Journal of the Brazilian Society of Mechanical Sciences and Engineering (2022) 44:233
https://doi.org/10.1007/s40430-022-03514-x

REVIEW

4D printing technology in medical engineering: a narrative review

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Received: 13 August 2021 / Accepted: 4 April 2022

Abstract

The addition of the time dimension to three-dimensional (3D) printing has introduced four-dimensional (4D) printing technology, which has gained considerable attention in different fields such as medical, art, and engineering. Nowadays, bioscience has introduced some ideas which can be fulfilled by 4D printing. Blending time with variations caused by the situation has many beneficial aspects such as perceptibility and adaptability. Since 4D printing can create a dynamic structure with stimuli-responsive materials, the applications of smart materials, stimulus, and 3D printing are the effective criteria in 4D printing technology. Smart materials with their flexible properties can reshape, recolor, or change function under the effect of the internal or exterior stimuli. Thus, an attractive prospect in the medical field is the integration of the 4D printing approach along with smart materials. This research aims to show the most recent applications of 4D printing technology and smart materials in medical engineering which can show better prospective of 4D printing applications in the future. Also, it describes smart medical implants, tissue engineering, and bioprinting and how they are being used for the 4D printing approach in medical engineering applications. In this regard, a particular emphasis is dedicated to the latest progress in the innovation and development of stimuli-responsive materials that are activated and respond over time to physical, chemical, and biological stimuli and their exploitation through 3D printing methods to fabrication 4D printing smart parts such as intelligent tissue-engineered scaffolds, smart orthopedic implants, and targeted drug delivery systems. On the other hand, major challenges in this technology are explained along with some suggestions for future works to address existing limitations. It is worth noting that despite significant research that has been carried out into 4D printing, it might be more valuable if some investigation is done into 4D bio-printing applications and how this approach will be developed.

Keywords 4D printing · 3D printing · Stimuli · Smart materials · Medical engineering

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1 Introduction

Rapid prototyping (RP) and additive manufacturing (AM) technologies have been used in many applications nowadays [1]. Generally, the AM technologies have seven principal ingredients, namely material extrusion, vat polymerization, material jetting, sheet lamination, binder jetting, powder bed fusion, and directed energy deposition [1, 2]. Three-dimensional printing (3D printing), introduced in additive manufacturing categories [3], was proposed for the first time by Charles Hull [4]. The initial model of 3D printing used a stereo-lithography (SL) technique and was inspired by photo-polymerization of liquid resin by ultraviolet (UV) light. In this approach, the printing process is carried out by a layer-by-layer method [5]. With the advance of technology, different techniques can be used in 3D printing methods, which are divided into several categories: stereolithography (SL/SLA), digital light processing (DLP), selective laser sintering (SLS), electron beam melting (EBM), selective laser melting (SLM), fused deposition modelling (FDM) or fused filament fabrication (FFF) [1, 6, 7].

It is worth mentioning that different materials such as metals, alloys, polymers, composites, ceramics and concrete are used in 3D printing technology [6]. Nowadays, 3D printing technology is used in several industries, such as automotive, textiles, construction, utility, aerospace, military industries, and many other operations [8, 9]. 3D printing is also applied to the medical and biomedical engineering (BME) fields, for instance, for pharmaceuticals, hearing aids, dentistry, implantable devices such as orthopedic implants, artificial hearts, encapsulation and bio-adhesion, bio-printing and tissue engineering, applications in healthcare and surgical instruments [10]. For example, researchers investigated on the fabrication of dental supplies through additive manufacturing technology [11]. They reported that 3D printed dentistry tools like implants and orthodontic wires are lightweight and have suitable properties; thus, this technology is practical for the fabrication of diverse dentistry instruments and principles [12].

Briefly, the main applications of 3D printing technology in medical engineering are shown in Table 1, along with a short description, and each's limitations.

Although 3D printing is considered a cutting-edge technology and undoubtedly has some faults, this manufacturing process has many valuable benefits. As shown in Fig. 1, in comparison with traditional manufacturing methods like computer numerical control (CNC), milling and turning, additive manufacturing supply benefits of comfortable design, more flexibility, and decrease manufacturing cycle time [11]. Despite the limitations of 3D printing technology, its benefits are enormous. To overcome the challenges of 3D printing, it is necessary to move to a novel technology known as 4D printing.

4D printing means “AM of objects able to self-transform, in form or function, when they are exposed to a predetermined stimulus, including osmotic pressure, heat, current, ultraviolet light, or other energy sources” [2, 13, 14]. With the 3D printing methods, the manufacturing of the objects is based on the three geometrical axes x, y, and z, but in 4D printing, there is a new dimension, the “time” dimension. This does not represent the time taken to carry out the printing. Instead, it represents the passage of time while objects undertake shape transformation and are mentioned as the main difference between 3D and 4D printing. In other words, according was reported by Momeni et al., 4D printing means “3D printing and time” [15]. To carry out 4D printing, one specific stimulus is required to commence the transformation. This can be humidity, heat, light, electrical field, and so on. In this case, unique materials are used to respond to these stimulus. These materials have programmable properties that can form at times specified by the stimuli. One of the critical features that 4D printing technology has in comparison with 3D printing is the possibility to build dynamic structures through the use of smart materials [16–18]. Since this technology has excellent potential to print living tissues or organs because these tissues have a dynamic structure [19].

There are more applications for 4D printing than 3D printing owing to 4D printing’s advantages [20]. In Table 2, the differences between 3 and 4D printing technologies are illustrated clearly.

Due to the use of smart materials in 4D printing, the objects can possess the following features: self-assembly, self-disassembly, self-sensing, self-folding, self-repairing, self-adaptability [21]. For instance, this innovative technology can manufacture a bone as part utilizing of stimuli-responsive materials, and this bone has the ability to extend in the human body over time [22]. So, 4D printing novel technology satisfies miscellaneous standards due to the use of smart materials and the fabrication of flexible parts. Figure 2 depicts the critical point is that all these

Table 1 Main applications of 3D printing in medical engineering

Application	Material	Disadvantages	Examples	Refs.
Orthopaedic implant	Metals such as (CoCr), (Ti6Al4V)	Inability to grow the implant, tailored to the age of the person	3D printing hip prosthesis by using SLM and EBM techniques	[127]
Artificial heart	Biocompatible materials	Deficiency of human heart hemodynamic function	3D printed artificial heart	[128]
Tissue engineering	Fibroblasts and keratin	Lack of physiological function of native tissue	3D bio-printed of skin with natural polymer composites	[98, 108]
Drug delivery systems	Cells or medications	Shortage of high precision control over drug loading time	3D printing drug loaded systems	[129]
Fabrication medicine	Water Poly-vinyl-pyrrolidone Hydroxyl-propyl methylcellulose vinyl-pyrrolidone-vinyl acetate copolymer		3D printed orodispersible tablets	[5]

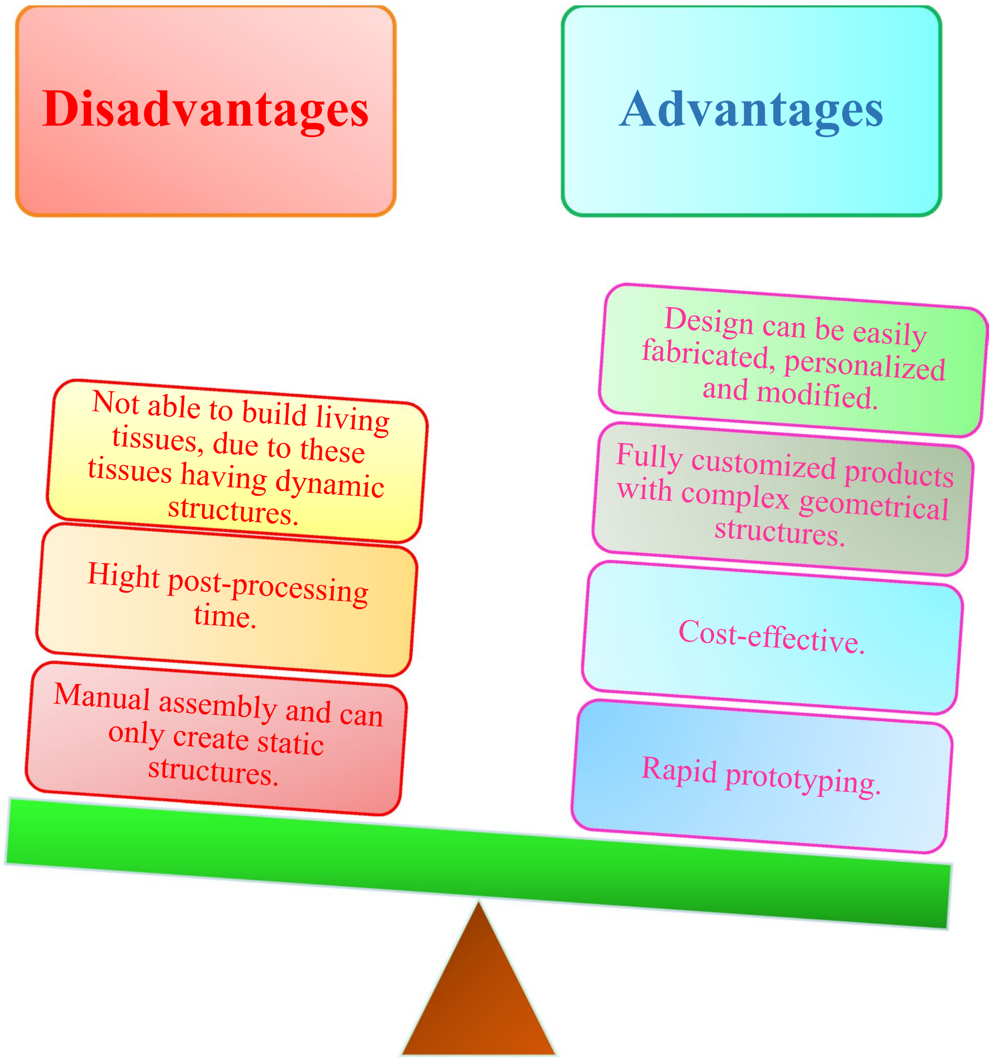


Fig. 1 Comparison between some of the advantages and disadvantages of using 3D printing

Table 2 Differences between 3D printing and 4D printing [18, 130]

	3D printing	4D printing
Formulated method	3D printing iteration of a 2D structure, layer-by-layer method	4D printing is the new generation of 3D printing
Materials	The usual materials, such as polymer, plastic, metals	Smart materials such as shape-memory alloys or shape-memory polymers
Design	3D digital data (scanning, drawing)	3D digital data for change (smart design)
Printer	3D printer	3D printer
Application	Industrial art, toys, robotics, entertainment, automotive, aerospace, apparel, bio/medical devices	Dynamically switching shape for all applications by 3D printing such as self-repairing, self-regeneration
Flexibility	No flexibility, characterized by rigidity/only creates static structures	Has flexibility, ability to create dynamic structures
Programming of material	Does not use smart and programmable materials	Utilizes programmable materials that can implement different functionalities

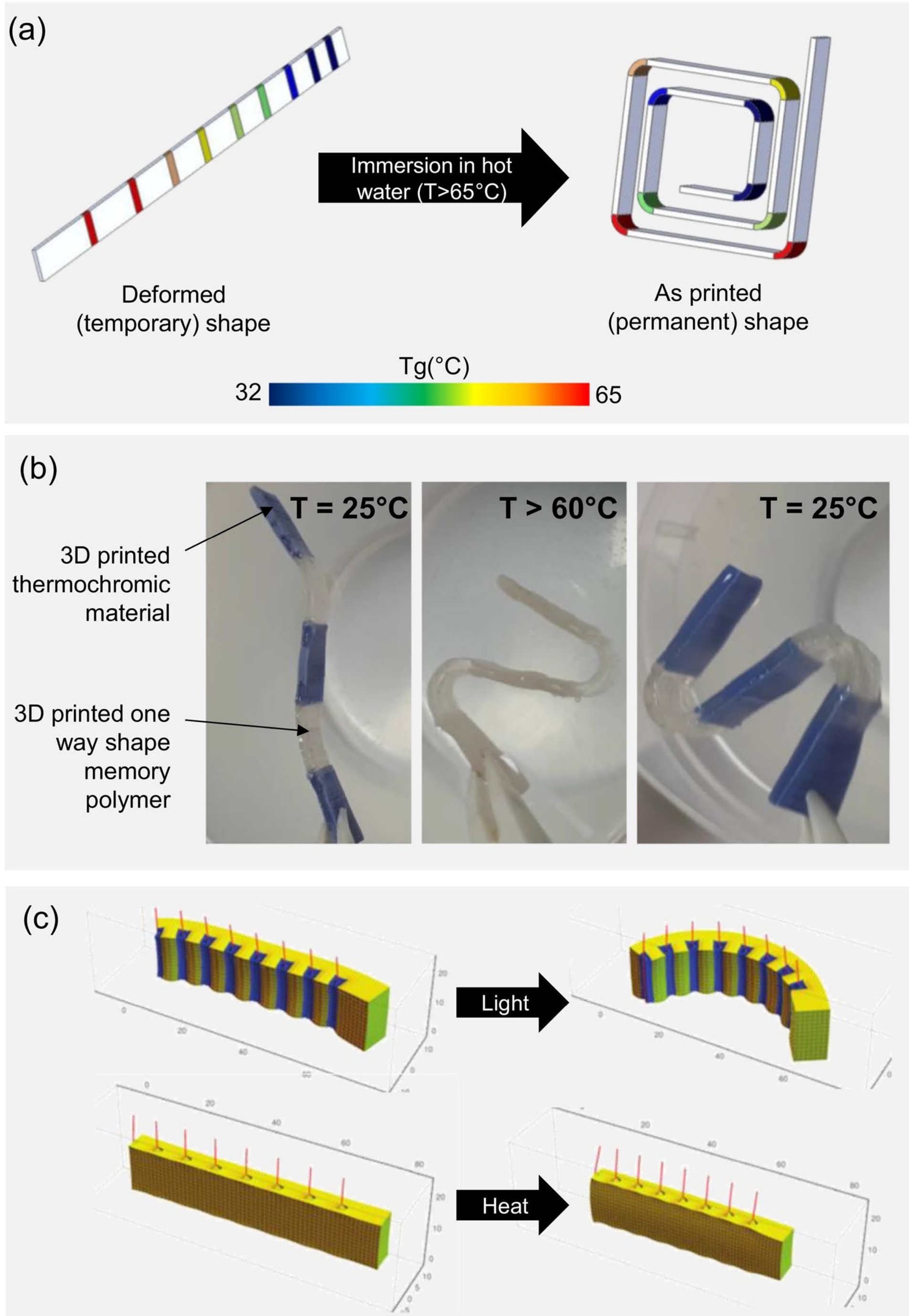


Fig. 2 Some properties of smart materials, when exposed to the stimulus **a** by hot water (Reproduced from ref [140] with permision from Nature.), **b** by heating **c** by light and heating Reproduced from ref [141], with permission from Royal Society of Chemistry

abovementioned features occur after the stimulus is applied to smart materials and over time.

This review investigates the recent medical applications of 4D printing and the materials used for such printing.

2 Research method

Review and original papers by keywords as "3D printing" and "4D printing" were studied with the aim of a better understanding and comparison of these technologies. In the following relevant articles on the Scopus, IEEE Explore, PubMed and Web of Science databases besides keywords as "4D printing applications," "smart materials in bioengineering" "stimuli-responsive materials" and "4Dp in biomedical aspects" were studied. Considering this technology has become the hottest and interesting topic in the last decade, it is necessary to show the latest developments and innovations in this field.

3 Research objectives

During the last decade, 4D printing technology has attracted the attention of scientists due to its unique capabilities and the elimination of limitations in traditional manufacturing methods and 3D printing, so the 4D printing subject has become a hot topic in additive manufacturing categories. Nowadays, this new technology is used in various research and applied products, including the fields of tissue engineering, manufacturing of medical tools and equipment, drug delivery systems, and so on. Therefore, for purposeful development and more efficient use of this technology, it is necessary to get acquainted with the newest applications and achievements of this technology in the biomedical engineering field. Thus, in this research, the latest applications of 4D printing technology in medical field along with limitations and future perspectives are presented. The main objectives of this paper are below:

- To study and brief review of additive manufacturing technology along with advantages and disadvantages.
- To identify 4D printing technology and comparison between 3D printing technology.
- To identify shape-changing behavior of 4D printed parts.
- To study the research status of smart materials, with their stimulus along with applications in the biomedical field.
- To investigate significant and effective parameters on parts printed through 4D printing technology.
- To identify a broad process of 4D printing in medical engineering applications.
- To discuss some limitations and future outlook of 4D printing technology along with some suggestions for future works.

4 Stimulus and responsive materials for 4D printing

Additive manufacturing or 3D printing materials are divided into various types, such as metal, glass, plastic, and food [23]. Nevertheless, most of the 3D printing materials are not applied to 4D printing because those materials do not react to the stimulus [23]. Consequently, the proper selection of materials is fundamental for 4D printing. Therefore, the materials used in 4D printing technology should have a more useful property in comparison with the materials used in 3D printing [23]. Stimuli-responsive-materials, also known as smart materials, can change their shape, features, or nature under the influence of specific stimuli [24]. Hence, the features of smart materials used in medicine can be attributed to tissue regeneration, drug delivery diagnostics, medical devices, etc. [25]. To accomplish the prosperous 4D printing of materials, it is essential to have a comprehensive knowledge of how environmental or external stimuli, such as those of a biological or physical nature, will influence these smart materials' properties. This knowledge sets the required foundation for 4D printing smart materials. Consequently, in the following section, several types of stimulus that have great potential in bioengineering applications are explained in detail.

4.1 Stimuli

It is worth mentioning that different kinds of stimulus, such as physical (temperature, light liquid/moisture), chemical (ionic concentration, pH), biological (glucose, enzymes), and combinations of different stimuli, have been considered [26]. All these stimulus are considered in the real world and occur in many cases which can make various changes in smart materials [27]. The choice of the stimulus type should be appropriate to the desired usage because each stimulus is proper for specific application and material. Additionally, the smart materials are selected according to the stimuli used [24]. The stimulus for the start transformation is applied so that the starting point of shape-changing objects printed by a 3D printer has the same stimulus [28–30]. Some of the stimuli that have more significant potential applications for medical and biomedical aspects are explained in the following.

4.2 Physical stimuli

These types of stimulus can be classified into light, humidity, electrical current, water, temperature, and pressure forces [26]. They often change the shape of the object by changing the physical arrangement of the material. As a result, this kind of intelligent material that responds to physical stimuli can be helpful in medical applications such as implants [26]. Since heat, moisture, and water stimuli have been used more in medical engineering so far, we will continue to give a brief and practical explanation of these stimuli in terms of biomedical engineering.

4.2.1 Temperature stimuli

The temperature stimulation, which is mainly used for smart materials, can be utilized in bio-4D printing applications. For illustration, an object can be placed at a high temperature under pressure to form a temporary position. By cooling the object and applying sufficient force, the object may be restored to the original state. This property of shape recovery is used for small bone defect implant replacements [26, 31, 32]. Thermo-responsive materials have the ability to change their geometric arrangement and reshape under the influence of temperature stimuli. According to Ashammakhi et al.'s study, despite more research being required on the properties of these materials, they are still known to have the ability to be printed by 4D printing technology [33]. Temperature-responsive materials are used in 4D printing technology for medical and engineering purposes. For instance, Senatov et al. used the shape recovery properties of temperature-responsive materials for repairing and recovering bone scaffolds [34].

4.2.2 Humidity/Liquid stimuli

Moisture-responsive materials can swell and change shape and function under the influence of liquid or humidity stimuli [35]. Since large parts of the human body contain water, this stimulus may be used for biomedical applications. Some smart materials can respond to this stimulus [26]. The moisture-responsive materials and liquid stimuli such as water are used in biomedical applications such as tissue engineering, drug and nutrition delivery, and soft actuators [36]. Besides, the swelling/shrinking degree of moisture-sensitive materials should be accurately checked in the development procedure to maintain fabricated constructions' integrity [33]. Although these materials and stimuli have suitable potential for future growth, further research is required.

4.3 Chemical stimuli

Variations in physiological situations such as a change in pH or ionic concentrations are usually crucial symptoms for distinguishable kinds of diseases, like cardiovascular system illnesses, infections and cancers, therefore, interpreting them as critical aims of consideration when designing and developing chemical-responsive materials [26, 37].

For instance, since the acidification of cancerous or inflammatory areas is often common, pH-sensitive materials can be used for drug delivery systems in targeted sites. Usually, natural and synthetic polymers can react under the influence of pH stimuli. Therefore, researchers can use the features of chemical-responsive materials along with 3D printing techniques in biomedical applications like fabricated drug-loaded systems. For example, Larush et.al fabricated the drug-release system by using the digital light processing (DLP) technique with pH-responsive materials. In their research, the tablets were printed using responsive hydrogels that had the ability to rapidly release the drug in relatively high pH environments [38]. In addition, pH-responsive biopolymers can be used in tissue engineering applications due to their attractive properties such as excellent biocompatibility, good biodegradability and, suitable bioactivity. Nevertheless, the use of natural pH-responsive polymers in pragmatic usage is confined due to low mechanical properties [26, 39].

Another type of stimulus that belongs to the group of chemical stimuli is ionic concentration. Although there are comparatively few investigates as the potential use of ionic strength as the stimuli-responsive material in 4D printing in the last decade [26], recently, novel studies have been done on this stimulus and the responsive-materials that react under the influence of this stimulus. For instance, Yasin et. al succeeded developing shape memory hydrogel based on ion-responsive material with an ability to reduce Fe^{3+} to Fe^{+2} by changes in ion concentration [40].

However, more studies are required on ion-responsive materials to become more aware of their applications in 4D printing technology and the benefits of using them in the biomedical aspects.

4.4 Biological stimuli

In patients-body, blood factors such as glucose levels, enzymes, proteins, and nucleic acids play a significant role in controlling the normal mechanism and normal functioning of organs [26]. Therefore, recognizing these important parameters and biomaterials that respond to biological stimuli is essential for the better performance of 4D printing technology to address the manufacture of biocompatible parts.

In the relevant work, researchers introduced a biological-responsive material through this innovative approach that enabled them to make bioinspired 4D printed parts containing bioactive features [41]. The stimulus they used to create bioactive properties in the fabricated parts was alkaline phosphatase and thrombin enzymes. They showed that the use of biological-responsive materials in 4D printing and tissue engineering is very useful and efficient.

As mentioned, one of the main differences between 3 and 4D printing technologies is the type of material used. The objects printed by 3D printing are not able to change shape. Structures that are printed with 4D printing are capable of reacting to a stimulus such as heat, light, pressure, mechanical force, electrical power, stress, acoustics, and so on [42]. In addition, thermo-responsive and liquid-responsive materials have more applications in 4D printing, and as a result, temperature and liquid stimuli are usually used in 4D printing technology [23]. Therefore, the adoption of proper stimuli depends on the applications' condition. As a matter of fact, the intelligent materials used in 4D printing have extended properties compared to the conventional materials used in 3D printing. Some of the characteristics of smart materials are:

a) They can be transformed after being printed.
b) They can change color and transparency.
c) They can produce electrical currents.
d) They have the ability to reform, repair, strengthen and restructure themselves and are used to make living tissues and for bio-printing.

Therefore, using smart materials is much better than monotonous and straight forward materials, and there is consequently a more comprehensive range of smart materials applications. The following section presents the materials used in 4D printing technology to explain their structure.

4.5 Stimuli-responsive materials

Stimuli-responsive materials are a kind of smart materials that can react and change under the influence of a particular stimulus. Smart materials can be classified into shape-changing materials and shape memory materials [15, 20].

4.5.1 Shape changing materials (SCMs)

These materials can be transformed after being stimulated, and their basic structure determines the type of change in shape. When the stimulation is removed, the materials revert to their original position, meaning they are reversible [39].

4.5.2 Shape memory materials (SMMs)

Buehler and Wang discovered SMM in 1962 [43]. Shape memory materials come in different types. SMMs does not need any predetermined transformation as prepared, but it should be programmed for the material that understands what the object changes to after stimulation. The next step is known as the recovery phase, where the object will return to the initial state by applying a specific stimulus [5]. These materials have the shape memory effect (SME) property, which means they can "memorize" permanent shapes [20, 44, 45].

The main difference between SCMs and SMMs is that in shape-changing, when the stimulus is removed, the material returns to the original position. In the shape memory case, transformation occurs when the material is stimulated. However, the material needs programming for the second memory feature [20, 46]. SMMs can be classified into two classes: one-way shape-memory materials and two-way shape-memory materials [15, 20].

In one-way shape-memory materials, the primary shape is subsequently recovered from the temporary position; a new programming stage is needed to remodel the temporary shape in every period [23]. Conversely, the two-way shape-memory materials do not require the reprogramming stage to recover their temporary shape [23]. In addition, SMMs have different types that can be transformed under the influence of external actuations for specific conditions.

The use of shape memory polymers (SMPs), shape memory hydrogels (SMHs), and shape memory alloys (SMAs) is common for medical engineering purposes [47]. Researchers prefer to use shape-memory materials rather than shape-changing materials because shape-memory materials have more and better capabilities [48]. Hence, in the following section, different shape-memory material types are reviewed.

4.6 Shape memory alloys (SMAs)

Shape memory alloys (SMAs) are a class of stimuli-responsive materials that can convert thermal energy into mechanical force [45]. SMAs have much variety, but SMAs based on nickel-titanium (Ni–Ti) have more applications in different industries such as electrical, mechanical, and aerospace [49, 50]. Also, SMAs have useful properties, such as being biocompatible, highly corrosion-resistant, and demonstrating a super-elasticity effect (SE). For attaining and use of these features, Ni–Ti is prepared in several geometries for customized applications [45]. Since these materials can react under heat stimuli, they have excellent potential for biomedical engineering [43]. Hence, SMAs can be used for medical engineering purposes, such as implantable devices, catheters, orthodontic wires, vascular surgery, drug delivery, cardiology, closure devices, surgical instruments, radiology, and neurology [43, 51, 52].

The SMAs for manufacturing or printing are often linked to the selective laser melting (SLM) technique. For example, Habijan et al. [53] investigated the potential for carrying materials to human mesenchymal stem cells (hMSCs). According to their study, they linked SMAs to SLM techniques to build implants for facial, pelvic and cranial repairs.

However, the use of these types of smart materials is limited due to their low degradability rate. For instance, to fabricated implants (like bone scaffolds) that have an important role in tissue regeneration, it is a very crucial issue that the scaffold absorbed by native tissues in the suitable moment atomically by the passage of time, but in the alloys, because they have low biodegradability rate, the implant may remain in the human body for years, which can cause stress-shielding phenomenon or additional surgery may be needed to remove it. So, it seems like that more investigation is required to use shape memory alloys in 4D printing technology to address existing limitations and concerns.

4.7 Shape memory polymers (SMPs)

SMPs, known as actively moving polymers, are the types of smart materials that are capable of memorizing [54]. These materials have different types, but the most common are cross-linked polycyclooctene, polynorbornene, and epoxy-based polymers [55, 56]. SMPs can shape change with environmental changes or external stimuli such as moisture, light, pH, and temperature. [54, 57].

In comparison with SMAs, SMPs have additional properties to SMAs, such as cost-efficiency, increased flexibility, greater chemical resistance, biodegradability, response to light stimuli (SMAs cannot react to light stimulus), but SMPs have low tensile strength and stiffness in comparison with SMAs [58, 59]. Nevertheless, SMPs are more applicable than SMAs in biomedical engineering [43, 60].

As discussed, these smart material types can respond to multiple physical stimuli. These materials have also shaped memory effect properties and can reshape at different temperatures. [61]. Thus far, these material categories have been used in many fields, especially in medical engineering such as surgical sutures, splint airways, and vascular stents. For example, according to an investigation, 280,000 people suffer from heart disease every year [62]. So, there is thus a widespread need to develop cardiovascular stents. Since today's metal stents have some disadvantages, such as lag growth capacity and causing hyperplasia, it is felt that there is a need to produce new stents with better properties [63, 64]. Hence, for expeditious and increased construction of the stent, 3D printing was used. However, one of the limitations of fabrication using 3D printing is that this technology can only create static structures, and the objects, therefore, cannot reshape under the required conditions. For example, when 3D printing builds an implantable stent, these implants cannot grow in tandem with the implant. However, 4D printing of smart implants can add this growth capability. For instance, as shown in Fig. 3, Qi Ge et al. printed a cardiovascular stent using 3D printing and shape memory polymers [65]. This stent has the potential to be much better than metal stents because it uses shape memory polymers. As a result, this stent has a shape-changing ability and can respond to heat stimulus, and stent morphology changes under the required conditions.

In the same research, Bodaghi et al. used smart materials to make a stent whose diameter could change under certain conditions and stimuli. [66]. In other words, as shown in Fig. 4, the stent structure has a self-expanding/shrinking property.

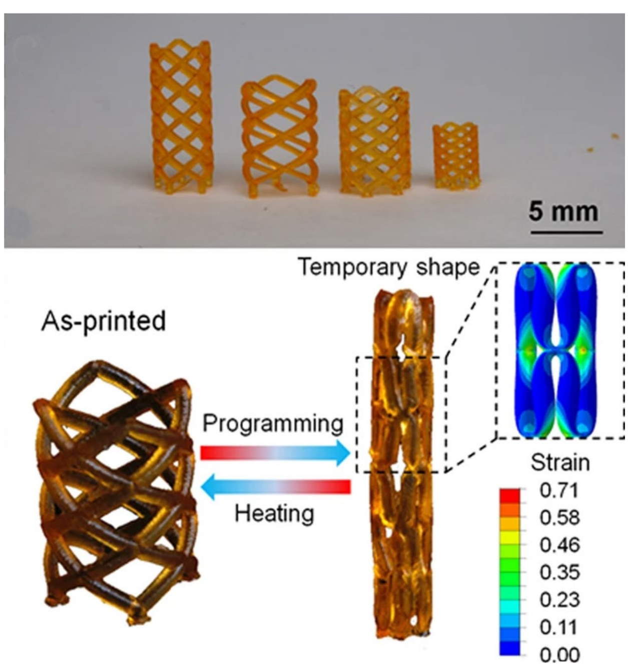


Fig. 3 Schematic of a cardiovascular stent fabricated by 4D printing technology permission needed. Reproduced from ref [65]. with permission from Nature

4.8 Shape memory hydrogels (SMHs)

Hydrogel is another type of shape-memory material. Through employing the potential of 3D printing to make structures out of smart hydrogels, the fabricated 4D bio-construction or living tissue hydrogel scaffolds can have the ability to self-fold or self-unfold in response to stimuli. It is a vital issue because it helps to contribute significantly to the field of bio-printing 3D tissues. [24]. These smart material types can respond to water stimulus or other liquids, so these materials can be used when there is contact with water or other fluids. In 2016, Li et al. succeeded in building a micro-robot [67] for targeted drug delivery using a layer of hydrogels and a material sensitive to pH when dealing with a cancerous tumor that could inject a drug into the tumor and cause the tumor to die [68, 69]. Smart hydrogels are models with high water content that possess the capacity to react to an external stimulus such as pressure, ionic, electric, pH, temperature, magnetic field, light [24]. They have unique characteristics such as memory effect, self-healing, and controllable sol–gel transformation. By employing the potential of AM approaches to manufacture constructions created of smart hydrogels, the fabricated 4D printing constructions or bio-origami hydrogel scaffolds can have the

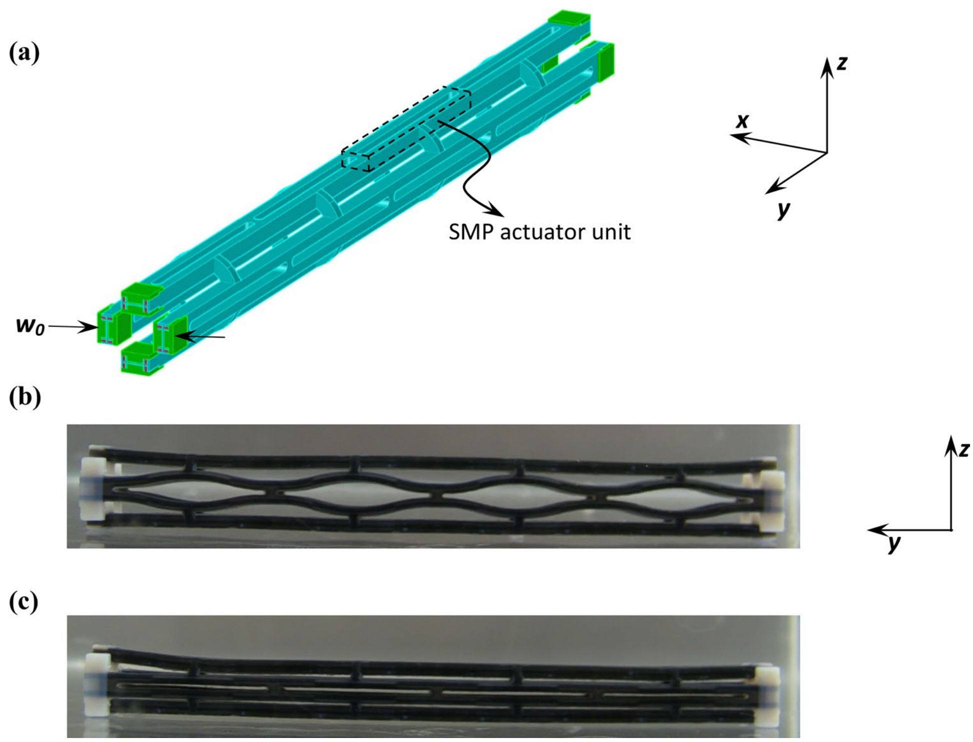


Fig. 4 Illustration of the 4D-printed thermo-responsive stent; **a** description of the stent design. **b** its arrangement at the time with the most extension (self-expanding), **c** contract occurs at the end (self-shrinking). Reproduced from ref. [66] with permission from IOP science

ability to self-fold or self-unfold in response to an external stimulus [24]. This will help to contribute significantly to the area of bio-printing of functional 3D tissues [24].

5 Structure and shape-shifting behavior

Smart materials are divided into various types of applications; each of these materials has a unique characteristic, such as changing their shape, known as shape-shifting [19]. Also, the transformation from the original states to a temporary states can be called shape switching and include folding, bending, swelling, twisting, surface curling, and the mixed deformation of bending and twisting [15, 23].

5.1 Self-assembly property

This phenomenon is well known as the main property of smart materials, and many researchers have paid attention to this feature [36]. Materials that have this property can be combined or integrated automatically. This feature was not seen in the products that were printed using 3D printing technology [37]. Firstly, Tibbits expressed this property and explained how this feature of smart materials could play a significant role in 4D printing technology. He stated that the automatic incorporation of small structures under the influence of external energy could create larger structures [14, 70]. However, using a self-assembly property may not be applicable in all cases, so it must use this attribute according to the goals set [71]. Self-assembly can be used for transforming the state of objects from one-dimensional to two-dimensional or from two-dimensional to three-dimensional [72]. Tibbits, using memory materials and implementing three methods: user input, environmental input, and material input, demonstrated the self-assembly property [14].

Shapeshifting happens in materials that are highly dependent on the type of materials and stimuli. Hence, the following section describes the different types of smart material used in 4D printing technology that can potentially have applications in the medical engineering field.

6 Application of intelligent materials in medical engineering

Another limitation of manufacturing with 3D printing technology is that the manufactured objects cannot change their shape to suit specific conditions. As mentioned above, when an implantable stent is built using 3D printing technology, these implants cannot grow in tandem with the implant. However, using 4D printing and fabrication of smart implants, this growth capability can be added, as their structure is dynamic, unlike the structure of 3D printing, which is static. Since smart materials and stimuli play an essential role in the objects manufactured by 4D printing technology, some of these applications are presented in Table 3.

Since smart materials have significant applications in 4D printing, various 4D printing applications are restricted

Table 3 Some applications of smart materials and stimuli in medical engineering

Stimuli	Shape memory materials (SMMs)	Relevant examples	Refs.
Light	Shape memory polymer and Black carbon	Young et al. used FDM technique and black carbon to print a sample of a flower that can respond to heat absorbed by light	[131]
Liquid/Water	Hydrogels	Using bio-printing and hydrogels, printed capsule at swollen state for drug delivery	[25]
pH	Synthetic and Natural Polymers (Such as gelatin, keratin and collagen), hydrogels	(a) Targeted drug delivery purposes: for instance, researchers Printed pH-responsive tablets to release the appropriate dose in a targeted moment. (b) Tissue engineering	[132]
Temperature and Magnetic	Poly (N isopropylacrylamide-co-acrylic acid)	Soft robotic and surgical application	[133]
Electric impulse	Metal-liquid composites (gallium indium alloy-liquid crystal elastomer)	Prepare novel composite ink for 4D Printing in soft robotics/actuators	[134]
Magnetic	Fe_3O_4-MBG-PCL composites	Tissue engineering (scaffold for bone regeneration) and drug delivery (anticancer drug loaded system)	[135]
Magnetic	PLA/Fe_3O_4 composites	Bone tissue engineering	[136]

because of unacceptable material characteristics, and the advancement of stimuli-responsive materials should be developed in correspondence with the progress of printer devices [15]. Thus far, the extension of advanced soft active materials with beneficial characteristics that are also agreeable with printers is important in developing the application of additive manufacturing technology [15].

7 4D printing technology

As discussed, 4D printing technology has many similarities with 3D printing because there is no significant difference between 4 and 3D printing devices. Both 3D and 4D printing are based on additive manufacturing technology, which creates objects layer by layer with a broad range of materials. 4D printing is advancement version of 3D printing technology that used stimuli-responsive materials to fabricate complicated and flexible objects with high resolution. In comparison with 3D printing, 4D printing sets up time as a further dimension to the fabricated object [73]. 4D printing employs stimuli-responsive materials with the same printing methods as being used in additive manufacturing technology. In other words, 4D printing technology uses 3D printer devices which are specially adjusted to use stimuli-responsive materials during layer-by-layer process, to fulfill different ongoing necessities of diverse areas [74]. However, here the manufactured parts with smart materials could change their, geometrical shape, and function. According to report Javaid and his colleague [75], 4D printing technology has critical useful advantages such:

- Ability to time and spatial control during printing processes.
- 4D printing could manufacture flexible parts with the dynamic structure that these parts have interesting features such self-fold/unfold, self-twisting, self-swelling, and self-assemble.
- Ability to use programmable smart materials to manufacture patient-specific products.
- Enhanced the performance of the manufactured products with 4D printing technology.
- This is the cost-effective manufacturing technology.

According to a report by Tamay et al., five essential factors can affect 4D printing technology. These are (a) AM or 3D printing processes, (b) type of responsive-materials, (c) kind of stimulus, (d) interaction mechanism linking the stimulus and the material, and (e) mathematical modeling of the material transformation. [76]. As the different AM methods are fundamental in 4D printing technology, a brief explanation of two of these processes that have more applications in medical engineering is described in the following.

7.1 Vat photo-polymerization process

Vat photopolymerization is an AM method in which resin material in a vat is moved to a rigid part employing UV light (curing mechanism). The vat-polymerization has two subsets, and the difference between them is in their light source: SLA or DLP [77].

7.2 SLA and DLP

Stereolithography (SLA) and Digital Light Processing (DLP) are two 3D printing techniques. If the process cures liquid sensitive material into the layer, this process is known as photo-polymerization [78]. If a laser beam is used in the construction process, it is known as SLA, and if other types of the light ray are used, it is known as DLP. Another difference lies in completing the construction process: in DLP, the beam radiation makes a complete cut of the layer, whereas, in SLA, intermittent layers are made. The advantage of DLP over SLA is a reduction in materials used, and thus, lower costs and less waste.

Since the SLA technique fabricated the rigid parts, the materials used for this method should have low viscosity [79]. In general, the SLA material is divided into three main categories: several resins (such as clear resin, dental resin, castable resin), polymers, and ceramic and metal composites [2]. Polymers have good employment potential in tissue and biomedical engineering because of their useful properties such as biodegradability and biocompatibility. For instance, Choi et al. were able to construct micro-scaffolds by combining a polymer material and the SLA technique [80]. Another case of the application of the SLA technique is related to bio-printing/bio-fabrication. Soham et al., by applying the SLA technique, succeeded in developing a tube with the contents of living cells encapsulated [81].

7.2.1 Advantages and Weaknesses of SLA

- There are several materials accessible for the SLA method, such as polymers and ceramics.
- Great quality and high-resolution printing.
- Fast printing speed.
- Requires support structure.
- Post-processing is required to remove support.

7.3 Material extrusion processes

In this method, materials are pushed through the nozzle, then poured on to the printer bed to build objects by means of a layer-by-layer process. The FDM is one of the 3D printing techniques that works according to the material extrusion [82].

7.3.1 FDM

The general steps of printing using the FDM technique are very similar to the printing stages in SLA. The difference in this technique is that the material is deposited from the nozzle to print the object. When each layer is placed in contact with the bottom layer, it cools and hardens. Generally, polymers and composite materials are usable in the FDM technique.

Thermoplastic polymers, which are used for FDM, should become a filament series, and then, they are prepared for 3D printing. Different types of material based on the polymers can be used in FDM, such as polystyrenes (PS), polyamide (PA), polycaprolactone (PCL), polyvinyl butyral (PVB) and polycarbonate (PC), but the use of polylactic acid (PLA) and acrylonitrile butadiene styrene (ABS) is more common [2, 83]. Recently, Bakarich et al. succeeded in introducing a new approach to bio-fabrication in the field of tissue engineering by using an FDM extrusion process and multi-materials. They were able to make a sample of an artificial tendon using hydrogel composites and the FDM technique that was very similar to the real human tendon [84]. Another example of the utilization of this technique is related to the innovation demonstrated by Jingchun Wang [85]. They succeeded in building a flower with multi-smart materials (a combination of PLA and T-PIGs) and the FDM technique, which has the ability to change shape and color simultaneously.

7.3.2 Advantages and Weaknesses of FDM

- An extended domain of polymeric materials is accessible.
- FDM is a cost-efficient approach.
- The support is not necessary in all cases (sometimes support is required only for unusual objects).
- The printing of structures with this method exhibits a low resolution.
- Fabrication using this technique exhibits low resolutions.
- The 3D printing speed is relatively lower than with other techniques.

8 Medical engineering applications

Although 3D printing technology has many applications in various fields, such as medical engineering, a desire to overcome its limitations has motivated researchers to use 4D printing technology. In addition, numerous novel and interesting ideas have been employed in 4D printing technology. Several unique approaches are appearing to increase its medical engineering applications or improve the administration of printing precision. In fact, the current 4D printing has worked out certain limitations and difficulties in recent trials, such as vascular stents, gastric drug delivery system, and muscle actuators [86].

In this section, firstly, the latest applications and innovations of 4D printing and bio-printing in the medical engineering field are presented. At the end of the section, Table 4 shows some recent applications and innovations of this technology that have been used so far in biomedical engineering.

8.1 Smart implants

Today, implants have excellent applications and are used in various fields, such as dentistry and certain types of surgery. Nevertheless, production of implantable devices by 3D printing technology or other traditional methods has certain limitations. One of the most important problems in making implants with traditional methods is that these implants are

Table 4 Some of the applications of 4D printing along with benefits there were not in 3D printing

Application	Smart-materials	Approach	Advantages	Refs.
Tracheal stent	SMPs	SLA 3D printing technique by using imaging method (MRI)	More flexible than the previous stent	[88]
Splint airway implant	PCL liquid	SLS technique by using imaging method (CT)	Ability to grow and transform in children + Helps improve breathing for children with TBM disease	[87]
Sensing System/ Smart Implants Prostheses	Piezoelectric material barium Titanate (BTO)	FDM	Biocompatible and can be safely used in implant processes to send signal containing information from the body	[89]
Bioinspired robotic finger	Shape-memory polymer (SMP)	FDM	Inspired by human finger, has three joints of SMP and three rigid segments of ABS, and can be programmed into the desired bend	[137]
Bio-scaffold	PLA/HA composites	FDM	Manufactured a scaffold with adequately high porosity as well as a suitable pore size needed for spreading cells and nutrients, has potential to be used for small bone defect replacement	[34]
Bio-printing of hydrogel	SMH based hepatic bio-construct	Psla	Dynamic fabrication+maintain a living structure	[138]
Soft Robots and Actuator	Polyelectrolyte	3D Printing method	High bending deflection by using Smart materials and optimized 3D printing method. Result = Increasing bending ability in comparison with use non-smart materials in 3D printing	[139]
Artificial appendage occluders	PLA/Fe_3O_4	FDM	Proper mechanical properties, shape memory performance, heat and magnetic responsive structure	

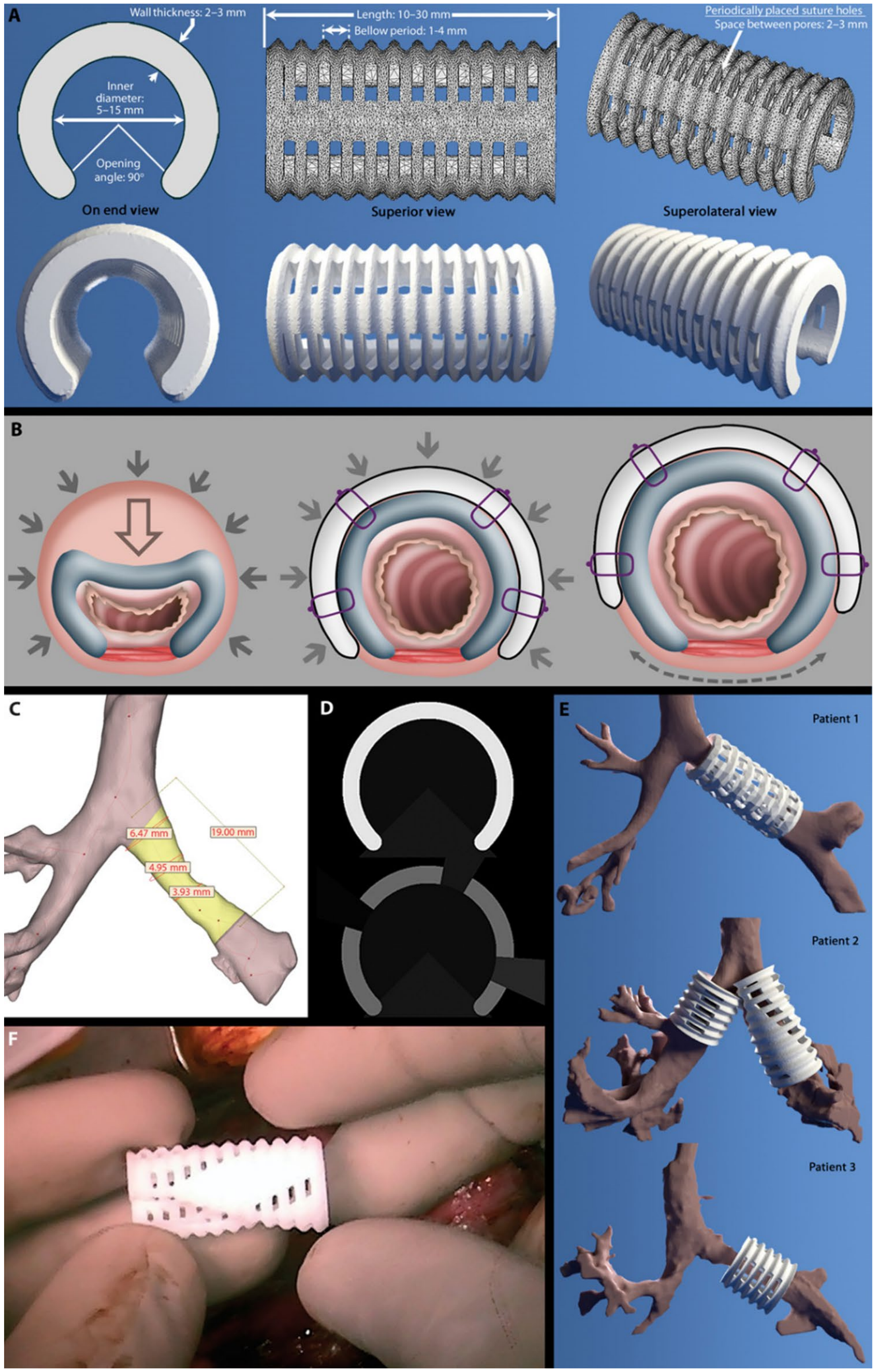


Fig. 5 Illustration of splint Construction and function: **a** Schematic of Stereo-lithography (STL) representation (top) and virtual rendering (bottom) of the tracheobronchial splint. **b** Function of work the tracheobronchial splint in treating tracheobronchial collapse in TBM. **c** Digital model by using CT scan. **d** Design parameters were input into MATLAB to generate an output as a series of 2D. **e** Virtual modeling of splint for three Childs. (f) Ultimate 3D-printed PCL tracheobronchial splint used to treat the left bronchus of a patient. Reproduced from ref. [87] with permission from Science

not capable of growth or reshape under required conditions. By introducing smart materials and mixing these materials with techniques that were available in AM technology, researchers succeeded in making intelligent implants. These devices can change shape and morphology under the necessary conditions. One of the most recent work using 4D printing technology was carried out by Morrison et al. [87]. They used the PCL/ Hydroxyapatite composite and selective laser-sintering (SLS) technique to create an implant for a child with severe tracheobronchomalacia disease. Via using imaging methods and a CT scan, they modelled the CAD and then printed the splint by means of the SLS technique.

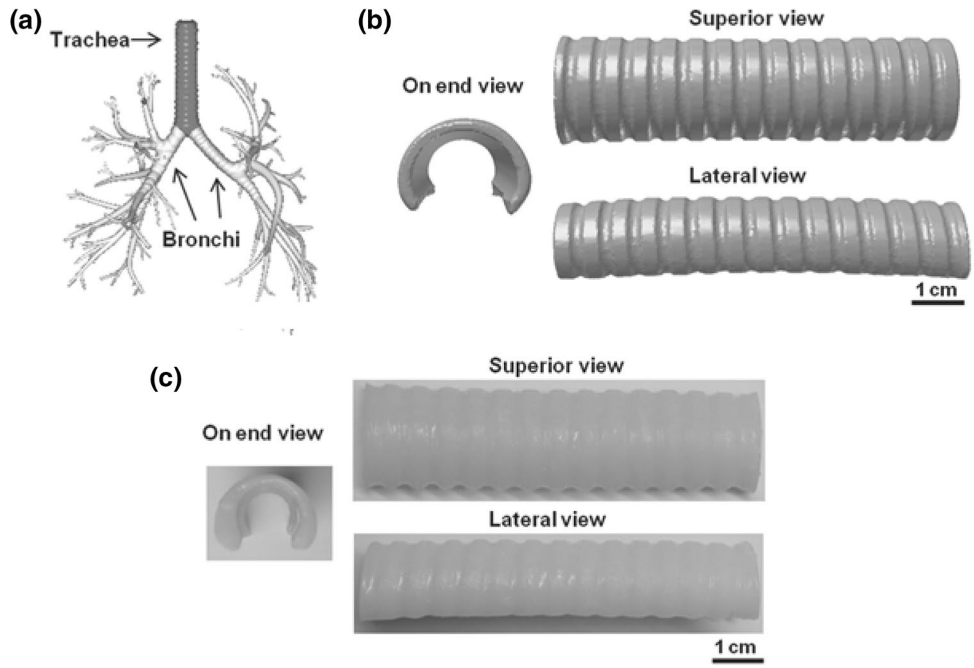


Fig. 6 Illustration of the process of producing a stent. **a** Imaging stage by MRI. **b** Prepare digital model (CAD). **c** Final stent structure in the original state. Reproduced from ref [88]. with permission from John Wiley and Sons

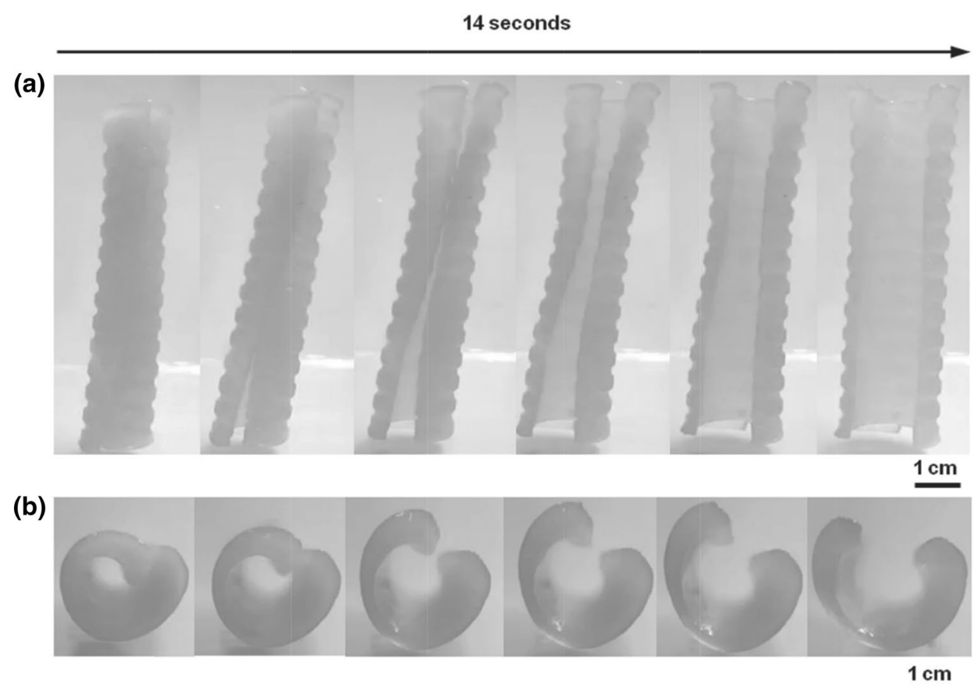


Fig. 7 Illustration the shape-changing behavior by thought time in airway stent. **a** The dorsal look of the stent shift. **b** At end view of the stent shape shifting. Reproduced from ref [88]. with permission from John Wiley and Sons

The splint made using this technology had the ability to grow and transform, as shown in Fig. 5.

Zarek et al. [88] carried out another work using 4D printing technology in the medical engineering field. They were able to build a tracheal stent that had the ability to recover the permanent shape from a temporary shape under the required conditions. As shown in Fig. 6, by using the MRI imaging method and SMPs, Zarek et al. fabricated the tracheal stent using the SLA 3D printing approach. It was more flexible than the previous stent. The use of shape-memory materials in making these stents gives the ability to have a primary and temporary form. The steps of transformation in the stent are shown in Fig. 7.

Another application of 4D printing in medical engineering is related to piezoelectric composite materials. The piezoelectric effect is defined as a linear electromechanical

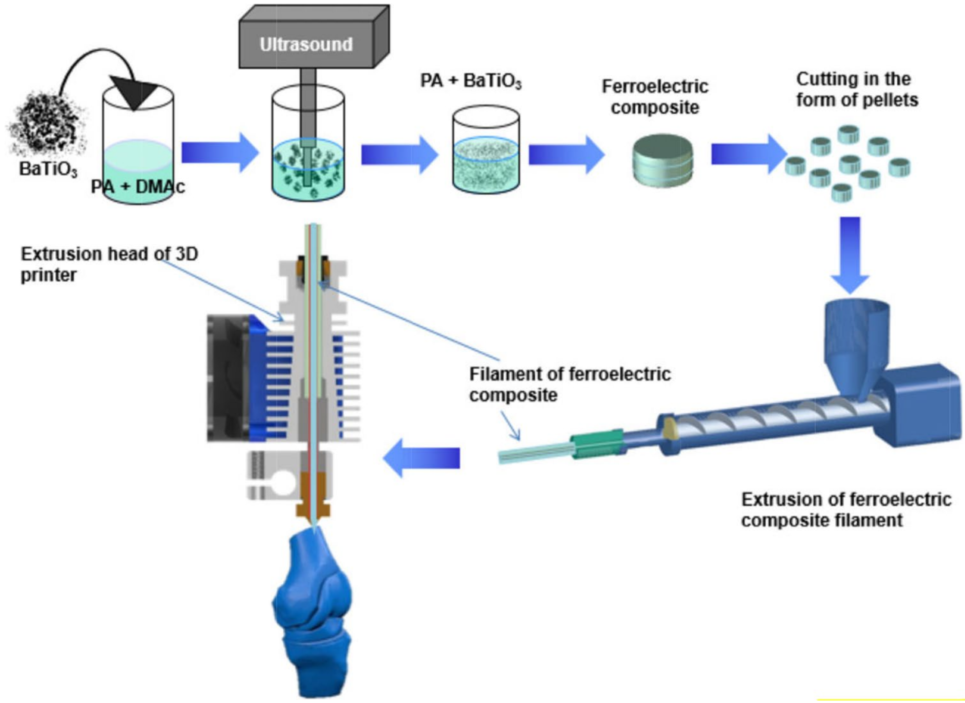


Fig. 8 Fabrication process of 4D printing ferroelectric composite sensor. Reproduced from ref [89]. with permission from John Wiley and Sons

reaction between two electrical and mechanical modes in insulating materials that do not have central symmetry. Piezoelectric materials are those that possess certain levels of charge if pressure or stress is applied to them. Materials with piezoelectric properties are advantageous for 4D printing and medical applications, particularly in medical domains such as implant technology [89]. This smart implant can provide information at any moment such as the force entering itself, the temperature at that moment, and also the residual life [89]. Barium titanate (BTO) piezoelectric materials were 4D printed due to biocompatibility and safety for the implant processes [89]. Figure 8 shows fabrication process of 4D printed ferroelectric composite sensor [89].

As mentioned, the main limitation of 3D printing technology in the field of orthopedics is the inability to grow and shape-changing the implants in accordance with appropriate conditions and age of people. Therefore, to address this major limitation, researchers focused on the development and advancement of smart materials to overcome this problem. Investigators and scientists are constantly concentrating on the potential applications of 4D printing technology. 4D printed orthopedics implants can grow as in human bodies are exposed. The shape-changing is the crucial issue to present this technology in the orthopedic areas. These orthopedic implants rapidly react to physical stimulus and also can change their shape and morphological position in accordance with required conditions [75]. These features of 4D printing allow a new perspective of the applications of implants in orthopedics fields. Additionally, researchers hope that with the advancement of imaging methods such as 4D CT scan and 4D MRI, they will be able to manufacture intelligent orthopedic implants in the future that have a similar function to natural tissues [22].

8.2 Bio-printing

Bio-printing means constructing living structures, such as tissues, organs or cells by means of 3D/4D printing [90]. In other words, according to the definition provided by Chua et al., bio-printing means "the use of material transfer processes for patterning and assembling biologically relevant materials–molecules, cells, tissues, and biodegradable biomaterials–with a prescribed organization to accomplish one or more biological functions" [91]. This technology has been used for tissue engineering [92, 93], tissue regeneration [94], neural engineering [95], cell production [33, 96], biofabrication [96], and pharmacy [5]. Nowadays, through the use of bio-printing technology, researchers have been able to construct and commercialize unaffected tissues, such as skin, but in terms of printing complex tissues, more research is needed [97].

Bio-printing technology has three necessary steps. Firstly, choosing materials, analysis, and data collection from the tissues and organs. In the next step, the data collected will be converted into an understandable electrical signal for the device, and in the last step, the tissue or organ is printed by the machine [98, 99]. A bio-ink is necessary for bio-printing purposes. These bio-inks determine the structural features of printed tissues or organs. Bio-inks have been made from biomaterials such as fibrin, collagen, gelatin, silk, alginate, cellulose, chitin, matrigel, and hyaluronic acid [100, 101]. It can also be used as a single, multiple, or a mixture with different materials [42]. The printer's bio-ink must have physicochemical characteristics such as chemical, mechanical, biological, and rheological [97]. Moreover, stem cells like human bone marrow stem cells, and embryonic stem cells (ESCs) can be used as bio-ink [102, 103]. Stem cells can be used to print vital organs as well as to regenerate damaged tissue such as skin wounds, as these cells have self-repair properties [104, 105]. Also, to fabricate electro-active tissues or organs, such as skeletal muscles, cardiac and neural tissues, biomaterials and nanomaterials are combined [106]. Zhu et al. combined G-GNR/GelMA pre-polymer and alginate pre-polymer to print a living construct [107].

Various methods can be used in bioprinting, such as extrusion printing, stereo-lithography, inkjet printing, laser-assisted, and DLP-based printing dynamic optical projection stereolithography (DOPsL), but use of the extrusion technique is more common [97, 108–110]. DLP and injection techniques are usually used to reconstruct complex and multicellular tissues [111, 112]. Among these methods, extrusion printing is mostly used because of its features such as being compatible with ink, high-throughput and cost efficiency [113]. Despite the advantages of extrusion printing, it has disadvantages as follows: the nozzle must always be adjusted carefully and it may also be flawed due to the interruption of the ink in the printing process [114]. The differences in the methods are shown in Fig. 9 [49]. In the relevant work, Koch et al. fabricated 3D complex skin tissues using 3D bio-printing technology. They used 20 layers of fibroblasts (murine NIH-3 T3) and 20 layers of keratin (human HaCaT) that were set in collagen to build a sample of the skin by using the laser-assisted technique [108]. Skins made with 3D printer technologies have some drawbacks:

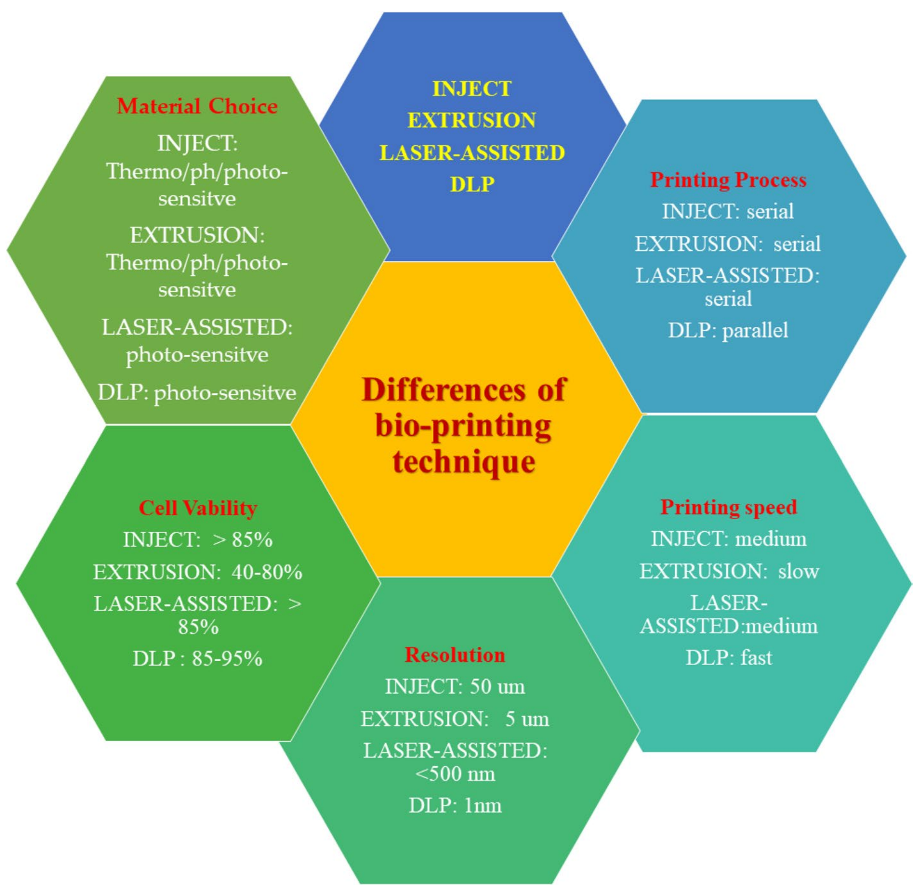
1) They cannot repair vessel networks.
2) They cannot transport nutrients and oxygen well.
3) They cannot dispose of waste [98].

It is expected that in the future development of 4D printing technology and smart materials, these limitations will be eliminated.

8.3 4D bio-printing

Although 3D bio-printing has advantages and applications, one significant limitation of this approach is that it considers only the original state of the printed structure and assumes it to be lifeless [96]. For example, living tissues have dynamic structures, so they can repair or regenerate themselves when

Fig. 9 Summary of differences between bio-printing methods presented in this review



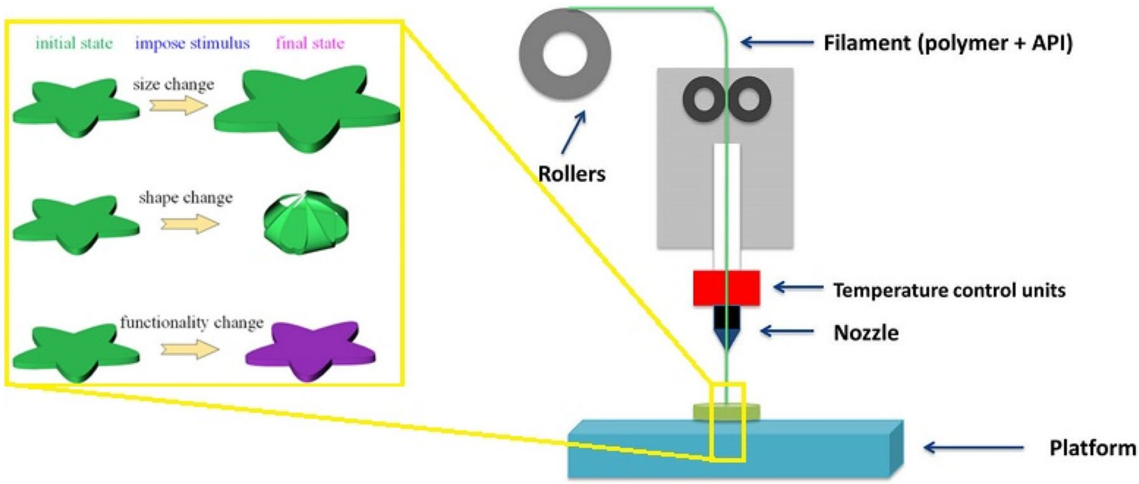


Fig. 10 Illustration of 4D bio-printing technology. Reproduced from ref. [86] with permission from John Wiley and Sons

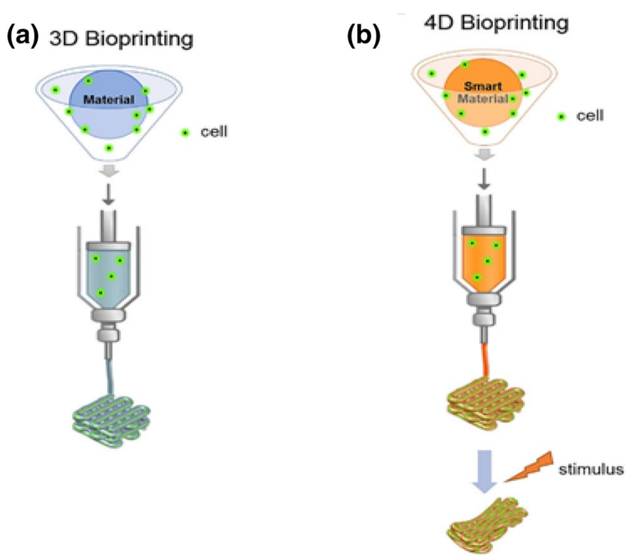


Fig. 11 Schematic of differences between 3 and 4D bio-printing technology, **A** 3D bio- architect, and **B** 4D smart bio-architect. Reproduced from ref [33]. with permission from John Wiley and Sons

they are damaged, but 3D bio-printing is not able to fabricate dynamic structures. According to Fig. 10, 4D bio-printing has been developed as a great approach where the fourth dimension, "time", is combined with the 3D bio-printing techniques. The printed bio-architects have the ability to reshape or change their functionalities when affected by stimuli [86].

Based on Fig. 11, in comparison with 3D bio-printing, 4D bio-printing uses smart biomaterials and cell traction forces that allow this approach to create lively and dynamic structures [33]. In addition, comparing 4D bio-printing with other cell deposition approaches, the structures made with this technology have a higher resolution. Using the potential and techniques of 3D printers with smart materials allows us to create organs similar to the native tissues [96]. Although 4D bio-printing is similar to 3D bio-printing, the main difference is that when undergoing a unique stimulus, the structures printed by 4D bio-printing can exhibit physical/chemical changes in their morphology. Therefore, the use of this feature gives 4D printing good potential for use in tissue engineering, organ transplantation, bio-robotics, and biosensors [33]. The principal benefits of 4D bio-printing are the capability to mass-produce tissue-engineering outputs, high-resolution printing such as different types of cell and the capacity to make excellent cell density tissues [91].

8.3.1 Drug delivery and bio-adhesion

Another application of 4D bio-printing is related to pharmaceutical, bio-adhesion, and drug delivery systems where drugs or cells are encapsulated and then released under the influence of a particular stimulus.

To produce a proper drug delivery device with 4D printing technology features, researchers must consider a number of factors and areas such as materials, chemical engineering, biomedical engineering, pharmacy, and pathophysiology. According to a report by Lu et al. [86], three main models can be used in bio-printing for drug delivery purposes: progressive, self-regulated and directly activated.

Mirani et al. [115] presented an example of innovation in the bio-adhesion field. They introduced a multifunctional hydrogel-based smart dressing for diagnostics and treatment of the wound. It consists of two fundamental parts: pH-responsive sensors and drug-releasing scaffolds [115]. The general mechanism of this system is that the amount of infection is measured by sensors, and then, the drug is passed through the scaffolding and injected into the wound. As displayed in Fig. 12(a), the sensors of the intelligent

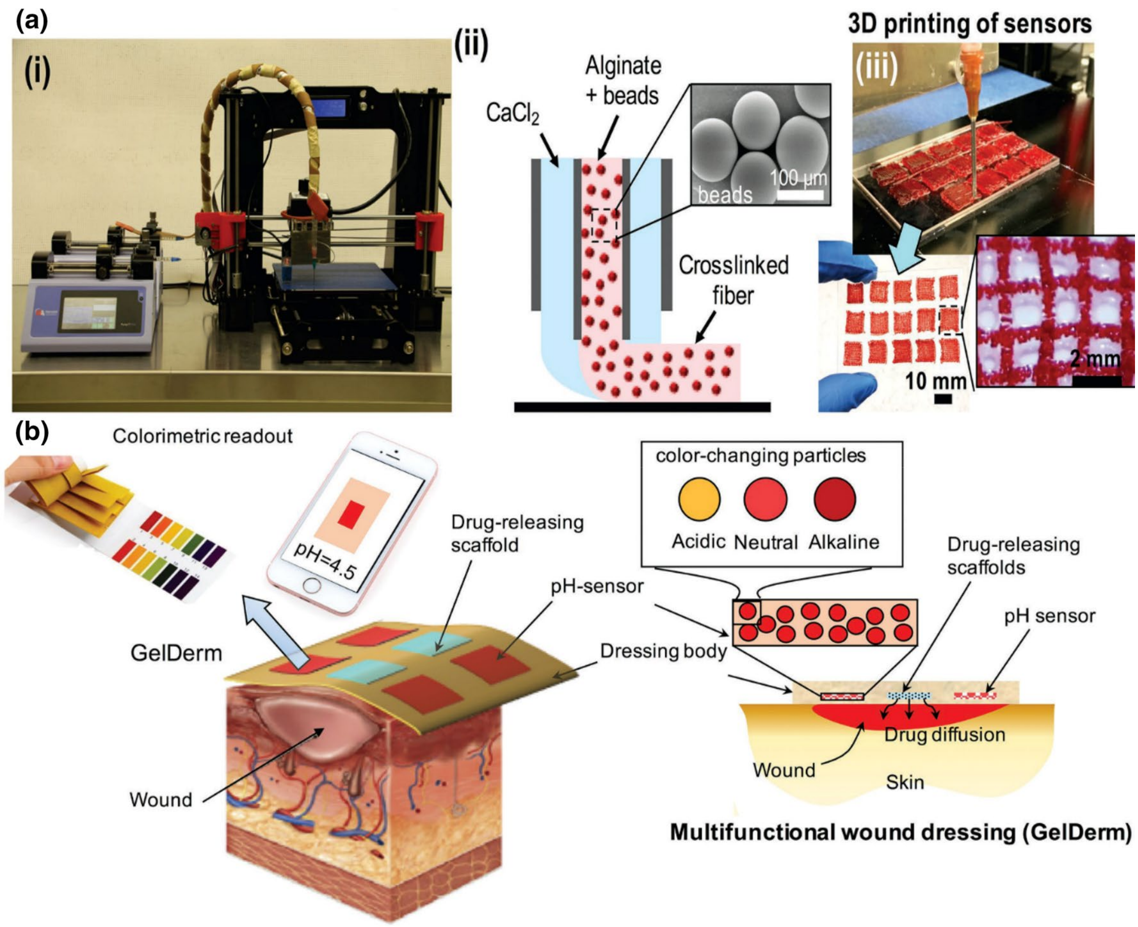
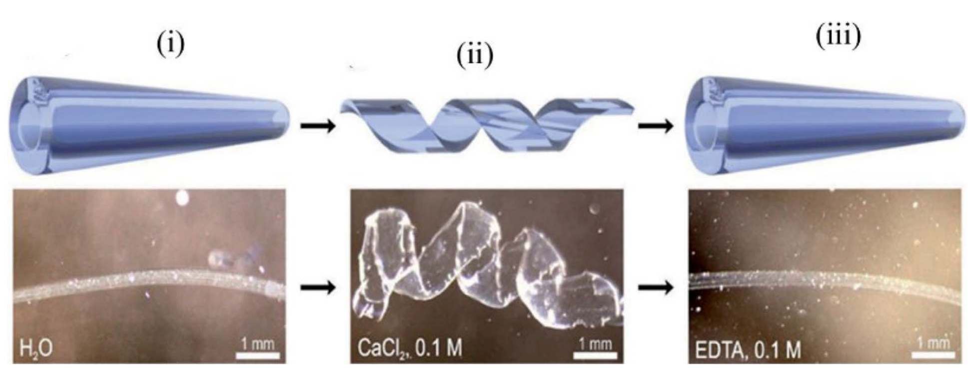


Fig. 12 Schematic of advanced Multifunctional Hydrogel-Based Dressing; **A-(i)** Bio-printing system to fabrications smart sensors, **A-(ii)** type of biomaterials which been used to sensors printing, **A-(iii)** Illustration the final sensors. **B** Description of GelDerm diagnostics and treatment system, with pH-sensitive sensors and drug-releasing scaffolds ingredients. Reproduced from ref [115]. with permission from John Wiley and Sons

bandage system are fabricated by 3D bio-printing techniques and smart materials. Figure 12(b) shows the overall function of this drug delivery system. The advantage of this smart system over traditional dressings is the ability to diagnose and treat simultaneously [115].

Thermal and liquid responsive polymers have excellent potential for encapsulation purposes because of their self-folding and self-swelling features; for instance, Azam et al. [116] were able to build a polymeric capsule that contained cells, and as the temperature of the capsule rose inside the body, the capsule was able to release the cells inside the body due to the self-folding feature of SMPs. A novel approach for bio-printing was introduced by Stoychev et al. [117]. They used multiple stimuli-responsive materials

Fig. 13 Display 4D bio-fabrication cell-laden tube in different liquids phases, **i** Tube response to water, **ii** tube response to $CaCl_2$, **iii** Tube responds to the acid. Reproduced from ref [118]. with permission from John Wiley and Sons



(PNIPAAm and PCL) to create an intelligent bio-scaffold that could release drugs or cells with changes in temperature.

As mentioned above, liquid responsive materials offer various benefits for cell encapsulation and drug delivery systems. For instance, Kirilova et al. [118] they have developed 4D bio-fabrication cell-laden based shape morphing hydrogels capable of self-folding and responding to several liquids (Fig. 13). Nevertheless, they are subject to concerns about delayed response time, weaker mechanical properties after expansion, and possible degradation/hydrolysis after numerous swelling circles. These concerns need to be considered, principally, when assessing the material's intended life span [26, 119].

8.3.2 4D bio-printing for tissue engineering purposes

Accidents are typical during human life and may be due to the fracture and damage of soft or hard tissues such as ligament rupture or bone defects. On the other hand, diseases such as cancer and diabetes can lead to dysfunction of other organs in the body or even lead to amputation. With the advancement of 4D bioprinting technology, many interesting novelties bring us the possibility of resolving the problems that exist with 3D bio-printing. In other words, this innovative technology enables researchers to build dynamic tissues with the ability to self-repair or self-regenerate. In relevant example, as shown in Fig. 14, Bakarich et al. [28] developed a 4D bio-printing smart valve that can control the flow rate of water under the influence of a temperature stimulus.

In relevant work to neural tissue engineering, Miao and colleagues are introduced a 4D programmable culture substrate self-morphing with capability to address improving dynamic cell growth and induce differentiation of stem cells [120]. They are printed 4D Self-Morphing Culture Substrate for culture and differentiation of neural stem cells (NSCs) via three various 3D printing methods (FDM, extrusion, SLA). As shown in Fig. 15, at the beginning, a sacrificial micropatterned poly (vinyl alcohol) (PVA) cylindrical pattern was manufactured through an FDM 3D printer, which was utilized to make Polydimethylsiloxane (PDMS) [120]. The printer's ink, including bisphenol A diglycidyl ether (BDE), poly(propylene glycol) bis(2-aminopropyl ether) (PBE), and decyl amine (DA), was then extruded into the PDMS mold to obtain an aligned micro-structured 4D substrate. In the following, microwells were printed via the SLA method. They reported the 4D culture substrate demonstrates a time-based self-morphing process that plays a critical role in controlling NSC behaviors in a spatiotemporal manner and improves neural differentiation of NSCs along with important axonal alignment.

The importance mismatch of mechanical properties between the native tissue and the implanted medical tools such as occluders is tending to cause wear and even perforation [121]. On the other hand, the restricted biocompatibility and non-degradability of Nitinol-based occlusion devices can readily guide to crucial complications, such as allergy and corrosion.

In relevant work to cardiac tissue engineering, recently scientists have succeeded in fabricating occluders devices for the left atrial appendage through 4D printing [121]. As shown in Fig. 16, Lin and colleagues 4D printed absorbable left atrial appendage occluders whose capabilities to activate and shape-changing under influence of heat and magnetic field stimulus. In this study, researchers prepared a multi-stimulus composite with blending PLA and Fe_3O_4 and printed single and double layer occluders devices for atrial left appendage via an FDM 3D printer.

These parts have the capability to remote-control 4D transformation due to the presence of magnetic nanoparticles in occluders structure. Due to its bioinspired design, suitable mechanical properties, good biocompatibility, and biodegradability, it seems to be used as a substitute for nitinol-based occluders.

The 4D bio-printing dynamic tissue scaffolds would be one of the most attractive medical applications in this technology. Nevertheless, the influence of reshaping or changing

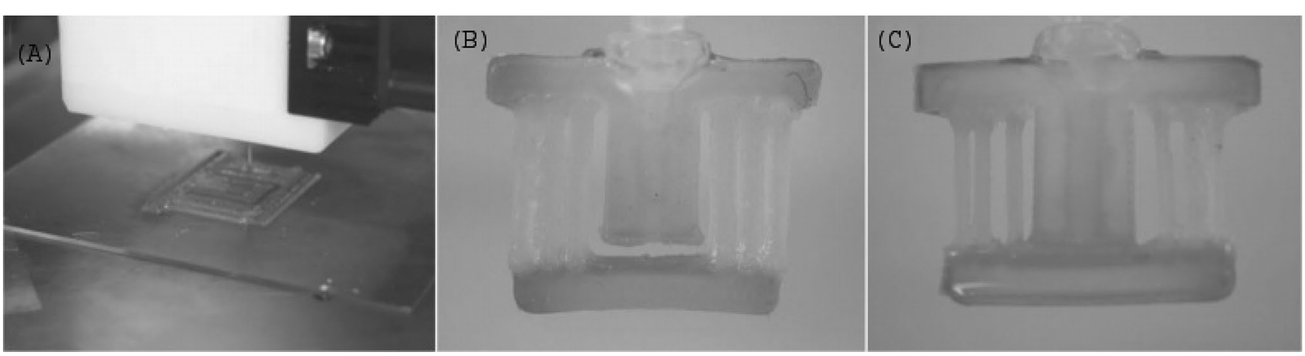


Fig. 14 Description hydrogel-based Smart valve. **A** The processes of bio-printing valve. **B** The 4D printed smart valve swollen in water at 20°. **C** The 4D printing valve self-swollen in water at 60 °C. Reproduced from ref. [28] with permission from John Wiley and Sons

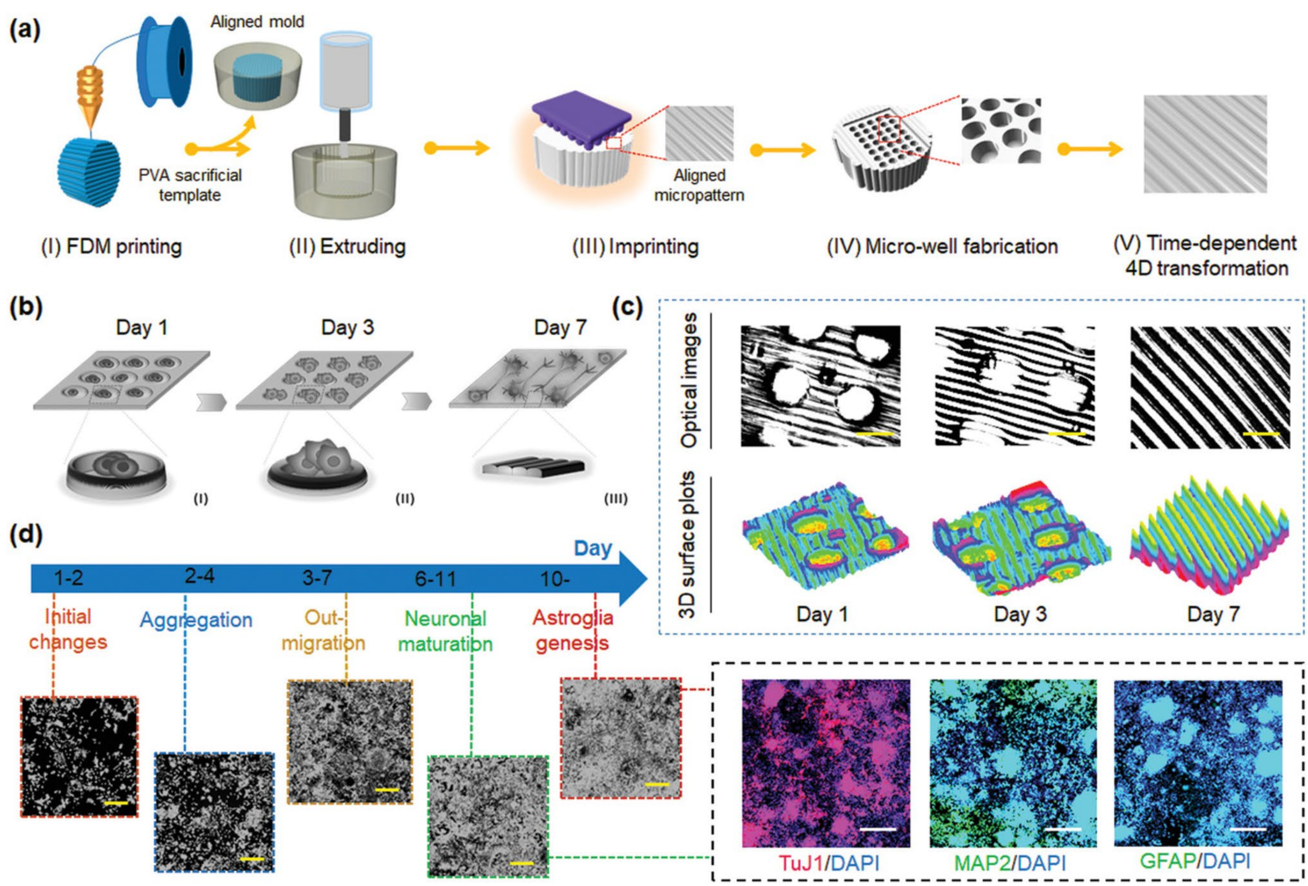


Fig. 15 Illustration of manufacturing process and characterization of 4D printed substrates for neural tissue engineering with shape memory polymer (SMP). **a** Illustration manufacture processes of microwell arrays to create 4D printed cell culture substrate. **b** Schematic illustration of the time-dependent 4D transformation of substrate within 7 days cell culture. **c** Optical images and 3D surface plots of the 4D substrates, displaying their shape-changing from microwell arrays to grid pattern during 7 days (scale bar: 800 µm). **d** Schematic illustration of microscopic images shows time-dependent differentials behavior of NSCs after 14 days from cell culture (scale bar: 200 µm). Reproduced from ref. [120] with permission from John Wiley and Sons

cell function requires more research to obtain a controllable fashion for inducting bio-tissue development [42]. In another research that was been done in this area, Li et al. [122] built a scaffold that has the capability of cell growth on its surface. They could fabricate scaffold using polymer/hydrogel composites and bioprinting, which has suitable mechanical properties in the tissue engineering field, such as printing the artificial bile duct.

In another study, Alagoz et al. conducted a study via bioprinting in the field of the additive manufacturing process [123], This shows how coating a layer on tissue engineering can improve the bone texture's mechanical properties.

8.4 Major contributions of the study

With the advancement of 4D printing technology, new opportunities have been emerging to produce biocompatible parts that perform a better function in patients' bodies. This interesting technology allows researchers to manufacture smart and patient-specific products through stimuli-responsive materials. The significant point in this regard is to have sufficient knowledge about intelligent biomaterials and their stimulus because the most important and effective parameter for desirable application in the medical field is the identification of smart materials. In addition to this important factor, other influential aspects such as fabrication techniques and design methods are of great importance in 4D printing. Drug delivery systems, smart orthopedic implants, and wound healing sensors produced by this technology have attracted a lot of attention because these smart products are able to provide purposeful and appropriate performance in requirement conditions. The main contributions of this paper are to discuss the latest advances in 4D printing in the medical engineering field, along with the limitations and future outlook of this technology, in order to provide a deeper perspective for researchers to better understand current achievements and find solutions to facilitate existing challenges. Briefly the main contributions of this paper are below:

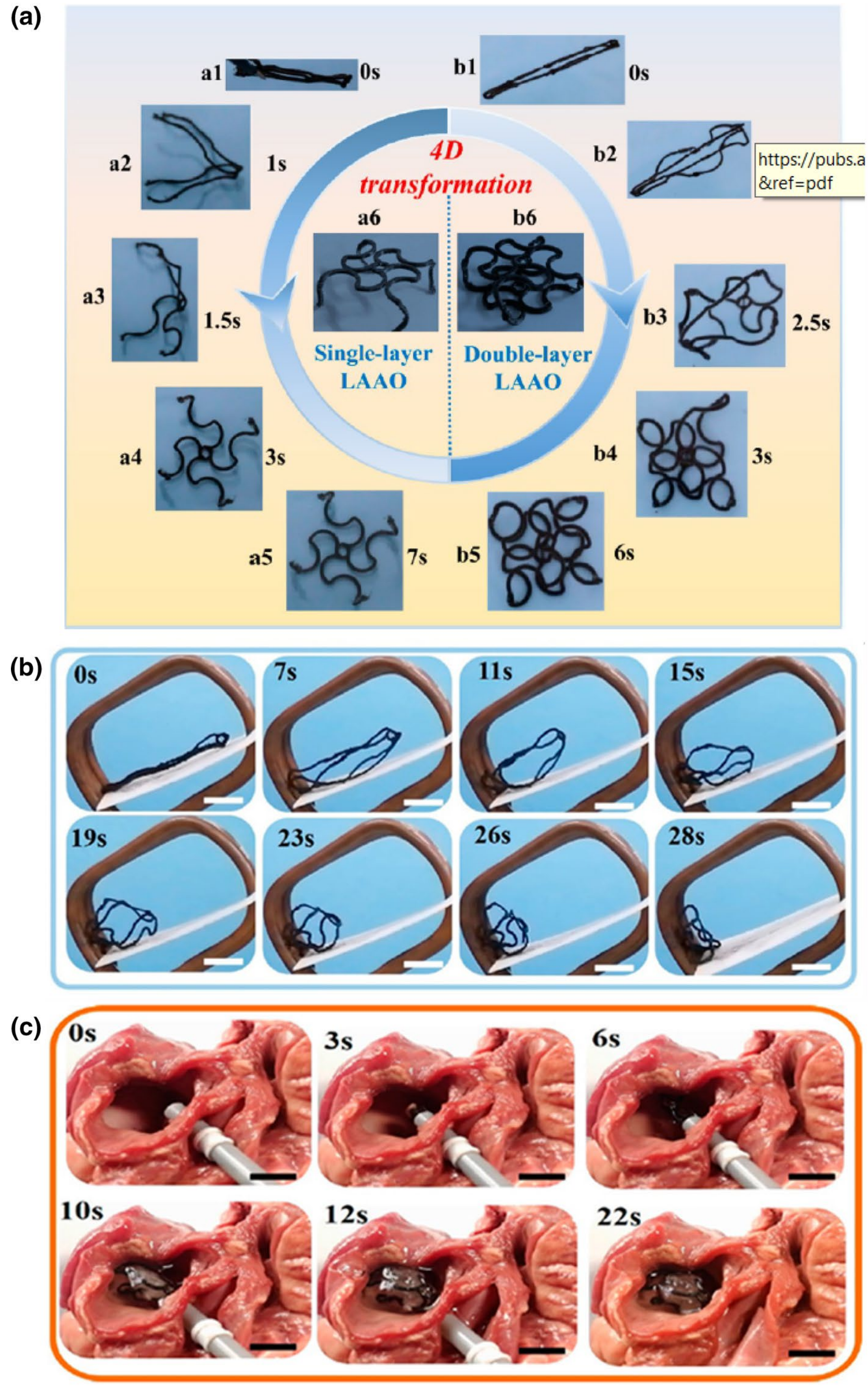


Fig. 16 Schematic of 4D printed bioinspired absorbable left atrial appendage occluders. **a** Shape-changing behavior under the influence of heat stimuli in single and double layer of occluders. **b** Shape-changing behavior under the influence of magnetic stimuli. **c** Schematic of feasibility and 4D transformation of implanted transcatheter in to swine heart tissue over time. Reproduced from ref. [121] with permission from ACS Applied Materials & Interfaces

- 4D printing technology manufacture smart parts with stimuli-responsive materials.
- 4D printed products can be a respond to a variety of stimuli and can exhibit shape-changing behavior.
- 4D printing is able to fabricate bio-architectures with dynamic structure, while this was not possible in 3D printing.
- This technology has been promising applications in various fields of biomedical such as tissue engineering, orthopedic implants, and drug delivery systems.
- Despite all the benefits of 4D printing, there are some drawbacks and limitations; however, if these challenges are addressed in the future, it is expected that this tech-

nology will have a promising prospect in the medical engineering field.

9 Limitations and future outlook

As explained in this paper, there has been a fast and promising growth in the 4D printing concept, particularly for medical engineering applications, that has tempted considerable interests in the last decade. However, this quick development can only be regarded as the early start of what 4D printing technologies are expected to present. Investigators in the biomedical area are facing certain challenges toward the presumption of 4D printing in the fabrication of dynamic engineered structures such as soft actuators, targeted drug-loaded systems, and customized-smart implants. Currently, three major challenges zones can be categorized as technological-based challenges, materials-based challenges, and design-based challenges.

The major limitation regarding technological challenges is related to printing methods. Currently, 3D printing techniques that are also used in 4D printing are limited. For example, although extrusion-based 4D printing is cost-effective and allows researchers to use multiple-materials, but on other hand, it offers a lower printing resolution compared to the laser-assisted printing technique, However, it is worth noting that the use of the laser-assisted method is expensive and only allows researchers to use single-material as printer ink [124]. Therefore, it seems that in order to achieve the aims of 4D printing and the manufacturing of smart products, 3D printing techniques must be optimized based on the use in 4D printing technology.

Regarding design-based challenges, one of the significant restrictions is the lack of special software for 4D printing. Up to date, most of the available software such as design and slicing software have been prepared for use in previous fabrications methods like 3D printing and so far, and no powerful software has been introduced to meet the requirements of 4D printing technology. For example, most existing slicing software, such as Cura and Simplify3D, are developed to work with FDM 3D printers along with filament-based materials that do not meet the essential requirements of 4D bioprinting. Therefore, it is recommended to introduce and develop powerful software for future works with the aim of more significant efficiency in 4D printing technology. In addition, the inability to control the timing and rate of response to stimuli in the biological parts that are implanted in the human body is among the design-based limitations. To this end, internet of things (IoT) and artificial intelligence (AI) systems can be used to solve these issues in future research [125].

The third issue of concern in this emerging technology that researchers are facing is material-based challenges. Most of the materials used in 3D printing technology cannot be used in 4D printing due to non-response to stimuli. In other words, conventional materials cannot change shape and form under the influence of external stimuli. Therefore, we face limitations in selecting materials for use in the biological field, especially tissue engineering and tissue regeneration. In other words, the number of intelligent materials that can be used in 4D printing is limited and they usually react only to a specific stimulus. The complicated physiological conditions of the human body are stabilized by various regulatory procedures [126]. Thus, stimuli-responsive materials triggered by several physiological signals are desirable in the medical area. To this end, it is suggested that new smart materials be introduced in the future that has the ability to respond to multiple stimuli. In addition, the discovery or introduce of smart materials that are capable of dual responses such as reshaping and color change, or resizing and changing functions simultaneously could give researchers more opportunities and capabilities to produce biological constructions and drug delivery systems.

Notwithstanding, the emergence of 4D printing technology, the progress in this technology has already demonstrated its effectiveness in medical engineering. Regarding the rapid and continued development, 4D printing is predicted to gain its top prospect soon, with the development of inexpensive, high-accuracy printer devices, and most significantly, with the finding of novel smart bio-materials.

10 Conclusions

4D printing technology has grown extensively in the last decade. Since its beginning and has extended its impact in various industrialized areas. 4D printing commonly utilizes additive manufacturing techniques with stimuli-responsive materials to induce a shape-changing mechanism with the passage of time. It supplies more excellent flexibility and adaption as one printed object can potentially serve considerable operations. In other words, 4D printing is the new generation of 3D printing. Stimuli-responsive materials used in this technology are of great importance as smart materials, and 3D printing technology allows printed structures to be dynamic. This characteristic shows that 4D printing has excellent potential in the future. To date, it has been used successfully in fields such as tissue engineering and organ transplants, which require dynamic constructions. Also, 4D printing can be developed using imaging methods such as CT scans and MRI to fabricate customized implants, specific prosthetics, and anatomic models. Even though many advancements have been made, 4D printing is nevertheless at an initial stage. Therefore, more research is required on 4D printing technology parameters, including stimulus-responsive materials, imaging methods, additive manufacturing approaches, and stimulus. Also, the material restricts the advancement of 4D printing. The materials used for 4D printing should be sensitive; however, not all materials are stimulus-responsive materials, and not all stimulus-responsive materials can be used for printing devices. Furthermore, most of the materials are only responsive to a unique stimulus. Therefore, exploring new responsive materials and making the current responsive materials printable is a further path of advancement for this technology. Notwithstanding the challenges, the prospect of 4D printing technology remains promising. The ensuing spotlight could observe the advancement of larger-scale printers connecting AM methods and robotics to print the multi-stimuli-responsive-materials and further progress on the nanoscale in targeting medical drug delivery deployment within the body.

Declarations

Conflict of interest The authors declare that they no conflict of interest.

Ethical approval The authors alone are responsible for the content and writing of the paper.

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