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Application and potential of 4D printing in medicine

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Abstract: 4D printing represents a groundbreaking technology that extends the possibilities of 3D printing by adding a dynamic dimension—time. By using smart materials capable of changing their shape or properties in response to external stimuli such as temperature, humidity, or pH, new horizons are opening, especially in the field of medicine. This article presents the basic principles of 4D printing, explains the nature of functional materials and mechanisms that enable programmable behaviour, and focuses on specific applications in the medical context. The most promising areas include implants that can adapt to anatomical changes, targeted drug delivery systems, bioprinting of tissues and organs, and novel types of rehabilitation devices. The article also discusses the benefits of this technology, such as reduced invasiveness of medical procedures, improved functionality of medical devices, and enhanced treatment personalization. At the same time, it reflects on the challenges associated with 4D printing development—from material selection and technical or regulatory limitations to the need for interdisciplinary collaboration. The goal of this paper is to present the current state of knowledge in this field, identify its potential and limitations, and support further research and clinical validation of 4D technologies in medicine.

1 Introduction

In recent decades, 3D printing has undergone rapid development, significantly influencing various industrial sectors. Whether in aerospace, mechanical engineering, robotics, biomedicine, or healthcare, 3D printing has established a prominent position across all these fields. Linked with CAD and CAM platforms, this technology facilitates the development of sophisticated geometries and components that are beyond the practical limits of conventional fabrication techniques. By gradually depositing material layer by layer, highly detailed and customized components can be fabricated.

In medicine and biomedicine, 3D printing has brought about groundbreaking innovations, particularly in the areas of implants, targeted drug delivery systems, tissue engineering, and regenerative medicine.

Technological progress has naturally paved the way for further innovation. As a result, 3D printing has become the foundation for a new concept—4D printing. This approach involves the production of structures capable of changing their shape or properties in response to external stimuli such as variations in pH, temperature, pressure, or humidity. While building upon the principles of 3D printing, 4D printing expands additive manufacturing into a dynamic dimension.

By incorporating time as the fourth dimension, 4D printing enables materials and structures to adapt their geometry, mechanical properties, or functions dynamically [1]. This transformation is made possible through the use of smart materials specifically designed and "programmed" to respond to environmental conditions.

2 Principle of 4D printing

4D printing extends traditional 3D printing by introducing the ability to program time-dependent transformations of objects in response to external stimuli. From a technological perspective, 4D printing requires precise control over geometry, fiber orientation, and internal stress distribution to achieve the desired shape or function upon activation. For instance, a polymer implant

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with shape memory properties can unfold into its target configuration at body temperature without requiring mechanical expansion [2].

2.1 Key factors and principles affecting 4D printing

The successful implementation of 4D printing relies on five key components:

1. Additive Manufacturing (AM) process – enables the direct production of structures from digital models without intermediate tooling. Technologies used include SLA (stereolithography), SLS (selective laser sintering), FDM (fused deposition modeling), 3DP (three-dimensional printing), SLM (selective laser melting), DIW (direct ink writing), and EBM (electron beam melting).
2. Material selection – materials must be compatible with the AM process and capable of responding to external stimuli. These so-called smart or programmable materials determine the type and nature of the transformation.
3. External stimuli – can be physical (temperature, humidity, light, magnetic fields), chemical (pH, redox agents), or biological (enzymes, glucose), and initiate structural changes.
4. Interaction mechanism between the material and the stimulus – ensures proper stimulus transmission and sequence of transformation.
5. System behaviour modelling – allows for prediction of timing and transformation dynamics, often using numerical simulations [1].

The integration of these components enables the creation of 4D-printed structures that actively change over time in response to specific stimuli.

F. Momeni and J. Ni defined three fundamental laws that describe shape transformation mechanisms in multi-material 4D-printed structures [3]:

First law: Shape transformation (e.g., bending, twisting, coiling) occurs due to differential strain between active and passive materials.

Second law: Four fundamental phenomena account for the observed strain: mass diffusion, thermal expansion, molecular transformations, and organic growth. These are activated by external factors including temperature, light, pH variation, or mechanical loading.

Third law: Transformations exhibit time-dependent behavior governed by two time constants, which vary with the material and stimulus type. A biexponential mathematical model has been proposed to simulate these transformations during the design of 4D structures [3].

2.2 Overview of 3D printing techniques suitable for 4D printing

Various 3D printing technologies can be employed for 4D printing, differing in their working principles, material compatibility, and resolution. The following overview presents the most relevant techniques suitable for 4D applications, along with their characteristics and example uses.

Fused Deposition Modeling - FDM

FDM is a widely used technique in which thermoplastic material is extruded through a nozzle and deposited layer by layer along the X, Y, and Z axes to form a 3D (or 4D) object. It is popular due to its low cost, simplicity, and flexibility for developing new materials.

Tian et al. [4] developed an FDM approach for carbon fiber-reinforced composites (CFRTC), enabling the fabrication of mechanically robust structures. Bodaghi et al. [83] demonstrated the use of FDM for shape memory materials (SMEs). Current research focuses on improving FDM's efficiency with novel smart materials.

Stereolithography - SLA

SLA uses photopolymers that solidify upon exposure to light (typically UV or visible). The light initiates a chemical reaction leading to resin cross-linking and the formation of solid structures.

This method allows for the precise fabrication of complex geometries, and research is ongoing to expand the range of compatible materials.

Notably, the first demonstration of 4D printing was achieved using SLS technology with UV light on a Stratasys Connex printer [5].

Selective Laser Sintering - SLS

SLS employs a laser to selectively fuse powdered material in successive layers. This technique accommodates a broad spectrum of substances, such as waxes, metals, ceramics, and polymers including PU, PCL, PEEK, and polyamide [6-8].

Selective Laser Melting - SLM

SLM is similar to SLS, but the powder is completely melted, resulting in a homogeneous structure with no post-sintering required. The laser beam's speed and intensity can be tailored to the material, making SLM particularly suitable for metal printing [9].

Directed Energy Deposition - DED

DED is designed for metal part fabrication. Material in the form of powder or wire is melted at the point of deposition using a thermal source, typically a laser or electron beam. It is also applicable for printing shape memory structures [10-12].

InkJet printing

Inkjet printing uses tiny droplets of material deposited layer by layer. It is employed in the fabrication of low-cost electronics and wearable devices (e.g., sensors, displays) on polymer substrates such as PET and PEN [13,14], as well as in bioprinting of cells and tissues [15].

Direct Ink Writing - DIW

DIW is similar to FDM but supports a wider range of materials, including thermoplastics, hydrogels, and sol-gel inks. It is particularly suitable for soft and bioactive systems.

Projection Micro-Stereolithography - PμSL

PμSL and DIW are advanced techniques used primarily in biomedical 4D printing applications, offering high precision and compatibility with sensitive materials at micrometer resolution.

2.3 Materials

From a materials perspective, 4D printing utilizes stimuli-responsive polymers (e.g., SMPs), hydrogels, or shape memory alloys (e.g., nitinol), whereas 3D printing primarily relies on thermoplastics, photopolymers, metals, or ceramics. Material selection is crucial to ensure the desired functionality of the object during activation [16].

The materials used in 4D printing are known as smart materials due to their ability to dynamically change their properties over time in response to external stimuli [17]. These materials exhibit complex functions such as self-assembly, self-healing, shape memory, or self-regulation [18]. In addition to morphological changes, 4D printing also enables changes in optical properties, such as colour, when exposed to UV or visible light.

2.3.1 Classification of smart materials used in 4D printing

The materials used in 4D printing are referred to as smart because they are capable of dynamically altering their properties in response to external stimuli. These materials are also called stimuli-responsive and can react to triggers such as temperature, light, electric or magnetic fields, humidity, pH, chemical substances, or biological factors. The result of such a reaction may include changes in shape, volume, colour, stiffness, or other mechanical properties.

The following figure (Figure 1) schematically illustrates the classification of smart materials according to the type of external stimulus and the material’s response. This overview provides a better understanding of what materials may be suitable for 4D printing depending on the desired functionality.

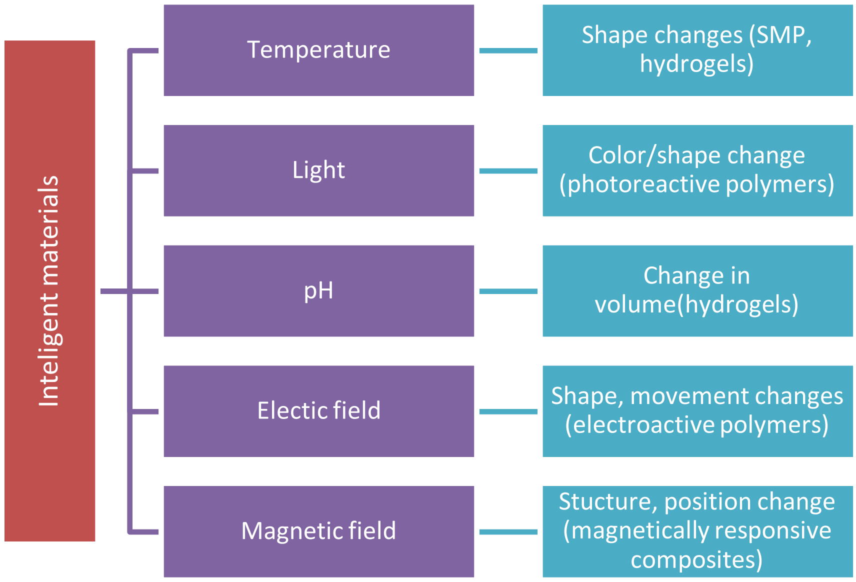

Figure 1 Intelligent materials and their stimuli reactions

From the perspective of responsiveness, smart materials used in 4D printing are most commonly divided into two main categories:

1. Shape-memory materials - SMM

These materials have the ability to "remember" their original shape and return to it after being exposed to a specific stimulus (e.g., heat or light). They enable the creation of temporarily deformed structures that later reconstruct into the desired form. They are used, for example, in the development of biodegradable scaffolds or implants that adapt to the target anatomical site after implantation.

2. Shape-changing materials

These materials change their shape or physical properties during the presence of a stimulus, but do not return to their original state once the stimulus is removed. Typical representatives include hydrogels, electroactive polymers, or magnetically responsive composites. They are primarily applied in controlled drug delivery systems, soft robotics, or the design of adaptive tissue structures.

Table below (Table 1) provides a classification of smart materials commonly used in 4D printing, based on the type of external stimulus they respond to, their response behaviour, and typical applications. The materials are divided into categories such as shape-memory, shape-changing, hybrid, and adaptive materials, each exhibiting unique functionalities that enable dynamic changes in shape, mechanical properties, or biological activity.

Shape-memory materials (e.g., SMPs and nitinol) can recover their original shape upon exposure to specific stimuli like heat or light, making them suitable for medical implants, scaffolds, and minimally invasive surgical tools.

Shape-changing materials respond by altering shape or properties temporarily during stimulation but do not revert back automatically, which is useful in drug delivery systems, soft robotics, and actuators.

Hybrid materials combine different responsive behaviors, such as changes in stiffness or volume, offering advanced applications like photothermal therapy or environmental control.

Adaptive materials such as bioinks respond to biochemical signals to facilitate tissue formation, playing a vital role in regenerative medicine and bioprinting.

This classification highlights the versatility of smart materials and their potential to revolutionize personalized medicine, biomedical devices, and responsive structures through 4D printing technology.

Table 1 Classification of smart materials used in 4D printing based on their stimulus type, response behavior, category, and typical applications

Material Type	Stimulus	Response Type	Category	Typical Application
SMP (Shape-memory polymer)	Heat, light	Return to original shape	Shape-memory	Scaffolds, stents, surgical implants
Nitinol (alloy)	Heat	Shape recovery	Shape-memory (metal)	Orthopedics, minimally invasive tools
Hydrogel	pH, temperature	Swelling, shrinking	Shape-changing	Tissue engineering, drug delivery
Electroactive polymer	Electric field	Contraction, bending	Shape-changing	Actuators, biosensors
Magnetic composite	Magnetic field	Bending, deformation	Shape-changing	Soft robotic structures, targeted therapy
Thermoresponsive polymer	Temperature	Change in stiffness, volume	Hybrid	Photothermal therapy, environmental regulation
Bioink	Biochemical cues, growth factors	Formation of functional tissue	Adaptive	Regenerative medicine, 3D bioprinting

The development of smart materials that react to external stimuli constitutes a crucial element of 4D printing within biomedical engineering. Such materials allow for the fabrication of dynamic constructs capable of altering their geometry or properties in response to environmental conditions. Their application in 4D printing paves the way for innovative healthcare approaches, particularly in the field of personalized and adaptive therapies.

2.3.2 Typology of used materials

Materials used in 4D printing can be divided into four basic groups:

- **Biological materials** (derived from plants or traditional medicines) – offering natural biocompatibility and biodegradability.
- **Bio-based materials** (e.g., natural polymers, hydrogels) – mimicking the extracellular matrix and supporting tissue regeneration.
- **Synthetic materials** (e.g., thermoplastics, shape-memory polymers – SMP) – providing high mechanical strength and precise property control.
- **Hybrid materials** – combining advantages of natural and synthetic components, such as bioactivity and mechanical strength.

The choice of material depends on the specific application requirements, such as biocompatibility, degradation profile, mechanical demands, or target tissue. Research continues to develop new or optimized materials that expand the possibilities of 4D printing in biomedicine.

Shape-memory Polymers - SMP

Shape-memory polymers represent one of the most widely applied smart materials in 4D printing. They are capable of reverting from a deformed configuration back to their original form when exposed to specific stimuli, such as heat or light [19]. This feature allows for the fabrication of constructs that can adapt automatically to patient anatomy after implantation. For instance, an SMP-based scaffold may reconfigure at body temperature to accurately fit the tracheal structure, thereby improving surgical outcomes [20].

Hydrogels

Hydrogels are another important type of smart materials used in 4D printing. They are polymer networks that respond to changes in temperature or pH by swelling or shrinking [21,22]. They are primarily used in tissue engineering and controlled drug delivery systems. For instance, a hydrogel system can release drugs in a controlled manner at a specific temperature, improving treatment accuracy [23].

Thermoresponsive polymers

These polymers change their physical properties (shape, stiffness, volume) depending on temperature. Wang et al. [24] developed a system based on dual thermoresponsive polymers with different phase transition temperatures, allowing precise control of thermal response. Using 4D printing, it is possible to create structures with tunable properties that undergo changes when exposed to thermal stimuli such as laser irradiation. This technology shows great promise for enhancing the safety and efficacy of photothermal therapy.

Electroactive and magnetically responsive materials

Materials responsive to electric or magnetic fields, such as electroactive polymers and magnetically responsive composites, are promising for the development of advanced medical devices. They can change their shape or mechanical properties and are used in soft robotic prosthetics, dynamic implants, or targeted drug delivery systems [21,25]. For example, Zhao et al. [25] designed a tracheal scaffold that responds to a magnetic field by combining magnetic particles with shape-memory composites, enabling real-time controllable adaptability.

Bioinks

Bioinks – biocompatible materials often containing living cells – play a crucial role in biomedical engineering. Their use in 4D printing enables the creation of structures that develop over time into functional tissues. For example, a skeletal muscle model produced using electrically aligned bioink demonstrated potential in regenerative medicine [26].

2.3.3 Rheological properties of polymers

In polymer-based additive manufacturing, rheological properties significantly affect the quality and accuracy of 4D printing [27]. Parameters such as viscosity, shear-thinning behaviour, and thixotropy influence material flow, extrusion capability, and shape fidelity. Optimizing these properties is essential for successfully producing complex and delicate biomedical constructs.

3 Applications of 4D printing in medicine

In the context of medicine, 4D printing brings groundbreaking possibilities: implants that activate within the body, drug carriers with targeted release, or scaffolds that dynamically change during tissue healing. These features enhance therapeutic efficacy, shorten treatment duration, and minimize the number of surgical interventions [28].

3.1 Biomedical implants and prostheses

4D printing technology introduces significant innovations in implantology and prosthetics through structures capable of actively responding to conditions inside the patient's body. Unlike traditional implants, which are rigid and static, 4D printed implants can dynamically adapt. Their shape, stiffness, or mechanical properties change in response to stimuli such as temperature, pH, or pressure. This improves their ability to conform to the patient's anatomy and the dynamic environment within the organism [29,30].

An example of such an adaptive solution is the use of biodegradable shape-memory scaffolds for bone defect repair. This approach allows precise individual customization while ensuring gradual biological integration at the defect site, consistent with core principles of 4D printing like shape memory, biodegradation, and osteoinduction.

3.1.1 Self-forming and adaptive implants

One of the promising applications of 4D printing in implantology involves self-forming and adaptive implants that adjust to the target environment within the human body after implantation. Their development relies on smart materials such as shape-memory polymers (SMPs) and stimulus-responsive hydrogels, which alter their shape or mechanical properties in response to specific physiological triggers like temperature, humidity, or pH [31].

A typical example includes 4D printed stents designed to expand at body temperature (37°C) once placed inside a vessel, restoring blood flow in a narrowed section [28]. Some stents are made from biodegradable polymers and gradually degrade after fulfilling their function, eliminating the need for surgical removal. Others use shape-memory metal alloys like nitinol, which, although non-degradable, provide superelasticity for safe and reliable deployment (Figure 2).

In orthopedics, implants capable of altering stiffness based on mechanical load are being explored, allowing better adaptation to bone biomechanics. Such implants can significantly improve healing, reduce stress shielding, and promote integration with living tissue [32].

Clinically, these solutions hold potential to reduce surgical invasiveness, improve patient comfort, and enhance long-term implant functionality. Despite these benefits, challenges remain regarding precise control of biodegradation timing and long-term biocompatibility of materials such as nitinol, which may cause microinflammatory reactions if not adequately managed.

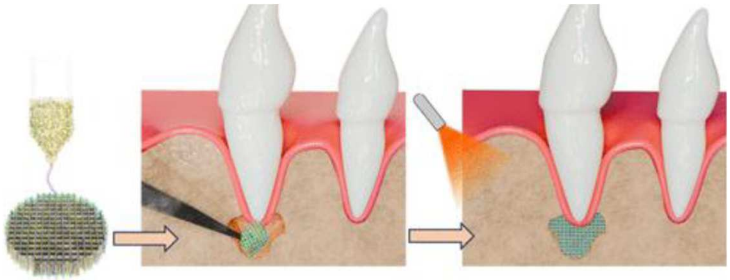

Figure 2 Self-expanding stent made of shape memory polymer (SMP) [33]

3.1.2 Regenerative medicine

Beyond orthopedic and vascular implants, 4D printing finds application in regenerative medicine by creating supportive scaffolds intended for tissue repair. Stimuli-responsive hydrogels play a crucial role; these materials can modify their architecture, porosity, or mechanical properties after implantation according to the healing process [34].

These so-called programmable scaffolds mimic the natural extracellular matrix and actively adapt throughout regeneration. During the initial inflammatory phase, they remain soft and permeable to nutrients, while later stiffening to stabilize newly formed tissue [35].

They are utilized in treatments of skin defects, burns, cartilage damage, and peripheral nerve injuries [36]. Some hydrogel structures are enriched with growth factors or patient-derived cells to enhance biological effectiveness. Multi-layered scaffolds combining different cell types or bioactive substances depending on injury depth are also under experimental investigation [1].

The primary advantage of 4D printing in regenerative medicine lies in scaffolds with temporally dynamic behavior—the structure evolves alongside regenerating tissue, providing optimal support at each healing phase. This functional adaptability sets them apart from passive 3D scaffolds, which remain static post-implantation. Given the rapid advances in biomaterials and bioprinting technologies, intelligent scaffolds are expected to play a key role in personalized regenerative medicine soon. While some hydrogel scaffolds for skin lesions have passed early clinical trials, most multi-layered and bioactivated constructs remain in preclinical stages.

3.2 *Tissue engineering and bioprinting*

4D printing technology significantly enhances the potential of tissue engineering by enabling the creation of biological structures with dynamic behavior. Using smart biomaterials, it is possible to fabricate scaffolds that actively respond to stimuli such as temperature, pH, or mechanical stress after implantation [1,35].

A key component of these dynamic systems is shear-thinning hydrogels—materials whose viscosity decreases under mechanical load, allowing easy extrusion during bioprinting. Once printed, they stabilize into well-defined structures. When combined with cells or bioactive molecules, they serve as bioinks that support cell growth and differentiation [37].

4D bioprinted scaffolds can adapt over time by adjusting porosity, elasticity, or releasing growth factors based on the regeneration stage. They are being tested in the treatment of cartilage, skin, peripheral nerve, and muscle tissue injuries [38].

Promising outcomes have also been achieved with bioprinted heart valves and artificial vessels that adjust elasticity or diameter in response to blood flow and pressure, improving long-term implant performance and reducing failure risks [39].

By combining biocompatibility, adaptability, and spatial precision, 4D bioprinting is a key tool in developing personalized, functional, and time-responsive tissue replacements.

3.2.1 4D printing of biological structures and organs

4D bioprinting represents a major advancement in producing functional biological structures that change their properties in response to physiological stimuli. These constructs are typically made from hydrogels combined with living cells and can respond to changes in temperature, pH, or mechanical stress (

Figure 3).

The goal goes beyond anatomical replication—4D bioprinted scaffolds are designed to mimic natural processes like remodeling, angiogenesis, and cell differentiation [39]. They support tissue regeneration and maintain mechanical stability during healing. Current research focuses on:

• heart valves that adjust elasticity based on blood flow,

• artificial vessels adapting their diameter to blood pressure,

• multilayered tissues (e.g., liver or pancreas) with diverse cell types and vascularization [1].

Although still in experimental and preclinical stages, results show strong clinical potential. Personalization based on patient-specific data reduces the risk of rejection. In the future, 4D bioprinting is expected to enable functional tissue and partial organ implants that dynamically adapt to the body's needs. Advances in vascularization and tissue integration point to realistic clinical applications in the coming decades.

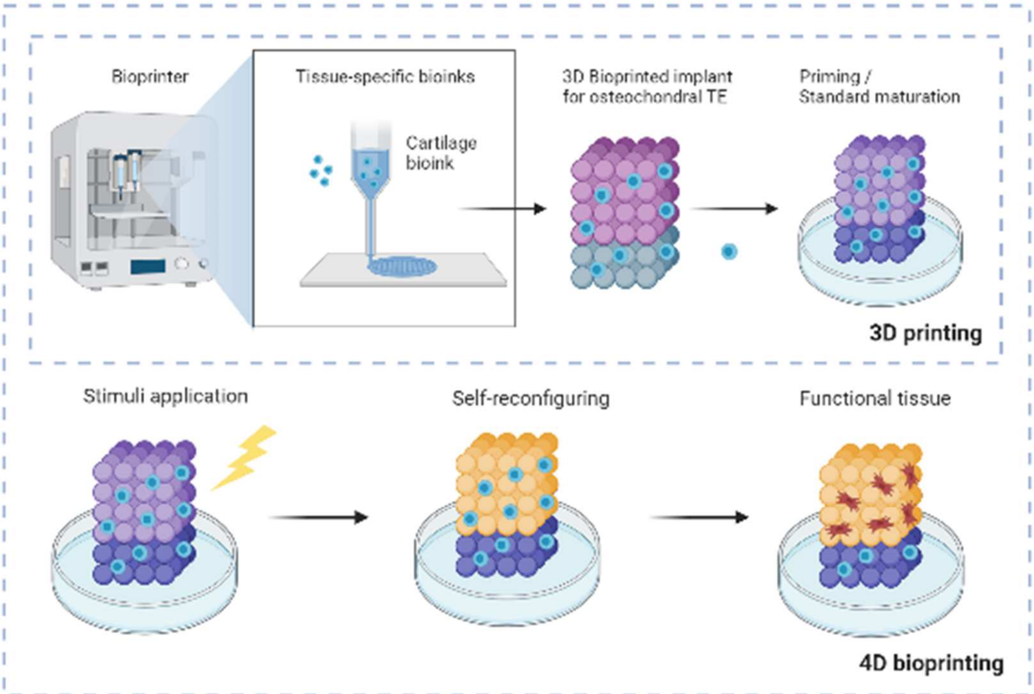

Figure 3 4D bioprinting process for osteochondral tissue engineering

3.2.2 Peripheral nerve regeneration

Peripheral nerve regeneration poses a major challenge, especially in large defects where traditional autografts or static conduits are insufficient. 4D printing enables the development of intelligent nerve guidance conduits (NGCs) that actively adapt to surrounding tissue after implantation—changing shape at body temperature or responding to humidity and pH, thereby improving contact with the nerve stump without manual adjustment [34,36].

These structures can incorporate conductive materials (e.g., MXenes, carbon nanotubes) to enable electrical stimulation of axons, enhancing regeneration [36]. A 2021 study demonstrated that a biodegradable, self-expanding 4D-printed conduit with enhanced conductivity improved both axonal regeneration and motor function in a preclinical model (Figure 4). While still in the experimental phase, this approach shows great promise for personalized, minimally invasive, and functionally active treatments for peripheral nerve injuries [40].

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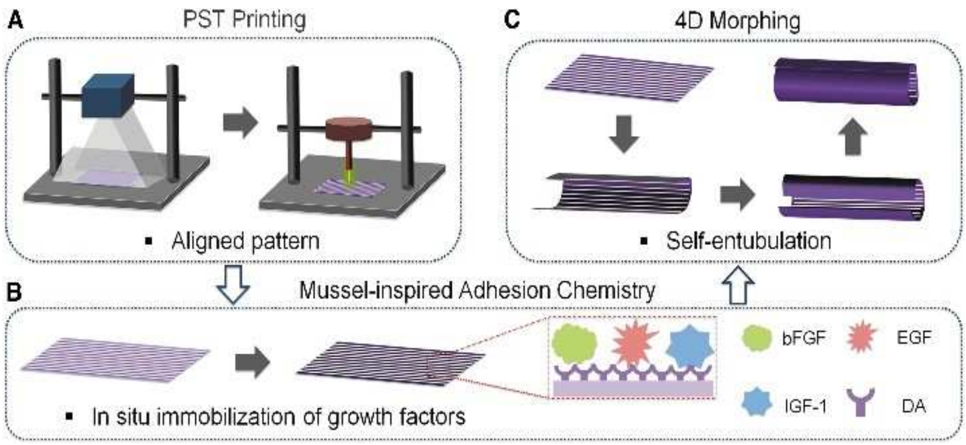

Figure 4 4D-printed nerve guidance conduit that self-closes after implantation, adapts to surrounding tissue, and supports peripheral nerve regeneration

3.3 Personalized medicine and pharmacy

Personalized medicine focuses on tailoring diagnostics and therapy to an individual's genetic, biological, and lifestyle characteristics. In this context, 4D printing is a crucial tool for designing smart drug carriers and medical devices that respond to specific in vivo conditions. Using 4D printing, drug delivery systems can be designed to release medications at precise times and locations, improving efficacy and reducing side effects. Smart implants or capsules can change shape or porosity based on local stimuli such as pH or enzymes, allowing targeted and controlled release [41].

3.3.1 Intelligent drug delivery systems

4D printing offers innovative opportunities in pharmaceutical applications by enabling smart drug delivery. Unlike traditional dosage forms that release drugs passively, 4D-printed systems can respond to specific physiological stimuli and release active substances in a targeted and adaptive manner.

Adaptive Drug Release Systems

A common example is pH-sensitive polymer capsules that remain intact in the acidic environment of the stomach but dissolve in the more alkaline intestines—ideal for treating intestinal inflammation or infections. Similarly, temperature-responsive hydrogels can change their volume or porosity depending on body temperature, regulating drug diffusion [38].

Multilayer and Multi-Component Tablets

4D printing allows the design of tablets with multiple layers or components, each releasing a different drug or excipient at a specific time or location. This is especially useful for patients with chronic conditions like diabetes, hypertension, or asthma who require complex dosing regimens [1].

Stimuli-Responsive Drug Carriers

The most advanced systems are stimuli-responsive carriers that release drugs in response to triggers like pH, enzymes, light, magnetic fields, or ultrasound. These are being developed mainly for targeted cancer therapy, aiming to maximize drug concentration at the tumor site while sparing healthy tissue [42].

Designing such systems requires precise control over material properties and drug distribution. 4D printing enables integration of active and passive components into a single structure, ensuring accurate dosage, targeting, and release timing.

Currently, these systems are under investigation in oncology, targeted antibiotic delivery, immunotherapy, and chronic inflammatory diseases.

3.3.2 4D printing of customized medical devices

4D printing technology enables the design of medical devices that actively respond to stimuli and adapt to the individual needs of patients. Implants made from shape-memory materials, such as nickel-titanium (nitinol), change their shape upon reaching physiological temperature, allowing precise deployment at the target site without the need for manual adjustment [32]. This principle is commonly used in endovascular procedures, such as the implantation of stents or vascular reinforcements.

In pediatric surgery, implants that respond to the growth of the organism are being experimentally tested, enabling adaptation without repeated surgical replacement during the child's development [30,39].

A significant area of 4D printing research involves active medical devices whose functionality changes in response to specific physiological stimuli. Examples include stents with programmable diameters that expand at body temperature or respond to changes in mechanical load at the target site, such as fluctuations in blood pressure (Figure 5) [30,38].

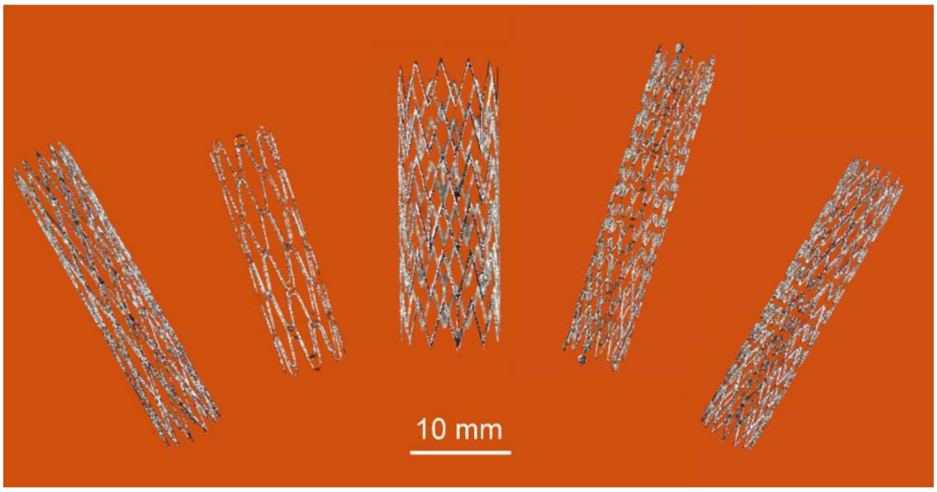

Figure 5 Self-expanding nitinol stents produced by 3D printing using selective laser melting (SLM) at the Lab22 laboratory (CSIRO, Melbourne)

Implants with modified surfaces can detect inflammation and release bioactive agents, such as antibacterial and immunomodulatory compounds. These systems enable targeted local drug delivery, enhancing efficacy while reducing side effects and the need for systemic therapy. Thus, 4D printing supports not only personalized design but also the development of smart devices with improved therapeutic performance [43].

3.3.3 Personalized pharmacotherapy and dosing

Modern pharmacotherapy faces the challenge of achieving precise dosing that considers individual physiological and genetic characteristics. Conventional drug regimens often overlook variability in metabolism, weight, age, genetic polymorphisms, or comorbidities.

4D printing enables the creation of personalized drug delivery systems that respond to specific physiological conditions and release active substances based on predefined parameters. Such systems can:

- release drugs at programmed time intervals,
- respond to stimuli (e.g., pH, enzymes, temperature),
- adjust dosing in real time based on patient status.

These features are especially valuable in chronic diseases (e.g., diabetes, rheumatoid arthritis, neurological disorders), where therapy must align with daily rhythms or symptom cycles.

Polymers with programmed degradation and stimuli-responsiveness, combined with genetic or biomarker data, allow for fully personalized dosing strategies. In the future, integration with wearable diagnostic sensors could enable real-time adaptation of drug delivery, leading to smart, adaptive, and highly individualized pharmacotherapy[34].

3.4 Adaptive sutures and bandages

Among the promising surgical applications of 4D printing is the development of adaptive sutures and bandages. These systems respond to changes in the wound or surrounding skin, enhancing treatment effectiveness and patient comfort. Most often, they utilize shape memory polymers (SMPs), which can alter their shape or tension in response to body temperature, moisture, or pH levels [4].

3.4.1 Self-tightening sutures

Traditional sutures require manual closure and are often removed later by a physician. With SMPs, it is possible to design sutures that automatically contract at a specific temperature—typically 37°C. They ensure even wound closure without the need for manual tension adjustment and adapt to changes in wound shape during healing.Research shows that self-tightening sutures may reduce scarring, minimize inflammatory responses, and support the natural healing process. These materials can also be biodegradable, eliminating the need for removal—especially beneficial for pediatric or geriatric patients (Figure 6) [44].

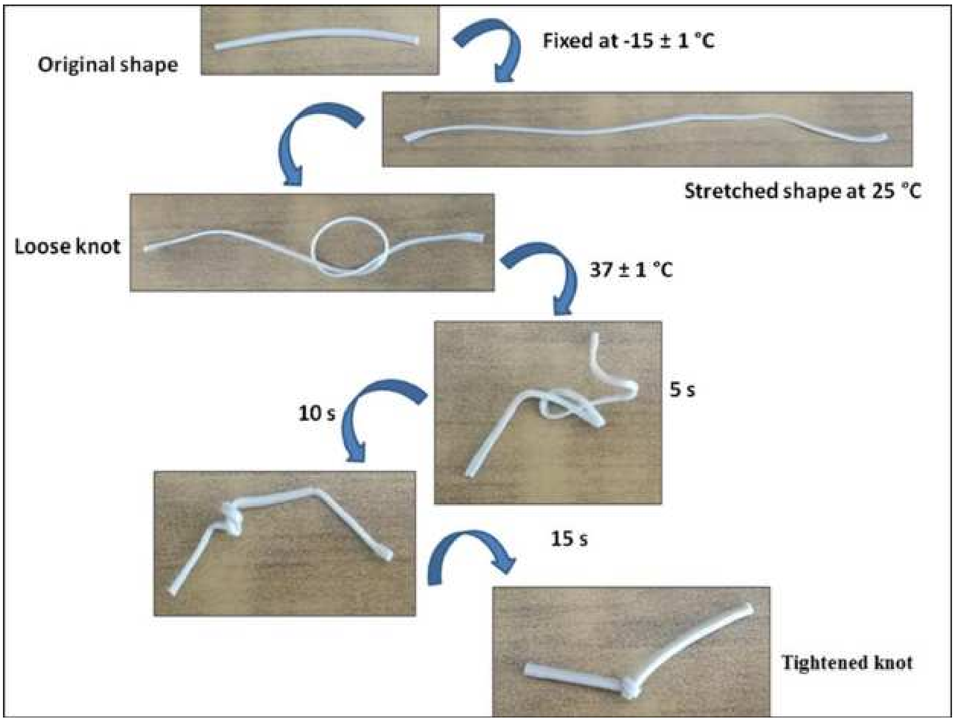

Figure 6 Self-tightening suture based on shape memory polymer activated at body temperature (37 °C)

3.4.2 Smart bandages

Beyond sutures, 4D printing is also used to create bandages that incorporate sensory layers or are made from hydrogels responsive to physiological changes such as temperature, pH, or humidity. Smart bandages can automatically release antibacterial agents upon infection detection or adjust their mechanical properties to optimize healing.

Hydrogel layers can be programmed via 4D printing to change porosity or viscosity depending on the healing phase—for example, maintaining moisture during the acute phase to promote epithelialization, and hardening later to protect the wound from external damage.

These technologies not only improve patient comfort but also enhance therapeutic efficiency, reduce healing time, and lower the risk of secondary infections [45].

4 Clinical implementation of 4D printing in medicine

Successful implementation of 4D printing in medicine requires not only technological advancements but also careful consideration of clinical aspects that determine its real-world application. This chapter focuses on key areas where 4D printing can provide therapeutic benefits, as well as the challenges that must be overcome to achieve its widespread clinical adoption.

4.1 Clinical benefits and therapeutic potential

4.1.1 Adaptive structures and biological integration

4D printing technology represents a breakthrough in medicine due to its ability to create smart structures that actively respond to physiological conditions in the body. Materials such as stimuli-responsive hydrogels and shape-memory polymers can adapt to temperature, pH, or mechanical stress. These responses improve biocompatibility, reduce the risk of complications, and enhance functional longevity of implants [1-3]. In clinical applications, implants capable of long-term interaction with surrounding tissue and active participation in healing—such as intelligent scaffolds or vascular grafts—are being tested.

4.1.2 Reduced surgical burden and reinterventions

4D printing facilitates the development of medical devices that self-expand after implantation or degrade once their function is fulfilled. Examples include self-expanding stents, growth-adaptive pediatric implants, or absorbable fixation systems. These innovations reduce the need for repeated surgeries and shorten recovery time [4-6]. Emerging applications also involve materials that release therapeutic compounds or transform their structure in response to temperature or pH without surgical intervention.

4.1.3 Personalized drug delivery

4D printing enables the development of drug formulations that respond to specific physiological stimuli. pH-sensitive capsules and temperature-activated hydrogels allow for more targeted drug release. Multilayer tablets can combine several active ingredients with staggered release times, improving treatment adherence and patient comfort [7-9]. These systems have the potential to significantly improve management of chronic conditions requiring

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tailored dosing schedules aligned with a patient's circadian rhythm.

4.1.4 Regenerative applications

4D printing is being used in regenerative medicine for tissue repair. Scaffolds produced with this technology can change stiffness, porosity, or release growth factors according to the healing phase. Applications are being explored in cartilage, nerve, skin, and liver regeneration [43]. When combined with stem cells and bioactive compounds, dynamic microsystems can enhance cell differentiation and improve vascularization in damaged tissues.

4.2 Barriers to clinical implementation

4.2.1 Material and technological limitations

The availability of biocompatible, stimuli-responsive materials remains limited. These materials often exhibit poor mechanical stability and are difficult to process. Manufacturing multi-material structures is technologically demanding and requires sophisticated equipment that is not yet standard in healthcare facilities [1,37]. Moreover, new printing protocols are needed to ensure reproducibility and precision in personalized production.

4.2.2 Regulatory and ethical challenges

Existing regulations such as MDR and FDA frameworks are not designed for programmable, individualized structures. There are no established standards for testing long-term material response, nor for ethical evaluation of autonomous material behavior. The complexity of such implants demands new approaches to informed consent and accountability for treatment outcomes [39,46]. Predicting long-term in vivo behavior increases the need for new types of clinical trials.

4.2.3 Economic and organizational barriers

Introducing 4D solutions is costly, particularly due to personalization and limited scalability. Integration into public healthcare reimbursement systems is challenging, as is coordination among developers, clinicians, and regulators [34,47]. New business models and cost-effectiveness evaluation systems are needed to capture the long-term benefits of such innovative solutions.

4.3 Outlook and recommendations for clinical adoption

In the coming years, 4D printing is expected to expand, particularly in personalized medicine and temporary implants. Key priorities include:

- development of new testing methodologies,
- legislative adaptation of regulatory frameworks,
- education of clinical personnel,
- and enhanced collaboration among research, industry, and clinical sectors [39].

Such a well-prepared environment will support the transformation of 4D printing from an experimental tool into an effective component of healthcare delivery.

5 Results and discussion

As this article is a review, the results presented here are not original experimental findings but rather a synthesis of data and conclusions reported in the existing literature. The following section highlights the most relevant outcomes of previous studies on 4D printing in biomedical engineering, with a focus on materials, techniques, and clinical perspectives.

Several studies have demonstrated that stimuli-responsive polymers and composites are central to the advancement of 4D printing. Smart materials such as shape-memory polymers (SMPs), hydrogels, and hybrid bioinks enable structures to alter their shape or properties when exposed to external triggers, including temperature, pH, light, or mechanical forces. Reported applications range from self-adjusting scaffolds in tissue engineering to minimally invasive implants and controlled drug delivery systems. These findings underscore the importance of material innovation as the foundation of successful biomedical 4D printing.

In terms of manufacturing techniques, selective laser sintering (SLS), fused deposition modeling (FDM), and direct ink writing (DIW) have been frequently adapted for 4D applications. Literature reports highlight the versatility of these methods in processing polymers, metals, and ceramics. However, scalability and reproducibility remain challenges, as many results are limited to small-scale prototypes rather than clinically applicable devices.

From a clinical perspective, pilot studies and proof-of-concept experiments suggest that 4D-printed constructs may provide significant benefits in personalized medicine. Examples include scaffolds that adapt to patient-specific anatomy, drug carriers that respond to physiological conditions, and stents that change shape after implantation. Nonetheless, long-term in vivo data are scarce, making it difficult to fully assess safety, stability, and biodegradation.

While the reviewed results demonstrate remarkable progress, several limitations persist. The availability of biocompatible and biodegradable materials is still restricted, hindering the direct translation of research into clinical practice. Moreover, reproducibility and scalability are major barriers to commercialization, as the transition from laboratory prototypes to clinical-grade products requires robust quality control. Another unresolved issue is the regulatory landscape, which lags behind technological advances and lacks clear guidelines for evaluating 4D-printed medical devices.

Interdisciplinary collaboration between material scientists, engineers, and clinicians is crucial to overcome these barriers. Ethical considerations such as patient safety, cost-effectiveness, and access to personalized treatments must also be addressed. Despite these challenges, ongoing innovations in smart polymers, bioinks, and computational design tools are expected to expand the clinical potential of 4D printing. Ultimately, the integration of stimuli-responsive materials with advanced printing techniques may reshape modern medicine by enabling adaptive, patient-specific, and functionally superior therapeutic solutions.

6 Conclusions

4D printing is an emerging and rapidly evolving field with the potential to significantly transform the future of medicine. The ability to create intelligent structures that can adapt to changing patient physiology or environmental conditions opens up new opportunities in personalized medicine, regenerative therapy, and targeted drug delivery. Although many applications remain in the experimental stage, research trends suggest that the integration of 4D printing into clinical practice is only a matter of time. Successful implementation, however, requires overcoming several technological, material, and ethical challenges. Future development will depend primarily on close collaboration among scientists, physicians, engineers, and regulators. If current barriers are addressed effectively, 4D printing could become a key tool in advancing healthcare toward greater efficiency, safety, and individualization.

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