermal expansion thresholds, pressure sensitivity zones, or moisture-induced deformation directly within the digital design environment. Unlike conventional CAD tools, these systems enable the incorporation of behavioural algorithms, real-time feedback conditions, and conditional response logic into the geometry itself. Additionally, these platforms support parametric modeling and embedded scripting, allowing seamless integration with sensor networks, control systems, and AI-based decision modules. This ensures that 6D-printed structures are not only geometrically accurate but also capable of intelligent, adaptive behavior during operation, aligning function with evolving physical or physiological contexts.[48,49]

2.2.4. Material slicing software

The four software that can be used to generate instructions for three dimensional prints are Repetier, Cura, Slic3r, and Simplify3D. This type of printing entails revision of slicing software in order to allow for layered production of several stimuli sensitive materials; as well as to allow for fine spatial control of more than one material. It therefore stands to reason that the advanced slicing software has to consider how these materials respond to external stimuli and how such responses change over time and space.[50]

2.2.5. Control systems and sensors integration

In 6D printing, the end-product objects have in-built sensors and/or actuators, etc., and these components both functional and geometrical have specific requirements for design as well as integration during 6D printing. MATLAB and Lab VIEW software are used to control the real-time feedback for these systems so that the printed object can have responsive features that enable it to adjust to the surroundings when left to its own devices.[51]

2.3. Processes that are involved when using the 6D printing technology

The 6D printing process can be broken down into several phases, each of which must be managed carefully to ensure that the structural and material designs from the pre-design phase are successfully translated into micro-scale structures. Fig. 3 provides a visual representation of the stepwise workflow in 6D printing, highlighting the sequential stages involved in this advanced technology.

2.3.1. Conceptual design and modelling

The process begins with the conceptual design of the object, where designers define the intended functionality and behaviour. Unlike conventional additive manufacturing, 6D printing incorporates temporal functionality and spatial interactivity into the design process, enabling the fabrication of objects that respond dynamically over time and adapt to environmental stimuli. CAD tools are utilized to create a 3D image of the object; multi-physics tools are employed to predict how the object will behave in terms of deformation, expansion or contraction depending on some external influence. This ensures that the object will perform as intended throughout its lifecycle.[52]

2.3.2. Material selection

The success of 6D printing depends on selecting materials that can respond predictably to stimuli. The choice of materials is critical and depends on what kind of response characteristics the object should have and what effects it as an object needs to experience like changes in temperature, light, humidity, or mechanical stress. They include smart polymers, shape memory alloys, piezoelectric materials, and hydrogels. For instance, if the intended application of the material is encoded for a change in shape as a function of temperature, then the material is shape memory polymers or alloys. If the object needs to respond to pressure,

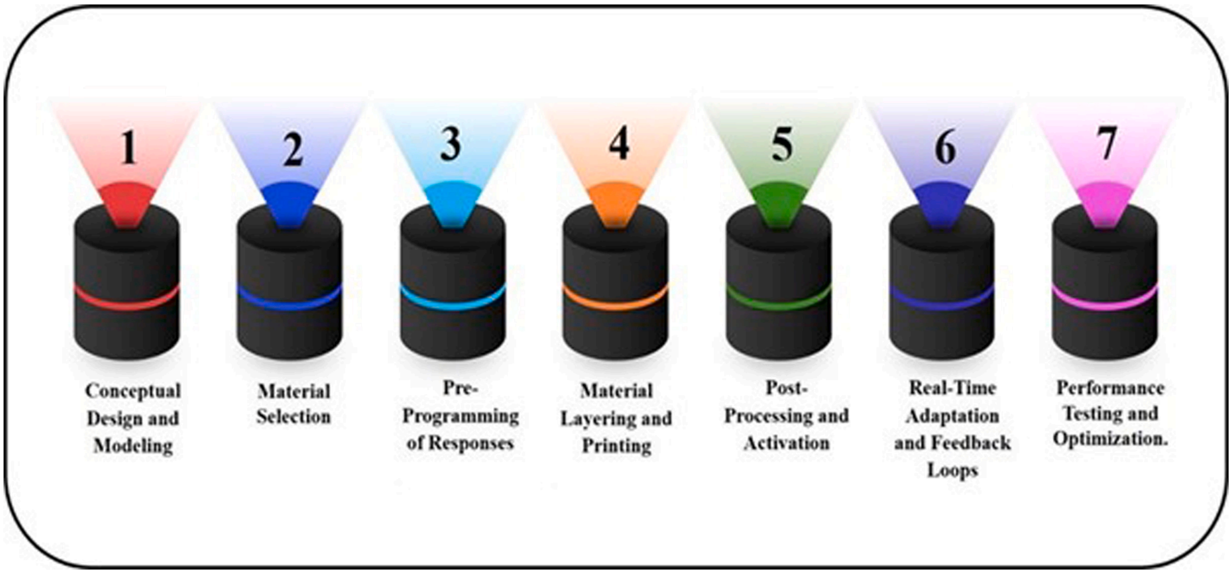

Fig. 3. Stepwise procedural workflow in 6D printing technology. This schematic illustrates the seven foundational stages in the 6D printing development pipeline, integrating smart materials, computational modeling, and adaptive feedback systems. It begins with conceptual design and modeling, where digital simulations define geometry and function. Material selection follows, focusing on multifunctional composites with embedded actuation or sensing potential. In the pre-programming stage, materials are engineered to respond to external stimuli such as heat, pH, or magnetic fields. Layer-by-layer printing employs advanced techniques like robotic extrusion to fabricate structures with spatial and functional fidelity. Post-processing and activation enable dynamic behaviour via thermal or chemical triggers. Critically, real-time adaptation is achieved through integrated sensors and closed-loop feedback, allowing the printed system to respond autonomously to its environment. The final stage, performance testing and optimization, employs AI and machine learning for iterative calibration, ensuring reliability and functionality. This workflow represents a shift from static fabrication to intelligent, responsive bio fabrication, laying the foundation for next-generation adaptive biomedical devices.

piezoelectric materials are embedded within the structure.[2,53]

2.3.3. Pre-programming of responses

At this stage, behavioural algorithms are embedded into the object's design, specifying how it should respond to defined stimuli such as moisture, heat, or pressure. This coding ensures that the structure can perform autonomous functions once activated, building on the foundational design considerations from Section 2.3.1.[54–56]

2.3.4. Material layering and printing

Once the design is finalized or the material characteristics are defined, the 6D printing process commences. This approach typically utilizes multi-material 3D printers capable of precisely depositing stimuli-responsive materials according to a programmed spatial configuration. Responsive materials are combined with stereo lithography (SLA), fused deposition modelling (FDM), selective laser sintering (SLS), and other advanced 3D printing technologies in combination with selective print heads. In the case of the object, each of these layers is printed with materials deposited in regions of the object that are predetermined to be activated at certain times.[57,58]

2.3.5. Post-processing and activation

The object may need to be post processed to guarantee that it responds as desired to the stimulus. For example, SMPs need to be heated to the activation temperature while on the other hand, hydrogels need to be exposed to some extent of water to swell. To recall the shape or the behaviour, the external factors like heat, light, or machining stress are applied ‘to teach’ the material. Once this activation process is completed, the object is ready for deployment.[59–61]

2.3.6. Real-time adaptation and feedback loops

The primary function of a 6D-printed object is to undergo adaptive transformation during its operational use, responding to external stimuli or environmental conditions. Unlike pre-programmed responses defined during the design stage (Section 2.3.3), this phase enables continuous sensing and *real-time adaptation* using embedded biosensors and AI algorithms. The object can monitor environmental changes and adjust its behavior dynamically without external intervention. For example, the 6D printed medical implant has the capability to be designed to adjust stiffness depending on the body temperature making it more comfortable for the patient. In some instances, these systems are accompanied by feedback; the sensors are also designed to detect changes in the surroundings, while the actuators initiate the response within the material. Software such as MATLAB or Lab VIEW controls these feedback systems, ensuring the object behaves as designed over its operational life.[2,18]

2.3.7. Other techniques such as performance testing and optimization

The object undergoes fabrication and activation of its functional mechanism, after which rigorous testing is performed to verify its operational reliability across a range of environmental conditions. The object's time- and space dependent behaviours are tested in controlled settings to validate the pre-programmed responses. If necessary, the design can be adjusted, and the object re-printed to optimize its performance. This iterative process ensures that the 6D-printed object can reliably perform in complex real-world environments.[16]

3. Applications in medical technologies

The principal medical applications of 6D printing are systematically summarized in the given section. It categorizes innovations across three primary domains: drug delivery systems, personalized prosthetics and implants, and biologically compatible scaffolds further delineating subfields such as cranial reconstruction, dental and spinal implants, as well as tissue-specific engineering for bone, cartilage, cardiac, neural, and dermal regeneration. The multifaceted application domains of 6D printing in healthcare are summarized in Fig. 4, which provides an overview of its integration into tissue engineering, advanced drug delivery, patient-specific implants, personalized treatment, cross-disciplinary innovation, and dynamic adaptability.

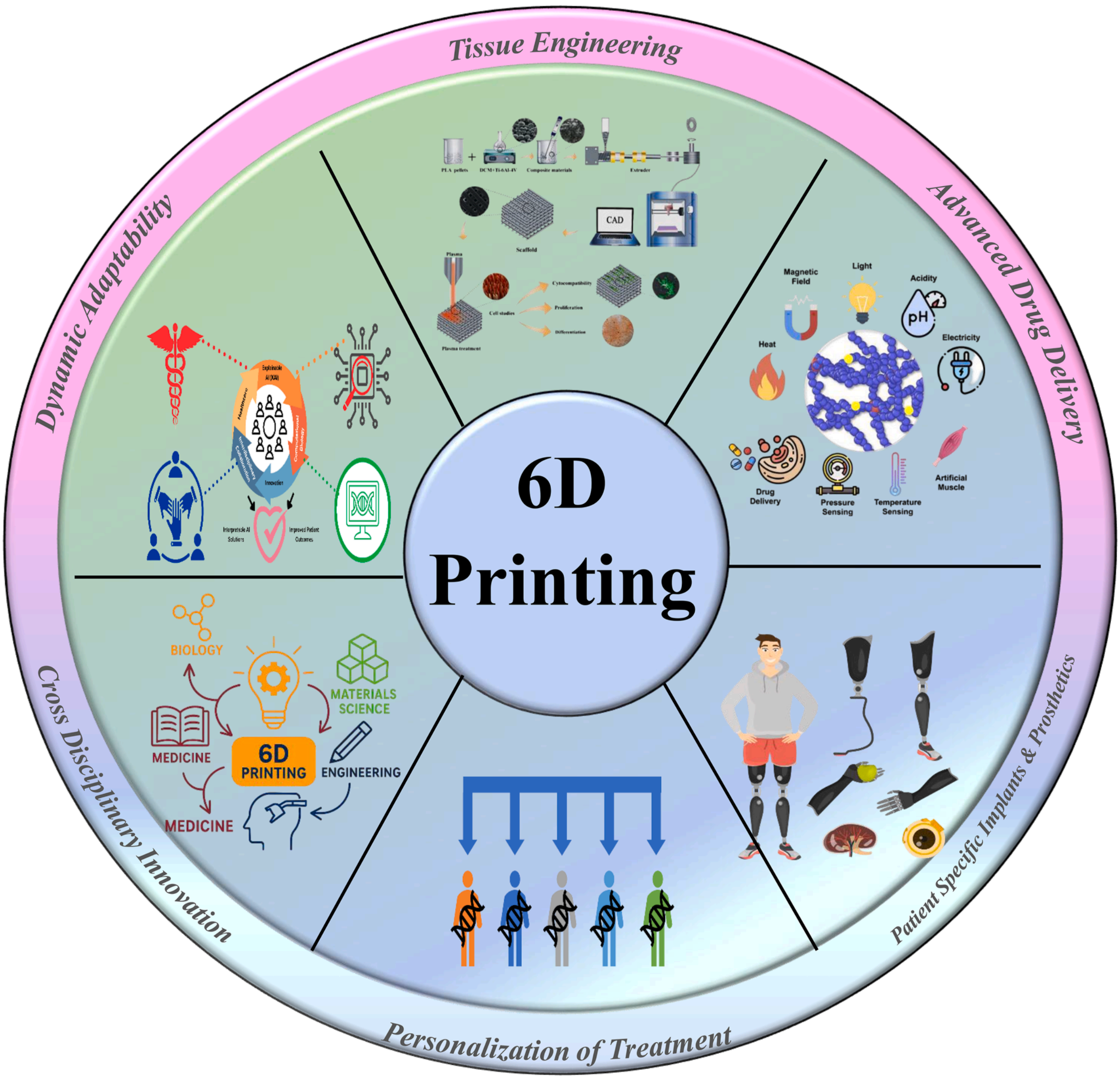

Fig. 4. Schematic overview of the multifaceted domains and potential applications of 6D printing. This diagram illustrates the core framework and six critical application domains of 6D printing in healthcare. At the center, 6D Printing is represented as the convergence of advanced additive manufacturing with dynamic responsiveness and intelligent design. Surrounding the core, six sectors highlight its integration in: Tissue Engineering, showcasing the fabrication of bio-scaffolds and organotypic constructs using Computer-Aided Design (CAD) driven bioprinting; Advanced Drug Delivery, enabling smart release systems via stimuli-responsive materials (e.g., heat, pH, light, magnetism); Patient-Specific Implants & Prosthetics, emphasizing anatomical personalization and functional restoration using biomechanical augmentation; Personalization of Treatment, where genomics and phenotypic profiles guide tailored therapeutic interventions; Cross-Disciplinary Innovation, denoting the synergy between biology, medicine, engineering, and materials science in designing next-generation devices; and Dynamic Adaptability, representing systems capable of responding to external stimuli or real-time feedback via embedded sensors or soft robotics. This holistic view underscores the transformative potential of 6D printing in achieving precision, adaptability, and interactivity in medical applications.

3.1. Drug delivery systems

6D printing that incorporates time, space, and material responsiveness is today revolutionizing drug delivery systems and treatment methods. Through introducing time as a functional dimension, 6D printing can provide the predetermined spatial and temporal drug delivery. This is enabled through the application of stimuli-sensitive materials that respond to the alterations in environment or physiological conditions of pH, temperature, or magnetic force. This targeted delivery can increase medicine effectiveness while simultaneously decreasing negative effects and raising patient quality of life. Some case studies are very supportive in making a claim about the utility of 6D printing in drug delivery systems for different therapeutic segments like diabetes, oncology, osteomyelitis, and cardiovascular diseases.

6D printing uniquely enables autonomous, adaptive drug delivery systems that cannot be achieved with 3D or 4D platforms. These systems incorporate real-time biosensors, microcontrollers, and AI algorithms that interpret dynamic physiological data to modulate therapeutic output. Such closed-loop feedback control is exclusive to 6D systems and essential for achieving personalized and responsive treatment protocols. For example, Odent et al. (2024) developed a glucose-responsive insulin patch embedded with electrochemical biosensors and microcontrollers that adjust insulin release in real time based on glycaemic levels. Similarly, Zhu et al. (2021) demonstrated a hydrogel-based system that offers a closed-loop therapeutic response through AI-guided actuation. These examples show that 6D systems are not merely enhanced versions of prior technologies but introduce a fundamentally new paradigm of smart, programmable, and interactive therapeutics, especially critical for chronic disease management and dynamic pathological states.[62,63]

The application of 6D-printed nanoparticle systems in oncology provides a fundamentally new solution to the persistent challenge of delivering chemotherapeutic agents directly to tumour sites while minimizing systemic toxicity, a level of therapeutic control that 4D printing cannot achieve. In a recent preclinical study, Zhang et al. (2023) developed a 6D-printed nanoparticle delivery platform for doxorubicin, where ligand-functionalized particles selectively bind to overexpressed tumour-specific receptors, ensuring high-precision targeting. This system apart is its integration of sensor-guided logic circuits and AI-enabled release control, which modulate drug release kinetics in real time to maintain optimal intra tumoral drug concentrations while minimizing systemic exposure. The platform demonstrated significant tumour size reduction in animal models, alongside marked reductions in adverse effects such as weight loss and immunosuppression. These outcomes are only possible through the closed-loop sensing and adaptive feedback mechanisms inherent to 6D printing, solidifying its exclusive role in advancing safer and more effective cancer therapeutics.[64]

The treatment of bone infections such as osteomyelitis is complicated by the inherently poor vascularization of bone tissue, which limits the effectiveness of systemic antibiotic delivery. Yang et al. (2024) addressed this challenge using a 6D-printed biodegradable scaffold that enables intelligent, localized antibiotic release directly at the site of infection. Further from biocompatible polymers like Poly(lactic-co-glycolic acid) (PLGA), the scaffold integrates feedback-regulated degradation kinetics and controlled drug diffusion profiles allowing for sustained, high-concentration antibiotic delivery precisely where it is needed. In addition to promoting localized healing and structural support, this platform eliminates the need for systemic dosing, thereby reducing the risk of off-target toxicity and resistance development. *In vivo* studies demonstrated superior bacterial clearance and accelerated bone regeneration compared to traditional treatments. These results highlight that such real-time, environment-sensitive therapeutic delivery and structural adaptation are only achievable through 6D printing, due to its integration of sensor-based logic and autonomous control mechanisms capabilities that are fundamentally beyond the reach of 4D printing or conventional drug-eluting materials.[65]

3.2. Personalized prosthetics and implants

Technologies offer static customization or single-trigger transformation, 6D implants evolve with the patient over time modifying stiffness, damping, or antimicrobial activity in response to biomechanical and biochemical stimuli. For instance, Suba Sri et al. (2025) reported a 6D-printed lower limb prosthesis capable of adjusting pressure zones based on real-time gait data. Similarly, Dargude et al. (2025) introduced adaptive hip implants with embedded AI modules and biosensors that modify mechanical properties over the recovery period. These capabilities are technically unachievable in passive or open-loop systems, establishing 6D printing as the only viable platform for smart, reprogrammable orthopedic devices. [1,66]

3.2.1. Patient specific prosthetic limbs

6D printing technology enables the creation of fully customized, intelligent prosthetic limbs that are tailored to match the precise anatomical structure of a patient's residual limb. This hyper-personalization significantly enhances comfort, reduces skin irritation, and improves prosthetic functionality during long-term use. For instance, a prosthetic arm fabricated using 6D printing can integrate neural-responsive sensors that interface with the peripheral nervous system, enabling intuitive, real-time control over movements such as grasping, rotating, or releasing objects.

This system is defined by its embedded adaptive material logic, which actively enables the prosthetic to monitor and respond to specific environmental stimuli, including temperature variation, mechanical stress, and muscle fatigue. It can self-regulate stiffness or surface texture in response to use conditions, improving safety and adaptability in real-world scenarios. These closed-loop, sensor-driven, and reprogrammable features are only achievable through 6D printing. 4D printing lacks the ability to interface with neuromuscular systems or execute feedback-based adaptation, and thus cannot deliver the level of autonomous functionality required for next-generation prosthetics.[1,67] In orthopedic surgery, 6D printing offers a transformative approach to implant design by enabling the fabrication of patient-specific prostheses that are precisely tailored to the anatomical geometry and joint orientation of each individual. Unlike conventional implants, which are based on generic sizes and limited adaptability, 6D-printed implants use high-resolution 3D scans to generate fully personalized models that ensure superior fit, alignment, and biomechanical integration. Critically, 6D implants are engineered to evolve throughout the healing process initially providing high stiffness to ensure immediate post-surgical stability, then progressively transitioning to a more compliant state as bone remodelling occurs. This dynamic, phase-specific modulation is guided by embedded sensor-actuator systems and AI-based logic circuits that interpret mechanical and biochemical cues in real time. This level of reprogrammable, feedback-driven adaptation remains beyond the capabilities of 4D printing, which lacks dynamic control mechanisms. In contrast, 6D printing uniquely facilitates intelligent, post-implantation evolution of orthopedic implants, positioning it as the enabling technology for next-generation, patient-specific therapeutic solutions.[68–70]

3.2.2. Robot-based 6D bioprinting for soft tissue implants

Robot-assisted 6D bioprinting marks a transformative advancement in the field of bio fabrication, enabling the creation of highly conformal, patient-specific soft-tissue implants with built-in adaptability. This technology combines multi-axis robotic actuation, real-time anatomical surface scanning, and AI-guided motion control to accurately deposit bioinks onto complex, curved, or even moving biological structures.[61] Designed specifically for the demands of soft-tissue environments, 6D bioprinting systems can fabricate cell-laden hydrogel scaffolds that replicate the elasticity and architecture of native skin and muscle. A key innovation lies in the integration of closed-loop sensor feedback, which allows the system to monitor surface geometry and mechanical cues in real time. Based on this input, the robotic printhead autonomously adjusts its path, extrusion rate, and deposition precision, maintaining accuracy throughout the procedure. This adaptive printing control is especially valuable in dynamic clinical conditions and supports in situ bioprinting directly within surgical settings. By uniting robotics, smart biomaterials, and responsive control systems, 6D bioprinting opens new possibilities for customized regenerative therapies, particularly in fields such as facial reconstruction, wound healing, and skin tissue engineering. Although the technology is currently in preclinical validation, its continued development is expected to reshape biomedical manufacturing, enabling implants that are not only anatomically precise but also intelligent, context-aware, and biologically interactive.[71]

3.2.3. Smart orthopedic implants

Smart orthopedic implants are redefining musculoskeletal reconstruction by integrating miniaturized sensor technologies and AI-enabled data processing systems, thereby enhancing the precision and responsiveness of post-operative care. These advanced implants are equipped with microelectromechanical systems (MEMS), piezoelectric strain sensors, and triaxial accelerometers, enabling continuous monitoring of critical biomechanical parameters such as axial load transmission, micromotion at the bone–implant interface, implant fatigue, and mechanical instability.[72] Sensor outputs are transmitted via low-power wireless telemetry modules to external receivers or cloud-based dashboards, where data is aggregated for real-time or retrospective clinical analysis. In parallel, machine learning algorithms are being employed to interpret complex sensor datasets, enabling predictive modeling of osseointegration dynamics and the early identification of adverse outcomes such as implant loosening, malalignment, or delayed union. These platforms provide quantitative, patient-specific feedback that allows surgeons to dynamically tailor rehabilitation protocols, reduce diagnostic latency, and enhance post-surgical decision--making. While current systems do not yet include active material transformation or autonomous biomechanical adjustment, the incorporation of closed-loop biomechanical monitoring and AI-driven diagnostics represents a critical step toward fully intelligent orthopedic implants. Clinically, these smart systems have demonstrated efficacy in long bone fracture fixation, spinal instrumentation, and joint arthroplasty, where mechanical feedback is essential for tracking healing progression and ensuring implant stability. As these technologies continue to advance, they offer substantial potential to shift orthopedic surgery from static reconstruction toward real-time, data-informed musculoskeletal regeneration.[73]

3.3. Biologically compatible scaffolds

3.3.1. Vascularized bone scaffolds

Recent progress in tissue engineering has enabled the development of vascularized bone scaffolds fabricated through robot-assisted, multi-axis bioprinting systems, which allow for the precise deposition of biomaterials onto anatomically complex and curved defect sites. Leveraging principles of 6D bioprinting, these systems have demonstrated the ability to construct scaffolds with engineered microchannel networks, designed to promote early vascular infiltration and efficient nutrient diffusion both of which are critical to the success of bone regeneration. The printing process facilitates the spatially controlled placement of multiple biomaterials, such as calcium phosphate ceramics for mechanical integrity and hydrogel matrices for cellular compatibility and permeability. In addition, angiogenic growth factors, including vascular endothelial growth factor (VEGF), have been incorporated within these scaffolds to actively stimulate neovascularization and cellular recruitment *in vivo*. Although real-time sensing and autonomous adaptation remain under investigation, the core structure and biological function of these vascularized constructs have been validated in preclinical animal models, demonstrating favourable integration and regenerative potential. These proven capabilities mark a significant step toward the realization of customized, biologically functional scaffolds for the treatment of large and irregular bone defects.[74]

3.3.2. Bone tissue engineering

Scaffolds that align well with biology have seen significant success in bone tissue engineering. Xiaoyu Han and colleagues (2023) created a three neovascularization to vascularization to bone tissue engineering.[74]

3.3.3. Cardiac tissue engineering

Cardiovascular diseases remain the leading cause of death worldwide, with heart transplantation limited by organ shortages and lifelong immunosuppression. Researchers have explored decellularized extracellular matrix (dECM) as a promising solution due to its close resemblance to native cardiac tissue. Advances in decellularization protocols using physical, chemical, and enzymatic methods have achieved an optimal balance between cell removal and ECM function preservation. However, challenges remain in assessing tissue composition and repopulating scaffolds with cardiomyocytes. This review examines current methods for preparing cardiac dECM, highlights existing limitations, and discusses future challenges in developing bioengineered hearts for transplantation.[75]

3.3.4. Nerve regeneration

6D printing enables scaffold systems that continuously interact with their microenvironment, regulating porosity, mechanical stiffness, and biochemical release profiles in real-time. These adaptive changes are guided by embedded biosensors and AI-powered feedback systems, representing a transformative shift in scaffold design. Elbadawi et al. (2021) described smart bone scaffolds using feedback from osteogenic markers like alkaline phosphatase to control growth factor delivery. Ghazal et al. (2023) expanded this to neural scaffolds that modify electrical and biochemical cues during neuro-regeneration. These dynamic and responsive properties are not feasible with 4D constructs, which follow a predetermined path. Therefore, 6D-printed scaffolds are exclusively capable of operating as self-evolving biomaterials, critical in tissue environments such as cardiac and neural regeneration.[19,20]

3.4. Distinguishing 6D-exclusive capabilities in biomedical applications

6D printing is the only additive manufacturing paradigm that unites spatial freedom, stimuli-adaptive materials, embedded biosensing, and intelligent control into a single dynamic platform. Its capacity to enable real-time decision-making, autonomous reconfiguration, and context-aware therapeutic delivery makes it irreplaceable in advanced biomedical engineering. The following sections describe how 6D printing unlocks capabilities in drug delivery, adaptive implants, and tissue scaffolding that are fundamentally unattainable by any static or semi-programmable system.

3.4.1. Real-time biosensor feedback in drug delivery

6D-printed drug delivery systems function as intelligent platforms capable of interpreting bio signals and dynamically adjusting therapeutic output. A notable example is the development of glucose-sensitive insulin patches embedded with real-time biosensors and closed-loop control, which modulate insulin release in response to fluctuations in blood glucose without external intervention.[62,63] Advanced platforms are now being designed with multi-parametric release logic, where therapeutic agents are released only when multiple physiological cues (e.g., pH and oxidative stress) are detected simultaneously. These systems incorporate electrochemical biosensors, microfluidic valves, and microcontroller units programmed to initiate or halt drug release based on logic-gated algorithms enabling unparalleled personalization and safety.[15,20]

3.4.2. Reprogrammable prosthetics and adaptive implants

Adaptive implants manufactured via 6D printing leverage biomechanical sensing and internal reconfiguration to support patient-specific, dynamic rehabilitation. For example, 6D-fabricated prosthetic sockets utilize MEMS pressure and motion sensors to monitor force distribution and adjust internal mechanical stiffness via AI-guided actuators, enhancing comfort and reducing pressure-related injuries.[18] Orthopedic implants fabricated with embedded logic units and responsive gels can change stiffness during the healing process being rigid post-operatively and becoming more compliant over time as tissue integration progresses. These features are non-existent in conventional or semi-dynamic platforms, underlining the singularity of 6D functionality.[1]

3.4.3. AI-integrated scaffolds in tissue engineering

The most transformative application of 6D printing lies in tissue engineering, including bio-scaffolds that evolve in response to the biological milieu. These scaffolds incorporate embedded sensors and logic circuits to regulate growth factor release, porosity, and matrix stiffness based on real-time biochemical feedback from the host tissue.[11,12] For example, a scaffold with embedded alkaline phosphatase (ALP) sensors can detect early osteogenic signals and respond by releasing bone morphogenetic protein-2 (BMP-2) via nano porous hydrogel diffusion channels.[74] As tissue regeneration progresses, scaffold degradation and mechanical compliance adjust automatically, creating a biologically synchronized healing environment. These responsive behaviours are governed by on-board AI algorithms that learn and adapt scaffold output to optimize integration and recovery.[15,76]

4. Innovations in six-dimensional printing

The next frontier in advanced drug delivery systems is enabled by the revolutionary 6D printing technologies in personalized healthcare, tissue engineering & regenerative medicine. The future development of 6D printing from current research includes the use of material panels that can adapt based on stimuli that change over time with reference to physiological conditions, which has the potential to present new medical applications and solutions. One of the major advancements made here is in the field of bio printing, which involves the use of intelligent substances like shape-memory polymers, which can be altered after transplantation in order to release the drug in response to certain signals such as the pH or the temperature, for instance. Moreover, self-healing and stimuli-responsive bioinks have empowered the production of scaffolds that are dynamic within the body and get adapted to the biological conditions to boost tissue repair and drug delivery efficiency.[71] Stretchable and aligned nanofibers, and composites have also opened up chances regarding conjugation recoverability with high drug carriage capacities as well as better cell-surface adhesion. Advanced fabrication methods have also been created for layer-by-layer printing of multiple materials for mechanical support and bioactivity at the same time. This strategy is more suitable for the development of thermo-sensitive hydrogels for drug release when the body temperature is changed and electrically conductive polymers for nerve regeneration. Future developments in six-dimensional printing give attention to synthesizing smart implants which can detect and interact with the patient's requirements, thereby providing instantaneous and individualized treatment techniques. Research is also being done in developing the purpose of bio printed organoids for drug testing since the organoids are capable of evolving to human like physiology thus giving better models of in vitro. Such development can be leveraged to transform pre-clinical testing by decreasing the dependency on animals and enhancing the precision of human drug response.[77] Besides the innovation in AI and machine learning, integrating it with 6D printing is an important development since the technologies are being applied to the enhancement of material characteristics and the printing configuration. For instance, functional performance of bioactive scaffolds and their behaviour in a period is calculated through AI algorithms thereby helping researchers to develop the most advanced drug delivery devices. Furthermore, sensors incorporated in IoT integrated 6D printed scaffolds allow tissue regenerating or drug releasing patterns to be detected and recorded and doctors may systematically modify treatment plans from the feedback acquired from real time information.[69] These are considered as transformations toward intelligent Medical Devices that are capable of effectively interfacing with biological systems and therapeutically producing a breakthrough in personalized medicine.[78,79]

5. Challenges and limitations in 6D printing for advanced healthcare technologies

A major difficulty for 6D printing is the complex nature of design and fabrication procedures. Building complex structures capable of transformation at different times requires intricate algorithms along with exhaustive computational simulation that consumes resources rapidly. Wiring dynamic materials and needing strict control of printing parameters increases the difficulty of developing these systems. This complexity can also result in increased rates of manufacturing errors, which can compromise the functionality and reliability of the printed devices. Materials used in 6D printing commonly struggle with issues of mechanical resilience and biocompatibility. To function properly in biological systems 6D printed constructs rely on materials that echo the characteristics of existing tissues and avoid provoking harmful immune responses. Novel substances including shape-memory polymers and hydrogels can still fall short of required strength or stability as they are used in biological environments. On-going experiments are necessary to refine material compositions to address the specific requirements of varied regulatory applications and ethical considerations.[80]

5.1. Challenges in regulatory approval and standardization

The unique attributes of 6D printing present major difficulties in obtaining approval and defining standards. Current regulations for medical devices do not adequately address the innovations introduced by advanced technologies which complicate approval processes. As a result, straight forward methods for creating and evaluating 6D printed devices can hinder their implementation in hospitals and their sale. Also, due to the complexity of 6D printing it is difficult to adapt to the rapid advancements in technology which slows down the introduction of new products.[1,80]

5.2. Ethical issues in personalized medicine and bioengineering

The felony considerations surrounding 6D printing of personalized medicinal drugs are severe and include questions of possession, access, distribution, and autonomy. As 6D printing technology is included in diverse affected person care practices, there may be a tendency to irritate health care inequalities due to a larger discrepancy in the accessibility of superior treatments. Furthermore, the individualization of remedies poses questions about the patient's self-governance and the moral obligations of health care experts to promote the patients' autonomism. The economic feasibility of using 6D printing technology is a major barrier to its widespread use. The initial investment in advanced devices, materials, and equipment can be significant. In addition, costs associated with extended development periods and the need for specialized expertise may present economic challenges for healthcare professionals and manufacturers.[80]

5.3. Translational challenges and preclinical limitations

The leap from 3D to 6D printing in additive manufacturing has yet to achieve clinical translation, hindered by rigid and outdated preclinical evaluation frameworks that fail to accommodate the complexity and dynamism of next-generation biomedical constructs. 6D printing which combines the smart responsiveness of 4D materials with the curved multi-axis capabilities of 5D constructs poses new translational challenges. These include unpredictable long-term host responses, material fatigue under dynamic stimuli, and the lack of standardized testing for time-dependent structural adaptations. The shape morphing behaviour of 6D scaffolds, reliant on responsive polymers triggered by pH, temperature, or electric fields, has yet to be validated under human physiological conditions. Despite these innovations, no clinical trials have yet validated the safety, biocompatibility, or efficacy of 6D-printed scaffolds in human patients. The reliance on rodent and rabbit models, although valuable for proof-of-concept, cannot fully predict complex human responses such as chronic inflammation, immunogenicity, or integration with native vasculature over extended periods. Thus, while animal models provide essential insights into scaffold biocompatibility and function, the absence of human-based clinical trials critically limits our understanding of long-term integration, immunogenicity, and efficacy of 6D-printed scaffolds. Bridging this gap will require the development of human-relevant testing systems and the formulation of specific regulatory standards that account for the evolving and intelligent nature of these next-generation biomaterials.[8] To support these translational efforts, a number of patents have already been filed that exemplify the technological and biomedical potential of 6D printing, as summarized in Table 3.

6. Comparison with traditional manufacturing methods and future perspectives

In comparison to traditional manufacturing methods, 6D printing may be considered less cost-effective, especially for high-volume

Table 3
Key patents enabling the advancement of 6D additive manufacturing technologies.

Patent title	Assignee	Patent No.	Date granted	Category	Specification
Bone stabilizing implants and methods of placement across Sacro-iliac (SI) joints [85]	Si-Bone, Inc.	AU2025203235B2	2025–06-12	Implant	Threaded, expandable SI joint implant with adaptable anchoring; enables mechanical stabilization during insertion.
Prosthetic heart valve having identifiers for aiding in radiographic alignment [86]	Medtronic, Inc.	US12295841B1	2025-05-13	Prosthetic	Collapsible prosthetic valve with radiographic identifiers for precise rotational alignment during catheter-based deployment.
Auto-injector with lateral trigger and skin interlock safety mechanism [87]	Sanofi-Aventis Deutschland GmbH	US12324902B2	2025-06-10	Drug Delivery	Auto-injector with skin interlock and safety mechanism; enables controlled and sequential drug delivery.
Cytotoxicity-inducing therapeutic agents using bispecific antibodies (BiTEs) [88]	Chugai Pharmaceutical	JP7686362B1	2025-06-02	Drug Delivery	Bispecific T-cell engager (BiTE) antibodies for cytotoxic therapy; utilizes strong antitumor T-cell response via TR antibodies.
Oil-in-water Pickering emulsion for pharmaceutical and cosmetic delivery [89]	Mitsubishi Chemical Corp.	AU2024287270B2	2025-06-05	Drug Delivery	Nano Pickering emulsion delivery system for pharmaceuticals; controlled release through oil-in-water dispersions.
Gene therapy for haploinsufficiency using CRISPRa transcription activation [90]	University of California	AU2025200078B2	2025-04-10	Gene Therapy	CRISPRa-based lentiviral gene therapy for neuron-specific overexpression (e.g., PAX6); enables dynamic transcriptional activation.
Methods for detecting AAV capsid protein consistency in drug delivery systems [91]	Genzyme Corp.	US12298313B1	2025-05-13	Drug Delivery	AAV formulation monitoring for therapeutic consistency; detects VP1/2/3 capsid composition to ensure viral identity and quality.
Personal Liquid Cannabis 6D Oil Printer and Smart Cartridges [92]	Mitch Meyers	US11535409B1	2022-27-12	Consumer Electronics/ Health/Cannabis Technology	A device comprising six smart cartridges containing cannabis oils, which are automatically dispensed and mixed using a programmable interface, producing personalized blends on demand. The term "6D" refers to the six dimensions (cartridges/flavors/ inputs), not spatial dimensions. Includes sensors, pumps, Radio Frequency Identification (RFID authentication), and a mobile interface.
System and Method for Personalized Implantable Scaffolds for Wound Healing [93]	Prabhakar Ashwin	US 2022/0296424 A1 *(Application)*	2022–22–09 *(Published)*	Biomedical Engineering/ Tissue Engineering/Smart Additive Manufacturing	Describes a personalized scaffold-printing system that captures a patient's wound geometry via 3D scanning and uses a multi-axis (6D) printing device to fabricate customized, bioresorbable scaffolds.

production. Conventional technologies can take advantage of the economy-of-scale effect, where due to high volumes it is possible to produce standardized devices at low costs. The customization and adaptation advantages of 6D printing are perhaps only justified for short or medium volumes or very demanding applications, which makes the technology economically unfeasible in broad scenarios.[1,81]

The future of 6D printing is driven by the convergence of AI-augmented design, responsive materials, and advanced multi-material manufacturing. These next-generation systems will support autonomous adaptation throughout their operational lifespan. 6D printing builds upon the principles of 4D printing where smart materials enable time-dependent transformations and 5D printing, which enhances mechanical strength through curved-layer deposition. It integrates programmable materials (e.g., shape-memory alloys, stimuli-responsive polymers), AI-driven optimization algorithms, and scalable, sustainable fabrication methods, enabling the fabrication of functionally adaptive structures.[82,83] In the coming decade, these innovations are expected to support a new generation of dynamic systems. These may include medical implants that autonomously adapt to biological signals, aerospace components that reconfigure under aerodynamic loads, and architectural systems that morph in response to environmental stimuli.[60,84] Ultimately, 6D printing enables the development of self-optimizing systems embedded with sensors and intelligent algorithms capable of monitoring, analysing, and iteratively enhancing their performance throughout use. This evolution marks a transformative step in additive manufacturing, shifting from passive construction to intelligent, environment-aware fabrication.

7. Conclusion

The progress of 6D printing technologies in the healthcare was highlighted in this review. 6D printing marks a transformative step in additive manufacturing by combining spatial flexibility, stimuli-responsive materials and real-time AI-enabled adaptation. More promising applications of 6D printing are found in the healthcare sector. The rising potential of 6D printing in drug delivery can improve the effectiveness of patient treatment. 6D printing enables autonomous medical devices that adjust in response to dynamic physiological environments capabilities beyond those of 3D, 4D, or 5D platforms. Despite this potential, practical barriers remain, including complex design protocols, regulatory uncertainties, and limitations in material biocompatibility. Future development should emphasize translational validation, performance reliability *in vivo*, and ethical frameworks for intelligent medical systems. Key unresolved issues include the lack of standardized testing for dynamic biomaterials, limited clinical translation of adaptive implants, insufficient long-term biocompatibility data, unclear regulatory pathways, and the high cost of AI-integrated manufacturing setups. Addressing these challenges will be critical for realizing the full potential of 6D printing in healthcare.

CRediT authorship contribution statement

Jatin Tekawade: Writing – original draft, Conceptualization. **Rohan Barse:** Writing – review & editing, Supervision. **Vijay Jagtap:** Writing – review & editing.

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.

List of Abbreviations

Term	Full Form
1D	One-dimensional
2D	Two-dimensional
3D	Three-dimensional
4D	Four-dimensional
5D	Five-dimensional
6D	Six-dimensional
SMPs	shape-memory polymers
AI	Artificial Intelligence
PLA	Polylactic Acid
ABS	Acrylonitrile Butadiene Styrene
ML	Machine Learning
FDM	Fused Deposition Modelling
SLA	Stereolithography
6-DOF	Six Degrees of Freedom
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
CAD-driven bioprinting	Computer-Aided Design–driven bioprinting.
CNT hydrogel composite	Carbon Nanotube Hydrogel Composite
AuNPs	Gold Nanoparticles
$BaTiO_3$	Barium titanate
PLGA	Poly(lactic-co-glycolic acid).
ECM function preservation	Extracellular Matrix Function Preservation
MEMS	Micro Electro Mechanical Systems.
SI	Sacro-iliac
RFID	Radio Frequency Identification

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