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Bajpai, A., Baigent, A., Raghav, S. et al. (3 more authors) (2020) 4D printing: materials, technologies, and future applications in the biomedical field. Sustainability, 12 (24). 10628. ISSN 2071-1050

https://doi.org/10.3390/su122410628

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Review

4D Printing: Materials, Technologies, and Future Applications in the Biomedical Field

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Received: 24 November 2020; Accepted: 12 December 2020; Published: 19 December 2020

Abstract: 4D printing can be defined as the fabrication of structures using smart materials that allow the final object to change its shape, properties, or function in response to an external stimulus such as light, heat, or moisture. The available technologies, materials, and applications have evolved significantly since their first development in 2013, with prospective applications within the aerospace, manufacturing, and soft robotic industries. This review focuses on the printing technologies and smart materials currently available for fabricating these structures. The applications of 4D printing within biomedicine are explored with a focus on tissue engineering, drug delivery, and artificial organs. Finally, some ideas for potential uses are proposed. 4D printing is making its mark with seemingly unlimited potential applications, however, its use in mainstream medical treatments relies on further developments and extensive research investments.

Keywords: 4D printing; additive manufacturing; smart materials; shape memory

1. Introduction

Additive manufacturing (AM), commonly known as three-dimensional (3D) printing, is a popular fabrication technique due to its ability to create complex, customizable structures from a 3D computer-aided design (CAD) file [1]. It is an attractive alternative to traditional fabrication processes (e.g., moulding and machining) due to the reduction in both difficulty and cost of producing detailed customizable architectures [2]. Developments since the introduction of 3D printing in 1984 have been improved fabrication accuracy, speed, multiple materials, and costs [3]. Nevertheless, an inherent shortfall of these structures is their static and rigid nature; retaining the shape in which they were originally printed and generally only performing one function [4]. The drive to incorporate active materials into the 3D printing process to overcome these limitations has led to the development of four-dimensional (4D) printing technologies to create dynamic structures [1].

4D printing is the fabrication process of 3D objects that can change their shape over time or in response to an environmental stimulus. This process demonstrates a radical shift in additive manufacturing [5,6]. It offers a streamlined path from idea to reality with performance-driven functionality built directly into the materials [5]. With this technique, a wide range of active programmable materials can be produced which have the capability to self-transform from one shape to another [5].

Systems that respond autonomously to a change in their environment are commonly found in nature, for example, the nastic movement of leaves and flowers can be triggered by humidity, light, or touch [7]. This property had not, however, yet been achieved in manufactured objects until recently [8]. At the core of this research is the development of additive manufacturing.

Printing methods using smart materials to produce four-dimensional architectures and metamaterials. These three-dimensional structures are dynamic and have the ability to self-transform in response to a predetermined environmental stimulus, such as electricity, light, temperature, or moisture, hence creating a fourth dimension of time [9]. The shape-changing characteristics of these structures derive from the use of stimuli-responsive smart materials during the printing process, which give the structure the ability to change its function, shape, or physical properties such as Young's modulus to form selective structures and configurations [1,10–12]. This review focuses on dynamic structures with shape-changing abilities. The characteristic differences between 3D and 4D printing are given in Table 1 and Figure 1.

Table 1. Characteristic differences between 3D and 4D printing technologies. Adapted from [12].

Characteristics	3D Printing	4D Printing
Build Process	• Structure formed by sequential layering of 2D material "ink"	• Extension of 3D printing but with shape-memory programming step
Materials	• Thermoplastics, ceramics, metals, biomaterials, nanomaterials	• Smart materials: shape-memory polymers (SMP), shape-memory alloys (SMA), hydrogel composites, biomaterials,
Shape flexibility	• Creates rigid structure	• Characteristics of structure change upon exposure to external stimulus
Shape-memory programming	• No programming step	• Thermomechanical training, multi-material printing to create differential stresses
Applications	• Medicine, engineering, dentistry, automotive, robotics, fashion, aerospace, defence etc.	• Adds dynamic element to all 3D printing applications

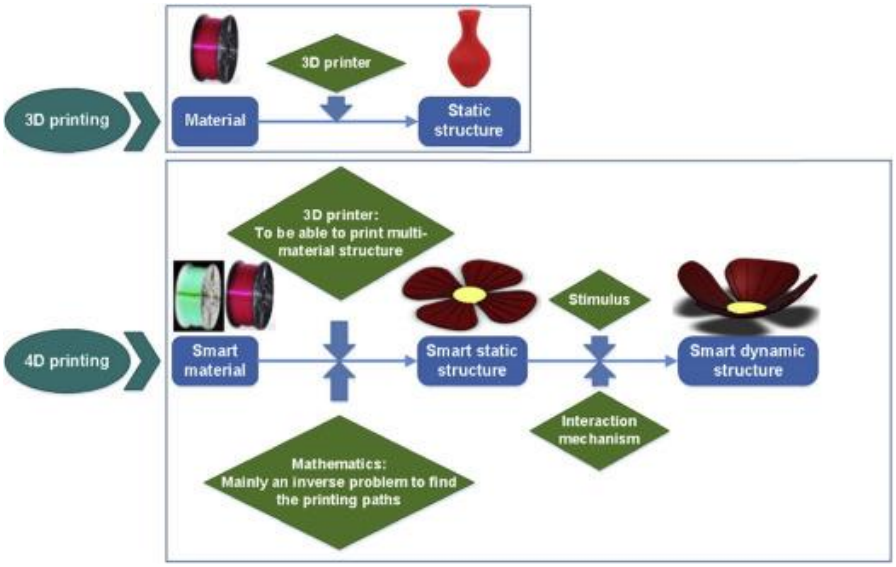

Figure 1. The key differences between 3D and 4D printing. 3D printing involves the deposition of material into a predetermined static shape. 4D printing, on the other hand, involves the careful deposition of a smart material into a predetermined, smart static structure. When this smart static structure interacts with an internal or external stimulus, it will transform its shape and become a smart, dynamic structure [13].

First introduced in 2013, 4D printing has since received great interest within material science showing potential for application within the fields of soft robotics, defence, and manufacturing, among others [14]. Fabricating 4D structures for use in tissue engineering and drug delivery systems provides a promising prospective technology for future generations, and hence this review will focus on biomedical applications [15]. This technology has the potential to supplement, or even replace, devices used in various surgical procedures, including skin grafts or organ donations. A desirable characteristic of smart materials is their ability to deform into a temporary configuration and recover to their original form by varying the applied stimulus [11]. This is called the two-way shape memory effect (SME) and has been exploited by material scientists to produce objects that can be actuated after printing [16,17]. Research developments have been successful in developing the SME to produce hierarchical self-morphing structures that can adopt multiple spatial configurations in response to a varying stimulus [18]. The structural response is dependent on both the materials and techniques used in the printing process. The shape-morphing capability is usually achieved by either (1) printing a combination of active and rigid materials in different regions of the structure to create areas of differential strain; or (2) by programming the temporary shape into the thermo-mechanics of the structure after printing. An active area for research into the SME is incorporating the thermo-mechanic programming within the 3D printing process [8,19,20]. The most suitable method will vary depending on the printing materials used and the desired structural response. Current smart materials deemed suitable include shape memory polymers (SMPs), hydrogel composites, shape memory alloys (SMAs), and shape memory composites (SMCs). However, while shape-memory materials seem to have been widely researched within material science, their conjunction with 3D printing is a relatively recent venture. Most AM methods such as Stereolithography (SLA) and Fused Deposition Modelling (FDM) involve the sequential deposition of layers of material onto a building platform [21]. These processes can fabricate devices on the nano/micro scale showing potential for use in drug delivery systems (DDS) and minimally invasive surgical systems [22]. The potential for this technology to develop customizable dressings, drug delivery systems (DDS), and implantable organs is surveyed within Section 4. Through the addition of the fourth dimension, 4D printing is seen as being particularly well-suited to the biomedical field, with current research focusing on drug delivery systems (DDSs), tissue engineering, regenerative medicines, and biomimicry [23]. This literature review investigates current approaches to achieve 4D printing; the principle technologies and materials are reviewed as well as recent developments and emerging applications for stimuli-responsive objects within the biomedical field. Finally, current research, future applications, and the limitations of this technology are discussed.

2. Additive Manufacturing Techniques

The 3D printing technology (also referred to as AM) is used to generate a 3D specimen in which layers of material are continuously formed under a computer-controlled program to create a physical object. ISO/ASTM52900-15 defines seven categories of Additive Manufacturing (AM) processes: material extrusion, vat photopolymerization, powder bed fusion, material jetting, binder jetting, sheet lamination, and directed energy deposition [24]. The main commercially available 4D additive manufacturing processes have been broadly categorised by their associated printing mechanisms; liquid solidification, powder solidification, and direct material extrusion [25]. These methods involve the light-curing of a photopolymer, melt-material extrusion, and direct-ink printing [26]. The technique is chosen depending on both the smart materials to be printed and the desired properties/function of the final structure. Parameters such as printing speed, laser frequency, and nozzle temperature directly affect fabrication accuracy, and hence these must be investigated and optimised to ensure the viability of scale-up for industrial manufacture. The printing process can also be chosen to enhance and facilitate the shape-memory functionality of the object. Independent of the AM technique, to fabricate a 3D structure requires a detailed Computer Aided Design (CAD) model of the physical architecture. In most cases, the design model is digitally sliced into thin horizontal layers, and the printer forms the

structure by sequentially printing each layer of the material [27]. The basic principles of commercial AM technologies are shown in Figure 2.

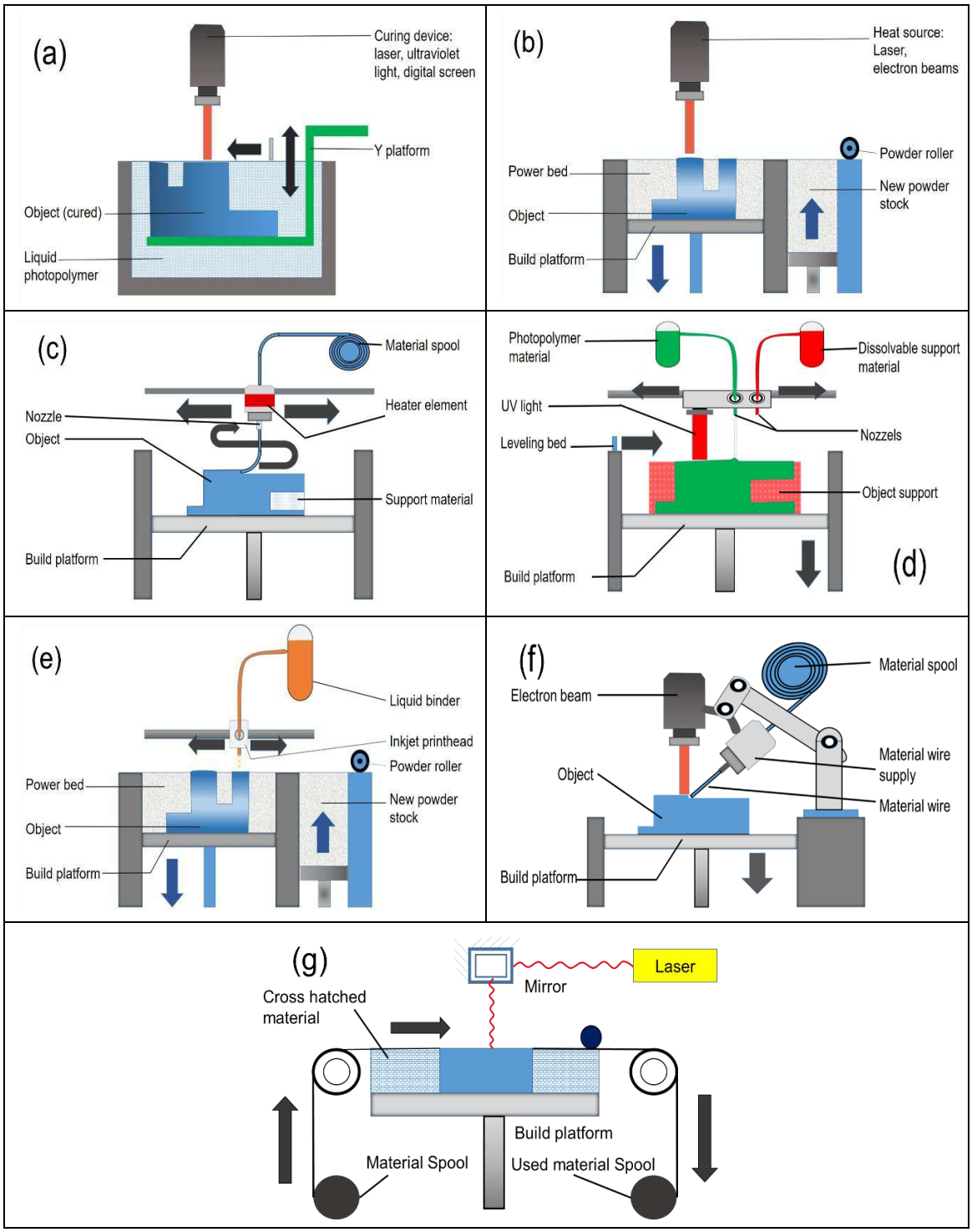

Figure 2. Different Additive manufacturing (AM) technologies used in 3D printing. (**a**) Photopolymerization; (**b**) Power bed fusion; (**c**) Material extrusion; (**d**) Material jetting; (**e**) Binder jetting; (**f**) Direct energy deposition; and (**g**) Sheet lamination. AM technologies currently used in 4D printing are fused deposition modelling (FDM); selective laser sintering (SLS); stereolithographic apparatus (SLA); and polyjet.

2.1. Vat Polymerization

This area of AM technology requires the use of a liquid photopolymerizable resin, which is hardened by curing with light layer-by-layer to fabricate the solid 3D structure. The main light-based techniques used in 4D printing are vat photopolymerization and photojetting.

2.1.1. Stereolithography (SLA)

In this technique, a monomer resin held in a vat is exposed to a UV light source, causing a localised polymerisation reaction that hardens the resin. When a layer is cured, the build-platform moves the structure to expose a fresh layer of resin to the UV light [26]. The light source can either be directed from above, known as "bottom-up" (Figure 3a), or from below through a transparent window called "top-down" (Figure 3b) [28]. Repeating these steps until the final layers are cured produces the solid 3D structure [29,30].

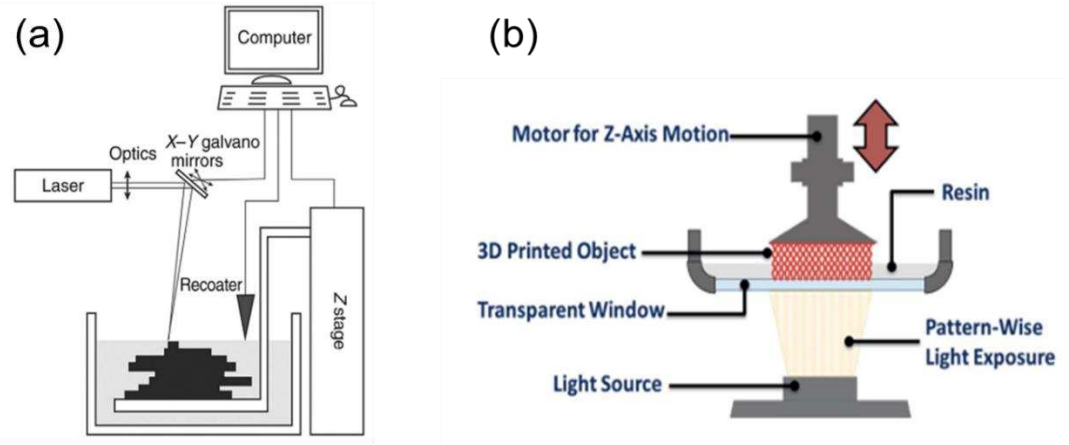

Figure 3. Photopolymerization fabrication techniques. (**a**) The light source is from above and is taken from [30]. (**b**) The light source is coming from below and is taken from [26].

Invented by Charles W. Hull in the late 1980s as the first commercially available 3D printing technology, stereolithographic apparatus (SLA) was initially adopted as an inexpensive and efficient way to manufacture prototypes and customisable designs [5,31]. SLA is now amongst the most widely used solid freeform fabrication techniques [28,32,33]. This AM process requires the use of liquid photopolymerisable and cross-linkable resins [34] and benefits from using materials that can achieve high curing rates and precise depositions when printed [32]. These material restrictions and the time-intensive nature of the vertical build-up of layers remain the major limitations of SLA as a 3D printing technology.

A major advantage of SLA is the ability to fabricate high-resolution objects of various sizes; submicron-scale to decimetre-sized objects have been produced using this method [28]. While most AM techniques can achieve structural details in the magnitude of 50–200 micron, Melchels et al. report the ability of SLA to produce details as small as 20 µm [28], and Boydston et al. have SLA-printed SMPs with accuracy between 0.1 mm and 1 µm [26]. This indicates the suitability of stereolithography for the fabrication of intricate biomedical devices where small, detailed structures are required for deployment within the body.

The area of liquid photopolymerizable smart materials is in its infancy, with only a small fraction of those available being biocompatible and therefore suitable for biomedical use [28,34]. Research efforts are being made both to enhance the properties of those already available and to discover new ones. For example, a review by Melchels et al. reports various biomaterials suitable for use with SLA to create porous structures for tissue engineering applications [28]. SLA is also suitable for multi-material applications and has been utilised by Arcaute et al. to fabricate shape-memory composites (SMCs) [34]. SLA and other light photopolymerization-based techniques provide an accurate and simple fabrication

process for creating dynamic architectures. If further developments can be made to improve printing speeds, this technique shows potential as a method for mass-manufacture of intricate 4D structures for biomedical applications.

2.1.2. Digital Light Processing (DLP)

Another light-based AM technique with the potential to fabricate biomedical devices is a digital light projection (DLP). This technology utilises a digital mirror device (DMD) containing several million mirrors. A 2D pattern of pixels is projected onto the mirror, which allows instantaneous polymerisation of the entire resin, as shown in Figure 4. By rotating the digital mirror device (DMD) and breaking contact with the light source the device can be turned on/off. The print times are only dependent on layer thickness and exposure times since the entire layer is cured at once [28].

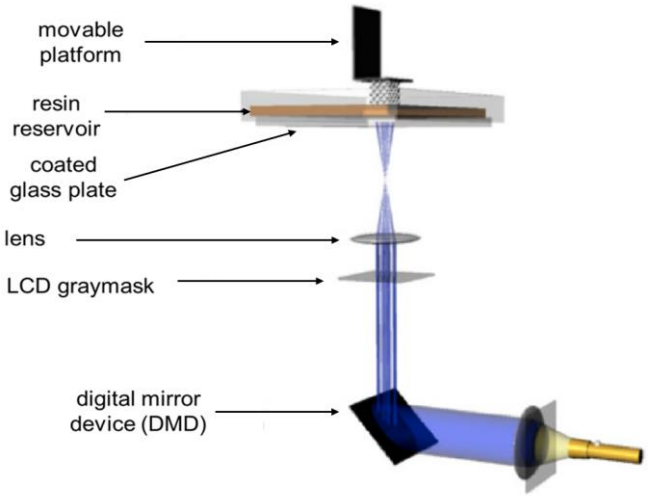

Figure 4. Top-down digital light processing AM technique. Taken from [27].

DLP is a suitable technique for fabricating SMPs, as recently evidenced by Invernizzi et al., who 4D printed a new thermo-responsive SMP material comprising of polycaprolactone (PCL) chains with cross-linked 2-ureido-4 [1H]-pyrimidinone (UPy) monomer units. DLP was chosen as an inexpensive fabrication technique, and the researchers were able to create a structure with self-healing capabilities suitable for biomedical applications [35].

2.2. Powder Bed Fusion

The basic principle of powder bed fusion AM techniques is the use of heat to melt or fuse a material together [26]. The main techniques in this area are selective laser sintering (SLS) and selective laser melting (SLM), which melt powders of polymers and metals, respectively [36]. These techniques do not require the use of any supports due to the unsintered powder compacted around the structure [37].

2.2.1. Selective Laser Sintering (SLS)

Selective Laser Sintering (SLS) is a similar technique to SLA, however, a high-powered laser is used to sinter a photopolymer powder rather than a liquid resin [37]. The newly formed layer is formed by sintering of the powder by an incident laser beam. A levelling roller is used to spread a fresh layer of powder over the previously formed layer, and the unsintered powder acts as a support for the overhanging layers [30]. The process of powder rolling and sintering is repeated until the final 3D structure is formed. A disadvantage of this technique is that the formed structure requires thorough cleaning to remove excess powder and the high temperatures involved mean this technique is not currently suitable for bioprinting [38]. Current 3D applications for this technology include the

printing of hearing aid shells. Its ability to print biomaterials indicates its potential to fabricate various personalised medical devices [34,39].

2.2.2. Selective Laser Melting (SLM)

Selective Laser Melting (SLM) uses a laser to melt metallic powders in the same layer-by-layer process by inter-stage curing from a high-intensity laser beam [40]. This creates a homogeneous and dense 3D metallic structure removing the need for structural supports or binders [26]. The printing set-up is enclosed in a chamber as the reactivity of metallic compounds requires an inert atmosphere [40]. The 4D potential of this technology derives from the ability to fabricate both shape-memory alloys (SMAs) and single metallic smart materials [1]. For example, Shishkovsky et al. recently fabricated structures made from the shape memory alloys Ni-Ti (Nitinol) and Cu-Ni-Al using SLM [40]. Figure 5 displays the general apparatus for SLM and SLS AM techniques.

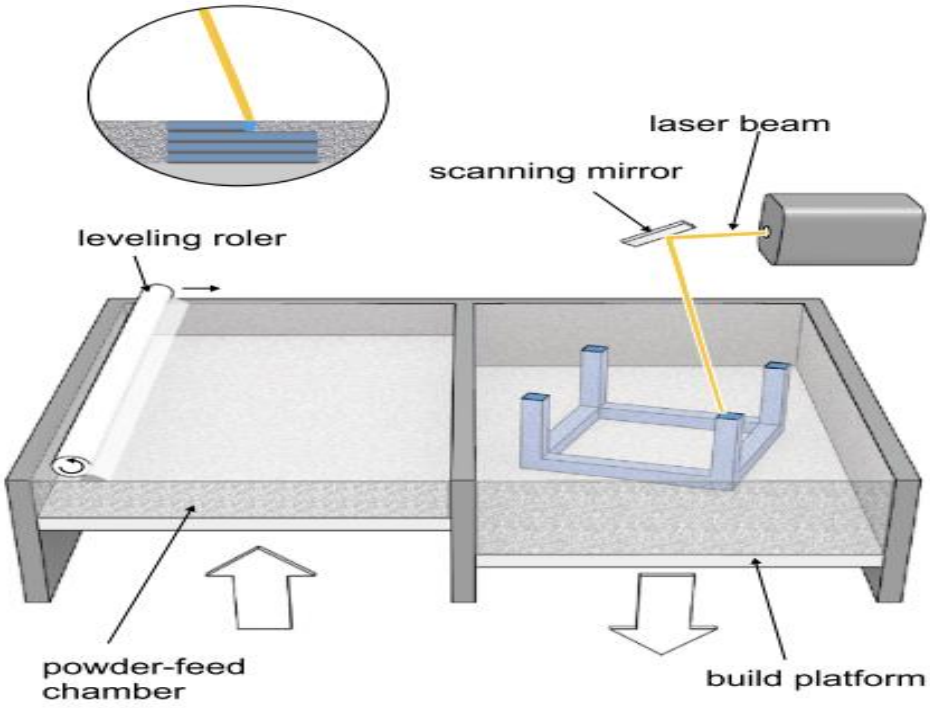

Figure 5. Apparatus for heat-based AM techniques selective laser melting (SLM)/selective laser sintering (SLS). Taken from [25].

2.3. Material Extrusion

2.3.1. Direct Ink Writing (DIW)

Direct ink writing involves controlling the orientation of an anisotropic filler within a polymer matrix. This generates stresses which are manipulated sequentially for individual pixels using ink writing. Although the time-intensive material layering and curing of light-based techniques is omitted, the pixel-after-pixel manipulation also results in slow fabrication times [2].

Slow printing times remain a major limitation, and hence an area of extensive research within both 3D and 4D printing technology. The layered process of the fabrication methods is slow and hinders the potential for wide-scale manufacture. A solution to this has been proposed by Huang et al., who reported a potential ultrafast 4D printing technique where light-curable monomers are briefly exposed to digital light, removing the need for sequential layering or manipulation of pixels. Short bursts of light exposure caused the pixels within a 2D monomer film to polymerise to different extents resulting in varying crosslinking densities throughout the material. This produced controllable differential swelling and stresses within the printed structure, which induced 3D shape morphing

capabilities of the SMP and hydrogel when immersed in water. The cross-linking densities of the smart material can be tailored by controlling the digital light exposure. Huang et al. report that this simple technique has the potential to fabricate complex geometries with shorter fabrication times because of the controllable stresses and short light exposure [2].

2.3.2. Fused-Deposition Modelling (FDM)

Fused-deposition modelling (FDM), also known as melt material extrusion (MME) or fused filament fabrication (FFF), is an AM technique based on the extrusion of thermoplastic filaments [26]. A reel of polymer filament is melted to form a semi-liquid before being extruded through a heated nozzle. The partially melted filaments solidify when deposited onto the build platform, and the 3D structure is built up from sequential layering of the extruded filaments [39]. A schematic for the mechanism (Figure 6a) and apparatus (Figure 6b) of this technique is shown below.

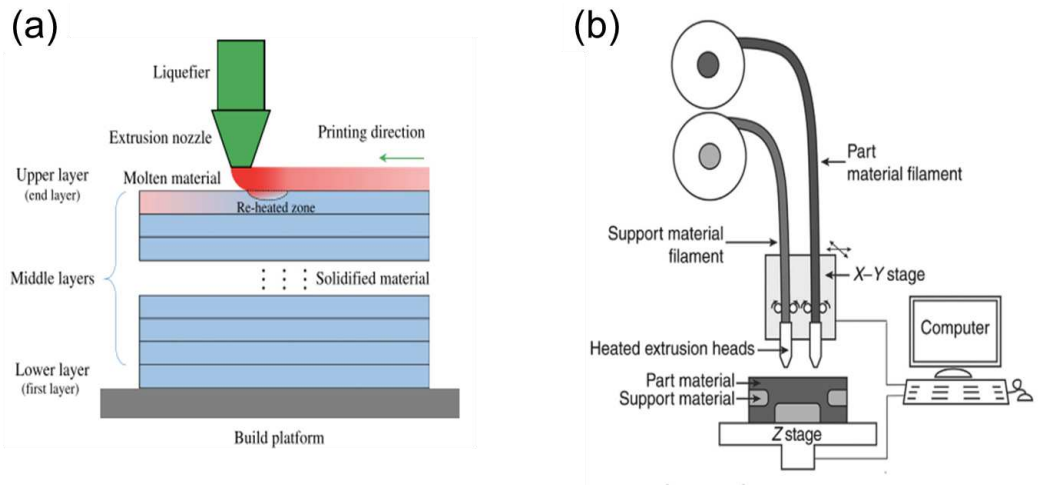

Figure 6. Fused-deposition modelling (FDM) extrusion-based AM technique. (**a**) Cross-section of printed material taken from [41]; (**b**) schematic of general apparatus taken from [30].

Filaments suitable for use in FDM have been produced from various thermoplastics, including polylactic acid (PLA), acrylonitrile butadiene styrene copolymer (ABS), polycarbonate (PC), and polyurethane (PU), which each exhibit variable stiffness, elasticity, and toughness [26]. FDM printers are simple, inexpensive, and reliable [42] with the potential to fabricate various medical devices such as modified release dosage forms for drug delivery systems, as evidenced by Goyanes et al. [39]. Bodaghi et al. have also utilised FDM to create a structure with triple-SME using a combination of hot and cold programming of an SMP [43].

Due to the high printing temperatures required, FDM can only be used with heat-resistant materials. It is therefore not suitable for printing cell-laden bioinks or hydrogels, which become denatured when exposed to high temperatures [42]. FDM is an interesting fabrication technique in the field of tissue engineering due to the potential for creating porous polymer scaffolds [27]. FDM is also unsuitable for fabricating polymers with low glass transition temperatures (T_g). Polymer filaments with low T_g lose their stiffness at ambient temperatures making extrusion through the printing nozzle almost impossible [42]. This can be prevented either by employing materials with higher glass transition temperatures or operating at temperatures far below T_g [42]. For example, a study by Kashyap et al. investigated the process of combining FDM with salt leaching to create a radiopaque, porous SMP structure with potential for use within interventional radiology [42]. The addition of fillers (Tungsten as a radiopaque agent and sodium chloride as a porogen for salt leaching) in the printing filament reduced the printability of the polymer due to increased viscosity, causing blockage of the printing nozzle. The researchers suggested incorporating a larger diameter printing nozzle to reduce blockage, but this reduced the precision and accuracy of the printed structure [42]. The group

considered that using filaments of higher stiffness at ambient conditions, hence polymers with higher T_g, could increase the pushing force and reduce blockage [42]. Extensive research is being focused on finding suitable materials for fabricating biomedical devices with incorporated shape-memory behaviour. Developments in the last decade have vastly reduced the cost of FDM printers. This supports the prospect of FDM as an inexpensive option for producing personalised medical devices such as drug delivery systems.

2.4. Material Jetting

In recent years there have been vast developments in 4D printing technologies, most notably the Photopolymer Inkjet (PolyJet) printer, which employs the photo jetting principle. Photo jetting is a 4D printing process whereby microscopic layers of resin are jetted onto the build platform. The resin is instantly cured by UV light before the next layer is deposited on top [10,26]. Recent developments have expanded PolyJet technology to facilitate multi-material printing. This works by concurrent extrusion of distinct materials through different nozzles in the apparatus. Printing both active and inactive materials in distinct areas of a structure can create hinges and joints, resulting in origami-inspired shapes that can self-fold, twist, and curl when exposed to the environmental stimulus as reported by Ge et al. [44].

Light-based printing methods such as SLA, DLP, and Polyjet, where a photopolymerizable ink is cured by light, are attractive due to their ability to fabricate detailed structural designs. There have been notable efforts into finding biocompatible liquid photopolymerizable materials, however, further research is required before there can be a wide-scale application of this technology in fabricating biomedical devices.

2.5. Microscopy Aided Design and Manufacture (MADAME)

Sidler et al. recently published a report detailing a new printing technology with potential use in fabricating wearable technologies and internal biomedical devices [15]. This technique uses multi-dimensional printing incorporated with programmable weaving to fabricate complex structures such as woven protein fibres. An interesting application of this technology is the fabrication of smart textiles for wound treatments. The textiles are tuned to individual patients' movements, can administer drugs, and can signal to the patient or carer when replacement of the textile is required. This method has further potential to produce smart dressings, drug delivery patches, and replacement body parts [15]. This study highlights the current drive to improve AM printing techniques for the biomedical industry. Table 2 displays a summary of the main AM techniques and smart materials currently used to fabricate 4D structures.

Table 2. Summary of common 4D AM techniques and applicable smart materials. Adapted from [45].

AM Process	AM Systems	Applicable Materials	Ref.
Liquid solidification	SLA	SMPs	[32]
		Soybean oil	[46]
		SMCs	[34]
	Direct laser printing (DLP)	SMPs	[35]
Material Extrusion	FDM	SMPs	[26]
		SMCs	[42]
	Hydrogel extrusion	SMCs	[47]
Material Jetting	PolyJet	SMPs	[48]
		SMCs	[44,49]
Powder solidification	SLM	SMAs	[40]
	SLS	SMPs	[38]
		SMCs	[44]

3. Smart Printing Materials

Due to the evolution of the discipline, the number of smart materials suitable for printing has increased in recent years. The smart materials used in 4D printing play an important role in receiving, transmitting, and processing the applied stimulus. The materials respond by performing the actuation; the shape-morphing, or functional modification resulting in an overall change in the structure [35]. A desirable stimuli response of the final printed structure can be achieved by exploiting the physical properties of the printing materials. Hence, the choice of smart material (or combination of materials) is entirely dependent on the application of the final printed object. For example, biocompatibility is a major issue in the fabrication of biomedical devices. A further area of increased interest is the fabrication of high-resolution structures that remain stable in both their temporary and permanent spatial arrangements.

Frequently, printing single smart materials will result in imperfect structures due to the limitations of their physical properties. By combining printing materials and employing multi-material printing techniques, desired thermomechanical behaviours can be created to facilitate controlled shape-memory behaviour of the printed structure [50]. Printing a combination of smart and inactive/rigid materials with different thermomechanical properties can allow hinges, joints, bends, or twists to be formed at interfaces in the structure, which respond to the stimulus by creating differential stresses [32,51]. For light-curing AM techniques, this can be achieved by employing printers with multiple nozzles that deposit various photopolymer liquids before curing with the UV laser [32]. For example, PolyJet printers have been modified for multi-material applications where different materials are printed within each layer of the structure [51]. Varying the composition of the printing mixture manipulates the heterogeneity of the structure and allows customisation of the material properties. In turn, this creates controllable SME initiation points and has expanded the capabilities of 4D printing [40]. For example, in the area of personalised medicine, devices can be tuned to actuate in response to temperature or moisture levels within the human body [46].

The one-way SME is exhibited when a deformed structure recovers to its original shape upon heating above its SME initiation temperature. For example, a deformed SMP will recover to its original configuration when heated above its glass transition temperature, T_g, and likewise, an SMA will recover when heated above its critical temperature. The dual-SME has the added ability to return to the temporary configuration by varying the applied stimulus (e.g., cooling). The dual-SME can be achieved by combining materials with different SME initiation points. For example, the multi-stage actuation of a thermally actuated SMP results from using multiple SMPs with varying glass transition temperatures. This creates a composite structure that will undergo several transformations depending on the applied temperature. The SMEs resulting from printing multiple materials depend on the model design and organization of the material layout [32].

The two basic requirements of a 4D printing smart material are printability and autonomous shape-memory in response to an external stimulus [11]. Biocompatibility is also a crucial property for biomedical applications, and other defining parameters may prevail depending on the chosen printing technique and desired final use. For example, photopolymerisation techniques require the use of light-curable liquid resins. The response time of a structure is the time taken to return to its permanent form, which will also vary depending on the printing materials used. Finding smart materials suitable for use with the techniques mentioned in Section 2 and those which will produce the desired response within a reasonable timeframe remains an active research area within this field. The following section examines the smart materials currently being used within the 4D printing industry and techniques used for SME programming.

3.1. Active Polymers

3.1.1. Shape-Memory Polymers

Shape memory polymers (SMPs) are a group of smart materials with the ability to inelastically deform to create metastable temporary shapes in response to an external stimulus such as light, moisture, or temperature change [32,43]. The SME can be controlled and programmed in SMPs, which makes them particularly useful for fabricating dynamic 4D structures [27]. Their low cost, light weight, ease of processing, and high programming flexibility make SMPs suitable for use within various industries, including aerospace and manufacturing, but it is their biodegradability and biocompatibility that promote their use in fabricating biomedical devices [35,43,46]. Since traditional manufacturing/processing of SMPs is still reliant on polymerisation, extrusion, and casting methods, additive manufacturing is an attractive alternative for fabricating these materials. This allows the creation of complex geometries and detailed structures [32]. Various 3D printing technologies have succeeded in fabricating structures from both single polymers and SMP composites, as shown in Table 2 [35]. The most popular group of biodegradable SMPs, according to Wang et al., are polyesters such as poly (lactic acid) (PLA) and poly-caprolactone (PCL), and polyether urethane, which are also recommended by Mu et al. for their biocompatibility [46,52]. Their application in 4D printing has attracted considerable attention in recent years. SMPs and their composites have shown potential for use as thrombus cleaners, surgical sutures, intravascular stents, and aneurysm occluders. Traditional 3D printing techniques use highly cross-linked thermoset polymer resins, resulting in hard and rigid 3D structures. To obtain the SME required of 4D-printed structures, dual-component polymers are used, which consist of a monofunctional monomer resin and a cross-linking oligomer resin [32]. The mono-functional monomer forms the linear backbone of the polymer chain. The two broad features causing shape memory behaviour in these SMPs are net-points (hard components) and switching segments (soft components) [8,32]. The traditional thermomechanical training of SMPs involves six steps, as shown in Figure 7.

(1) Heating the 3D printed structure above the glass transition temperature (T_g)
(2) Applying mechanical load to form the deformed configuration
(3) Cooling below T_g to "set" the temporary shape
(4) Removing load,
(5) Actuation
(6) Cooling

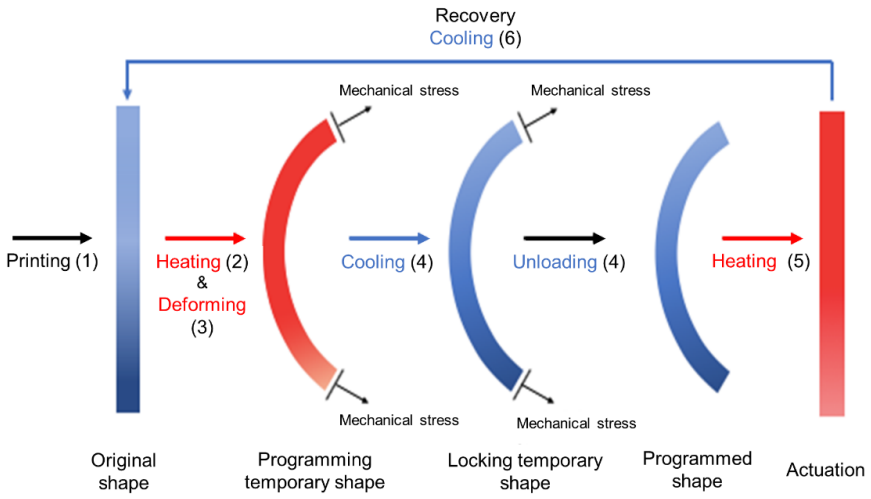

Figure 7. Thermally-induced shape memory effect (SME) programming and recovery mechanism for an SMP. Adapted from [20].

Upon heating the material above its SME initiation temperature (e.g., T_g), the monomer (soft component) facilitates plastic deformation into the temporary structure while the crosslinking oligomer (hard component) retains the "shape-memory" of the original printed configuration through thermally-stable covalent bonds [32]. Constant application of a mechanical force to deform the structure while cooling below T_g will programme the temporary shape into the material. This fixes the kinetics of the material into a higher energy state resulting in higher internal energy than that of the original structure [26,27]. Once exposed to the external stimulus (e.g., reheating above T_g), the material can surpass the kinetic barriers by releasing the motion of the polymer chain segments, and the structure will recover to its permanent shape [18,26,27].

The proportions of soft and hard segments within the SMP can be varied to tailor the thermomechanical properties of the material, such as the glass transition temperature, allowing the SME exhibited by the structure to be changed [18]. By mixing the resins which make up the polymer in different proportions, the visco-elastic properties of the polymer can be varied. For example, at temperatures above T_g an SMP will become compliant and rubbery due to increased molecular mobility of polymer chain concentrations of soft component monomer. Conversely, a rigid structure is produced at temperatures below T_g due to the restricted coiled state of the molecular chains in polymer increased concentrations of the hard component [53]. Teoh et al. report that a higher T_g increases the response time of a thermally-actuated SMP [18]. The study exploited this characteristic to achieve sequential/hierarchical response of a 4D printed structure by printing SMPs of varying glass transition temperatures. SMPs can be actuated by various mechanisms, including direct or joule heating (where electric current is passed through a conductor to release heat [53], light, moisture, pH or radiation, amongst others. However, the majority can be categorised as either thermo-, photo-, or chemo-responsive [11,53]. The most widely researched and applied group of SMPs are thermally-actuated; those which change form or function upon heating as they exhibit a variety of mechanical, thermal, and optical characteristics [19,54]. Thermo-response materials can be attractive for biomedical use if they can be tuned to respond to the temperature within the body. Mu et al. consider SMPs to offer a wide range of actuation mechanisms [52]. However, Pilate et al. suggest their resistance to electrical, light, and electromagnetic stimuli as a major disadvantage and limitation to their use [11].

SMPs provide various advantages compared to inorganic ceramics and metallic smart materials, including low density, simpler processing, chemical stability, high stress tolerance, and high recoverable strains [27]. SMPs can be fabricated to be transparent and are relatively inexpensive to produce compared to SMAs [11,51]. Their biodegradability, biocompatibility, and adjustable degradation rate make them particularly suitable for use in biomedical applications such as drug delivery systems (DDS) [11]. Their low melting points (and hence increased printability) and inexpensive manufacture have encouraged their use within AM processes compared with alternative materials [18]. 4D printing SMPs can achieve much faster printing speeds and higher structure stiffness than printed hydrogels [20]. The use of poly (ethylene glycol) (PEG) in tissue engineering applications has been widely reported [34,55]. PEG is a water-responsive polymer, so it can be employed where moisture-responsive actuation is required. For example, Yang et al. produced a two-way body temperature-responsive and one-way moisture responsive PEG with the potential to actuate in response to the temperature and moisture levels within the body [55]. Various researchers have criticised this material for having low thermal conductivity, exhibiting slow response speeds, and the requirement of low-temperature environments [11,51]. Their low tensile strength and stiffness also seem to restrict the use when firm structures are required [11]. SMPs are promising smart materials for fabricating biomedical devices, and research should continue in this field to develop their potential.

3.1.2. Multi-Shape Memory Effect (Multi-SME)

Additive manufacturing provides an alternative for encoding the SME into SMP structures from traditional methods of hot and cold programming [43]. Hot and cold programming mechanisms can

be integrated within the 4D printing process to produce SMP structures that exhibit the triple-SME [43]. Multi-SME exhibiting SMPs are structures with the ability to form more than one temporary form and sequentially recover from the temporary shapes in response to variations in the applied stimulus to return to their original form [45]. This requires the presence of multiple reversible transition points and can be achieved either by employing a polymer network comprising of multiple SMPs with different initiation temperatures or using one SMP with a wide-spanning initiation temperature. Triple-SMPs, which have two temporary forms, can achieve more complex shape-changing demands than dual-SMPs, which only deform into one temporary shape [43,56].

Mao et al. produced a thermally actuated self-folding object by 3D printing digital SMPs to form hinges in the structure when subject to temperature change [57]. The self-folding response was achieved by using materials with different glass transition temperatures, T_g. This altered the thermo-mechanics within the structure and resulted in a hierarchical response upon varying the temperature [57]. So-called digital materials have been widely used to produce sequential shape memory behaviour where multiple configurations are thermo-mechanically encoded into the structure [56,57]. Digital SMPs can be defined as composite materials comprised of multiple shape memory polymers with different SME initiation points (e.g., glass transition temperatures), resulting in sequential actuation of the structure in response to varying the stimulus (e.g., temperature).

Teoh et al. from the Singapore Centre for 3D Printing also performed research in this area and have printed a self-morphing orchid structure using SMPs of various glass transition temperatures to achieve hierarchical deformation in response to heat [18]. This study achieved shape change of both individual components (local response) and the overall system (global response) induced by heating [18]. Using different proportions of the materials VeroWhitePlus™ and TangoBlackPlus™ in each component resulted in varied glass transition temperatures and hierarchical self-folding of the orchid upon exposure to heat. Biomimetic hydrogel composites are discussed further in Section 3.1.3 [56]. Presently SMPs are used to make appliances, brackets, and occluders for biomedical applications [52]. A recent development was made by Invernizzi et al., who were able to produce a thermally actuated 4D printed SMP with self-healing capabilities [35]. This was the first study to report self-healing properties achieved in a 4D printed architecture, a desirable property for biomedical applications. The researchers concluded that the structures maintained their shape memory behaviour after healing and also highlighted their potential within the field of soft robotics [35]. With further research and development in this field, the ability to manufacture dynamic, personalised structures that mimic natural tissues may be possible. The self-healing quality of polymers can be achieved by re-crosslinking through the polymer's physical and chemical properties. Damage repair characteristics are achieved by doping the polymer with a healing agent [52]. Self-healing and repair are a major research focus particularly in the field of tissue engineering.

3.1.3. Hydrogels

A hydrogel is formed of cross-linking polymer chains made from hydrophilic monomers. The chains are arranged in a three-dimensional network that gives hydrogels their ability to absorb large volumes of water without dissolving. This makes them differ from dry-state polymers as they expand significantly upon absorbing the water and can revert to their original size when dried [58]. They were first developed by Wichterle and Lim in the 1950s, who synthesised a water-responsive polymer gel by crosslinking poly-hydroxyethyl methacrylate (PHEMA) with ethylene dimethacrylate [59]. Due to their biocompatibility, hydrogels are commonly used in the manufacture of contact lenses, wound dressings, nappies, and drug delivery systems [59]. Their 3D network structure and ability to swell with water provide conditions similar to those within the extracellular matrix [19]. This, along with their biomimetic nature and moisture-driven shape transformation, makes hydrogels suitable for various other biomedical applications such as producing structures that imitate cellular environments and replacing or improving tissues within the body [60]. Consequently, hydrogels are

a popular area of material science research and are now one of the principle polymers used in 4D printing alongside SMPs [20].

On their own, hydrogels are considered as being poor printing materials due to their soft nature, low Young's modulus (generally limited at a few hundred kPa [49]), and linear shape transformation restricting their use in biomedical devices [37]. The response period for these structures is also relatively long, particularly for large architectures, due to the swelling mechanism relying on diffusion transport. A reversible actuation cycle of 10 to 20 h was reported by Mao et al. [49]. As such, they are often combined with other materials such as non-swellable, stiff shape-memory polymers, or filaments to create hydrogel composite materials that display complex shape-morphing capabilities with increased stiffness [20,49]. The water-absorbing hydrogel can be printed alongside dry-state polymers to form hinged or jointed structures. This creates differential strains in the structure, the hydrogel swelling but the non-absorbent polymer maintaining its original form, resulting in an overall change in the configuration when immersed in water due to localised swelling [20]. This technique produces a structure that, after printing, does not require further processing to achieve the desired shape change.

The use of hydrogel composites within 4D printing processes has been explored in several clear successes to create dynamic biocompatible structures. Ding et al., for example, displayed the ability to print a thermo-responsive hydrogel composite with an inherent SME [20]. To the best of the authors' knowledge, this study was the first to propose an alternative AM technique that embeds the shape memory behaviour into the structure while it is being printed. This compares with traditional methods of thermo-mechanic training after printing or creating differential strains by printing a combination of active and inactive materials. Controlling the photopolymerisation during printing allowed the construction of high-resolution structures with embedded controllable strains [20].

The typical shape-memory programming of SMPs described in Section 3.1.1 involves a 6-stage process where the printed structure transitions temporarily to the second configuration and returns to the original printed shape by varying the stimulus. In contrast, Ding et al. produced a structure that, once printed, deformed into a new permanent shape that would not return to its printed configuration [20]. The shape change was onset by heat and the resultant configuration remained relatively stable when subject to varying temperatures, as illustrated in Figure 8.

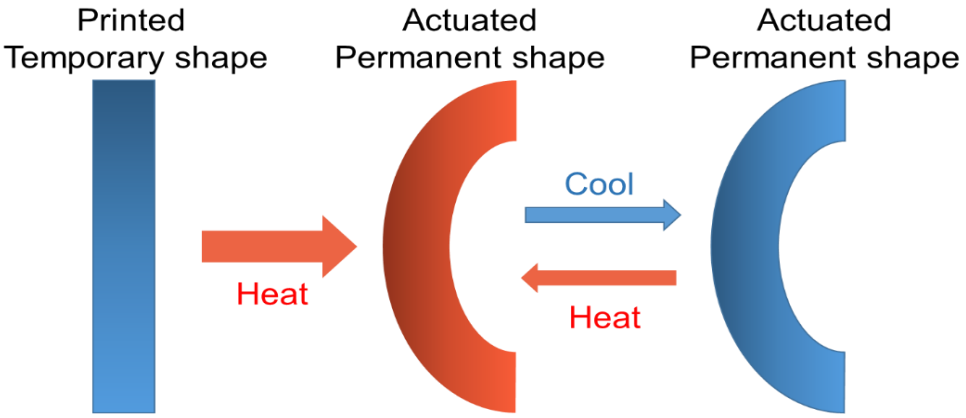

Figure 8. SME programmed during printing. Object printed in temporary shape and forms permanent shape upon heating. Actuated configuration is relatively stable and maintains its shape even when cooled. Adapted from [20].

They also discovered that the multi-SME could be achieved through further thermomechanical loading of the structure. Multiple temporary shapes were coded into the material, and the structure continuously returned to its new permanent configuration [20]. Gladman et al. have reported successes in 3D printing a biomimetic hydrogel composite ink that displayed localised and anisotropic swelling when immersed in water. In this study, stiff cellulose fibrils were embedded within an acrylamide matrix to create a composite ink that could mimic the shape-changing characteristics inherent in

the cell wall of plants [7]. The polymer was crosslinked by UV photopolymerisation. Controlling the shear alignment of the fibrils during the direct ink writing process created anisotropic swelling within the matrix resulting in complex, controllable shape-morphing capabilities. Manipulation of the swelling response was achieved by changing the direction of the printing path during the extrusion of the material. Precise, controllable folding of a 3D printed flower structure was achieved following water-actuation for two structures with different bilayer directions [45].

Similarly, Huang et al. digitally printed a hydrogel composite, where they achieved complex and precise shape-change by tailoring the localised swelling. This was implemented by using precise control of the light exposure time rather than varying the printing path direction [2]. Mao et al. used PolyJet technology to create a self-folding hydrogel SMC. They used a hydrogel bound by SMP and elastomer layers to form the composite used to fabricate a structure with reversible shape-transformation capabilities. The material performed autonomous folding upon immersion in low, followed by high-temperature water. The structure unfolded and returned to its original shape when immersed in hot water [49].

Hydrogels can only be actuated within water or moisture-based environments, therefore, their use is limited in dry conditions. While this may be considered as a disadvantage for certain applications, this is seen as an advantage for biomedical applications as the hydrogels can be tuned to shape-morph in response to moisture within the human body [18]. These early successes indicate a seemingly unlimited potential for the use of swellable hydrogel composites to fabricate biomedical devices. With further development in the issues of printability and response-cycle times, it seems that a future where medical devices are 4D printed using these smart materials is not so far away.

3.2. Shape-Memory Alloys

Shape memory alloys (SMAs) are a group of smart materials that exhibit both a low-temperature martensite phase, where the material is flexible and deformable, and a high-temperature austenite phase, where the material is rigid [4,40]. Once activated (either by stress, heat, or the application of both [61]), the martensite is formed into austenite. The austenite transforms back into martensite on cooling or removal of the stress resulting in reversible shape-morphing ability [1]. The thermo-mechanics of the SMA can be trained to sustain the permanent structure in the austenite phase giving the structure the ability to deform into a temporary shape in the martensite phase and recover to its permanent form upon heating [4,51,53]. It is this reversible crystallographic transformation between austenite and martensite phases that causes the SME within SMAs [10,62]. The SME is embedded into SMAs after printing by bending the structure into the desired shape and then annealing at a temperature above its SME initiation temperature. Once reheated above this critical temperature, the structure will return to its original shape [51].

Pseudo-elasticity, also known as super-elasticity, is an important property of SMAs, referring to the alloy's high strain recovery when loaded/unloaded with stress. The transformation from the martensitic phase causes spontaneous recoverable deformations giving the material "mechanical memory" [1]. Super-elasticity differs from the SME because the shape memory is induced by mechanical loading rather than temperature-induced phase transformations [1]. One SMA which exhibits both properties is the Nickel-Titanium alloy, Nitinol [1]. This alloy generally consists of approximately 50 wt.% nickel and 50 wt.% titanium [53,63], however, small variations in the binary alloy composition have been shown to have considerable effects on the material's physical properties. For example, super-elasticity is created when there are slight increases in nickel concentration. Figure 9 displays the high recoverable strains for Nitinol, which occur at relatively constant stress compared with 316 stainless steel [63].

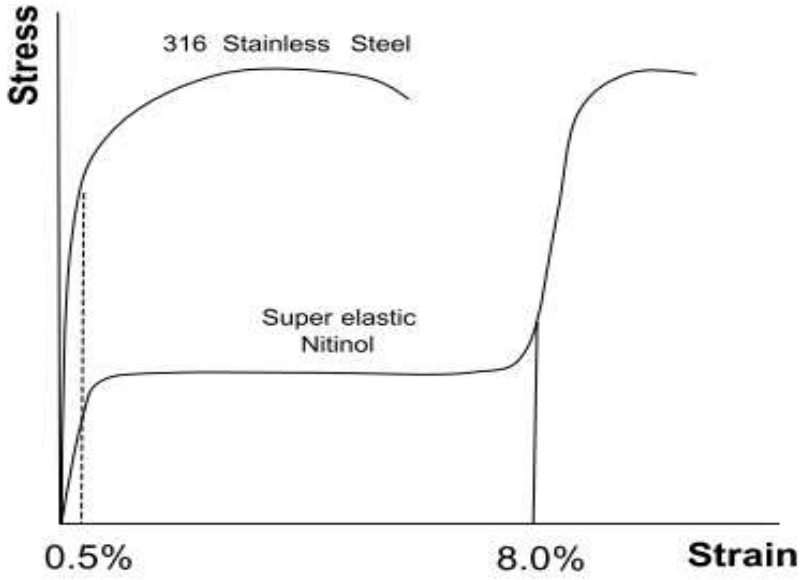

Figure 9. Stress/Strain curve comparison for super-elastic Nitinol and 316 Stainless steel. Taken from [63].

Figure 9 comes from a report by N.B. Morgan, which outlines the potential for nitinol to produce recoverable strains near 8% and exhibit considerable flexibility [63]. However, a recent study by Shishkovsky et al. reports recoverable strains between 10% and 12% [40]. The recoverable strain value will depend on the Nitinol composition. When compared to the recoverable strain of 0.5% reported for 304V stainless steel (a well-established material for fabricating medical devices), Nitinol is clearly superior. Due to its biocompatibility and impressive shape-memory behaviour, Nitinol has been used within biomedical devices since the 1980s in a variety of areas such as orthopaedics, neurology, and cardiology [63]. SMAs offer various advantages over SMPs; such as higher tensile strength aiding their ability to fabricate larger structures, high moduli, and large operating temperature ranges [51]. However, their use within 4D printing technology is somewhat less developed. Their high cost, high density, more complicated programming, and reduced biocompatibility/biodegradability provides certain limitations for their use within 4D printing [51,52]. A major issue with the use and development of SMAs for biomedical applications is biocompatibility.

3.3. Shape Memory Composites

As evidenced by various examples given previously, there has been a drive to overcome the physical property limitations of using individual materials by creating shape memory composites (SMCs). For example, SMPs and SMAs are promising smart materials used in 4D printing, but both have their own associated complications. In order to gain the benefits from both of these materials, a recent study at Hanyang University 4D printed a thermo-responsive shape memory composite (SMC) using FDM by combining the SMP Nylon 12 with the SMA Nitinol with potential for use as biomedical stents [53].

The SMP Nylon 12 was first manufactured by extrusion methods before being used as the filament for FDM, and the SMC was formed by embedding a Nitinol wire [53]. Although both groups of smart materials exhibit the SME and can return to their original shape after deformation, their properties, and the mechanisms of their SMEs vary significantly [53]. An optimum SME response time was achieved by varying the proportions of SMP and SMA, with the resulting composite displaying a lower density and higher tensile strength (Figure 10) than the individual SMP and SMA [53].

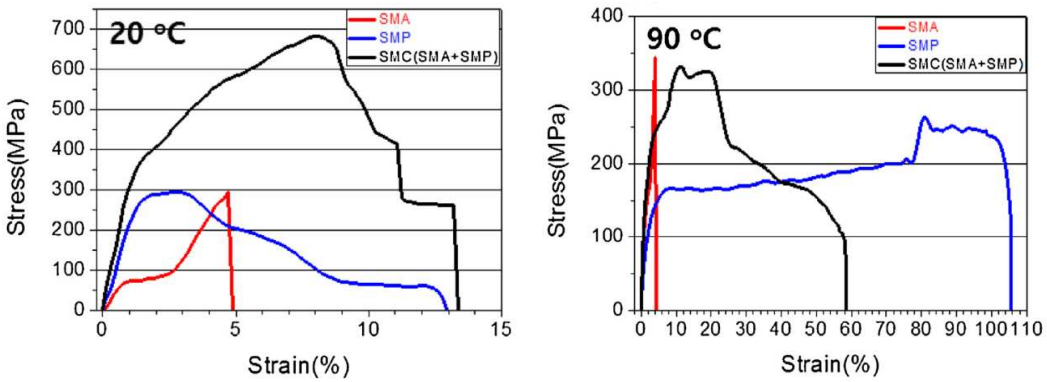

Figure 10. Comparison of stress-strain behaviour for SMP, SMA, and SMC. Figure taken from [53].

Composite structures of this sort provide an interesting alternative as 4D printing materials by overcoming the limitations of the individual materials and extending their potential applications. This reveals the potential of SMCs for use as biomedical devices with improved properties, tuneable SME, and a widened range of actuation methods. Table 3 provides a comparison of SMAs and SMPs with suitable printing techniques and actuation methods for each.

Table 3. Comparison between SMP, SMA, and SMCs. Suitable AM techniques and actuation methods.

Material	Advantages	Disadvantages	Suitable AM Techniques	Actuation Methods
SMP	Simple programming [52]	Low tensile strength [11]	FDM [42]	Heat, light, ultrasound, pH, solvents, metal ions [52]
	Biocompatibility and biodegradability [11]	Prone to degradation [16] Low thermal conductivity [11]	SLA [32] PolyJet [1]	
	Low density [27]	Single stimulation mode [52]	Extrusion [2]	
	Self-healing capabilities [52]	Slow shape-memory behaviour [52]	SLS [30]	
SMA	Can use for large-scale fabrication [51]	High cost compared with SMPs [51]	SLM [40]	Electricity, heat, magnetism [52]
	High tensile strength [51]	High density [27]		
	High moduli [51]	More complicated programming than SMP [35]		
	Wide operating temperature range [51]	Less biocompatible and biodegradable options available [51,52]		
SMC	Good strain recovery [53] Can achieve lower density and tensile strength than SMA [53]	Not well developed [64]	FDM [53] SLS [44] PolyJet [1]	Electricity, magnetism, light, microwave, UV, water, solvent [52]

4. Recent Developments in the Biomedical Field

The potential application areas of 4D printing technology span between the areas of manufacturing, aerospace, and soft robotics, amongst others. The field of personalised medical devices shows promise for current and future generations as a solution to a variety of healthcare issues intensified by the ageing population. Complex, fully customisable structures can be printed by transforming detailed medical images such as X-rays, CT, and MRI scans into 3D CAD models for the printing apparatus [12]. While this technology has received growing interest and major developments have been made, it is still a relatively new venture, and there are currently no clinical trials implementing 4D printed biomedical devices. The following section discusses current research developments in the field with

reported potential for use within tissue engineering, drug delivery systems, and minimally invasive surgical implants.

4.1. Tissue Engineering

Tissue engineering is an expansive field of great interest in the scientific community and has vastly developed in the last decade. In its most basic definition, tissue engineering is a way of devising biological substitutes to mimic native tissues for damage repair and organ restoration. The basic principle originally involved seeding cells onto scaffolds allowing proliferation and direct cell differentiation to produce biocompatible 3D structures [34,65]. Biocompatibility and biodegradability of the materials are crucial to avoid rejection by the body, and mechanical strength is also important to support cell growth. While there have been various reported successes in using both synthetic and natural polymers with this method, the complexities involved, such as with growing organs within a lab, requires different fabrication techniques [66,67]. Implementing smart materials in tissue engineering applications could help to produce highly desirable self-healing or self-regenerative scaffolds [23].

4.1.1. Implantable Organs

The first human organ was successfully transplanted in 1954 [65], and the evolution and progress of the field in years since has increased demands for implantable organs [1]. As of 18 January 2019, there were 6062 people on the NHS organ transplant waiting list in the UK [68]. Biomimetic 4D printing gives a promising future to the biomedical field by reducing the national shortage of organs available for transplant. The applications of 3D bioprinting in the field of tissue engineering are well-established [65]. However, Morouço et al. show concern about the dynamic nature of tissues inhibiting the potential of static 3D printing to create complex organs. They suggest the time-dependent aspect of 4D printing could revolutionise the additive manufacturing potential for these applications [23]. Studies by both Ji et al. [38] and Miao et al. [19] highlight the potential of bio-inks and tissue engineering to solve the biological issues of future generations. Aside from the potential of printed tissues for transplantations and repair as a way of combatting national organ shortages, fabricated organs could also be applied in drug testing and physiological research [69]. While there have been various notable successes, this technology is in its infancy, and the application of 4D printing to fabricate human organs requires further research before the clinical application is seen.

4.1.2. Skin Reconstruction

Tissue engineering and particularly skin bioprinting propose a potential solution for the treatment of severe burns, surgical wounds, or skin fragility diseases [47]. Compared to skin grafts taken from unaffected areas of a patient's body, printed skin is thought to provide improved healing times, reduced pain, and potentially a better cosmetic outcome [52]. In addition, patient skin grafts are not always possible, particularly in the case of severe burns. Self-healing is ubiquitous in nature, and hence an area of broad and current interest within the material science community.

The fast production, large volumes, and accuracy achievable by additive manufacturing techniques have the ability to make bioprinted skin clinically available in the future [47]. Despite these successes, there is limited data available on 4D-printed tissue scaffolds. Morouço et al. have summarised the potential of 4D bioprinting for use in regenerative medicine and the ability to create synthetic structures to mimic natural tissues [23].

4.1.3. Bone Reconstruction

Bone is made up of 65 wt.% inorganic material, 25 wt.% organic material, and 10 wt.% water [70]. Bone is capable of self-healing upon fracture or when small defects are to be bridged (generally considered as less than two times the diameter of the affected bone) [70,71]. The main challenges for bone replacement made up of the biomaterials must possess properties like (i) high mechanical

properties, (ii) porosity, (iii) biodegradability, and (iv) refined high graded structure to mimic the indigenous tissue [72,73]. The successful mimicking of indigenous tissue with all-inclusive mechanical properties has been shown by fused deposition modelling (FDM) of ceramic and or metal reinforced polymers. Due to the lack of adequate materials, it is still ambiguous to bioprint scaffolds which can mimic the high mechanical properties of bone and permit vascularization. The use of 3D printing to fabricate intricate scaffolds for bone reconstructions and replacements has been reported in recent years [34,46,74], see Figure 11. Typical procedures for treating bone defects involve allotransplantation using metallic fixators or implants. The replacement of bone using polymer scaffolds has gained popularity due to high biocompatibility, biodegradability, light weight, and elimination of stress shielding response [27]. Most notable successes have utilised SMPs such as polylactide (PLA), polycaprolactone (PCL), polyurethane (PU), and other copolymers. Despite various 3D printing successes, the incorporation of time-dependent smart structures is a relatively new and undeveloped concept in bone regeneration.

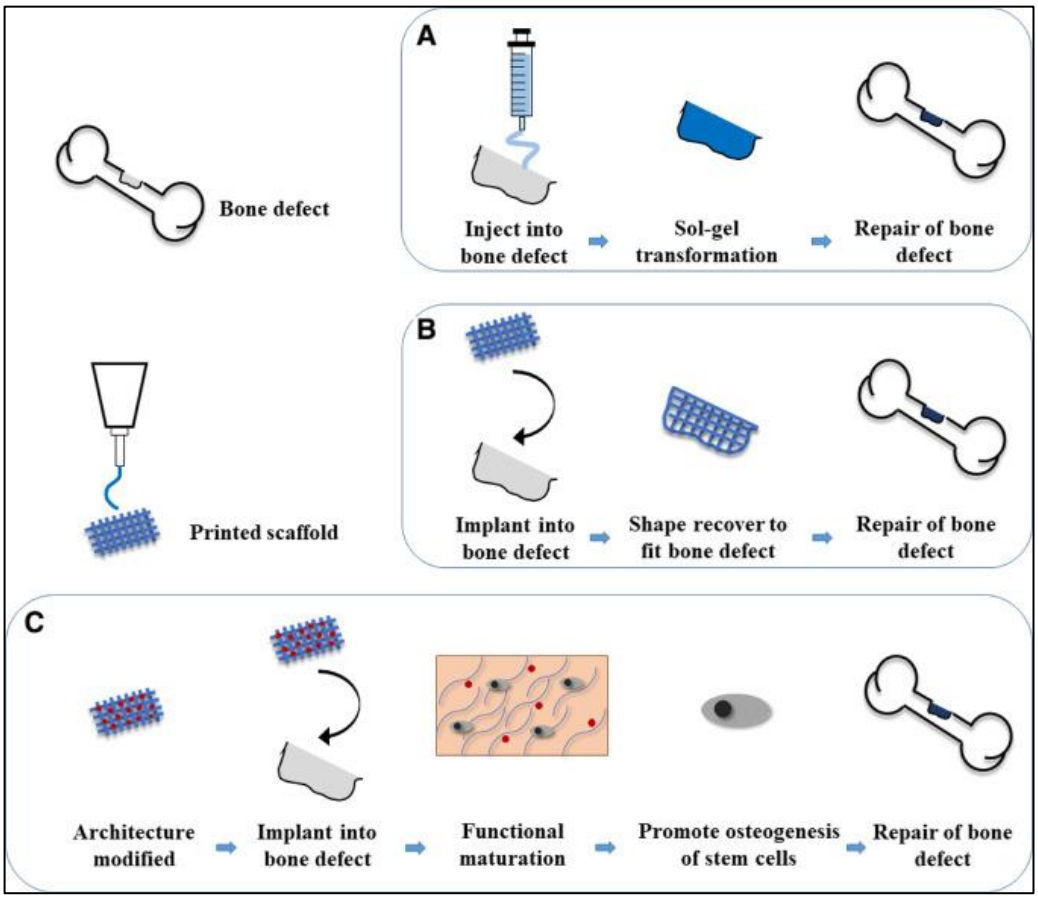

Figure 11. Applications of 4D printing in bone tissue engineering. (**A**) Injectable thermosensitive hydrogels for 4D bone tissue regeneration: the hydrogel could be injected into the irregular defect area and transform to a gel state under body temperature. (**B**) 4D printing of bone tissue based on shape-transformation mechanism: a shape memory scaffold changes its size to occupy the void space, realizing personalised bone defect repair. (**C**) 4D printing of bone tissue based on the establishment of biomimetic microenvironment: the 4D printed biomimetic scaffold with modified architectures can induce the functional maturation of neo-bone tissue and promote the osteogenesis of stem cells, enhancing the formation of new bone tissue [74].

The National University of Science and Technology in Russia has published several reports on the topic of 3D printing to fabricate SMP scaffolds. Senatov et al. reported the successes of utilising SMPs as self-fitting biomedical implants. The term "4D printing" is not directly mentioned in these reports, however, by the definition of 4D printing used within this review, these studies were deemed relevant. All three reports discuss 3D printing of polylactic acid (PLA) with 15 wt. % nano-hydroxyapatite (HA) to create a porous scaffold with shape-memory behaviour [27,75,76]. SMPs are a suitable material for fabricating self-fitting implants as they provide good support to the remaining bone structure and remain in their intended position [27]. The FDM printed PLA/HA structure was proven to support the growth and survival of bone marrow mesenchymal stromal cells. This highlights the potential for the implant to be vascularised, which is thought to be essential to the success of bone replacement by prosthetics. The scaffolds showed impressive resistance to cracking and potential for use as a replacement for damaged vertebral trabecular bones [75]. These studies indicate the suitability of 4D printing SMPs for bone restructuring applications. The integration of shape-morphing scaffolds results in minimum incision during surgery as the implant can be inserted while in the smaller temporary configuration and actuated once in a position to recover its printed shape. Printing implants larger than the bone defect ensures that the implant does not move once in position.

The PLA/HA scaffold described above has an SME activation temperature above human body temperature (≈37 °C), and hence required external heat for its activation. This is a limitation of these studies as a reduced SME initiation temperature is desired to allow autonomous actuation once inserted into the body [76].

A study by Miao et al., however, has shown the ability to print 4D structures for bone regeneration that respond to human body temperature. A renewable soya bean oil epoxidized acrylate was printed using SLA and showed the potential to build porous biocompatible scaffolds to support the growth of multipotent human bone marrow mesenchymal stem cells. Varying printing parameters, such as laser frequency and printing speed, had significant effects on the thickness and width of the printed structures. Increased printing speed resulted in decreased scaffold width/thickness, while increases in UV laser frequency resulted in slight increases in width/thickness. The scaffold deformed into its temporary configuration at −18 °C and fully recovered to its original shape at physiological temperature (≈37 °C) [46]. Compared with conventional biopolymers which are synthesised from crude oil, a finite resource with a diminishing supply, renewable polymers made from plant oils offer a greener and more cost-effective option [46]. The renewable resin was like the traditional bioactive materials PLA and PLC and even showed improved performance when compared with polyethylene glycol diacrylate (PEGDA) [46]. Chawla et al. used an approach by generating first cartilage callus, which can be later transformed into bone tissue by resorption and remodelling, and he showed fabricated MSC-laden, silk-gelatine-based bioprinted scaffolds in two steps: (i) initially exposed to a three-week chondrogenic differentiation; (ii) then, two-week differentiation in osteogenic conditions [77]. While the biomedical application of 3D printed biological polymers such as proteins and polysaccharides has been widely reviewed, the use of plant-based polymers is still in its infancy, and further research is required before it can gain commercial use. The main focus of future work should be on the deposition of the matrix, mineralization, mineralization, remodelling, and mainly mechanical properties. Betsch et al. used a novel method to print the cartilage tissue based on magnetically directed collagen fibre alignment. It was the first time of 4D bioprinting with multilayers on the chondrogenic differentiation of human knee articular chondrocytes [78]. Recently, Bashir et al. fabricated a modular light-controlled skeletal muscle-powered bio-actuator that can ideally mimic the muscle motion. When exposed to a light stimulus, the muscle can generate a tension force up to 300 μN (0.56 kPa). Moreover, the muscle actuators enable controllable directional locomotion and rotational steering. The fabricated artificial muscle can be used to replace damaged muscle in the future [79].

4.1.4. Stents

A stent (e.g., coronary artery stent, carotid artery stent, airway stent) is a short, tiny tube situated into a hollow structure such as an artery, a vein, or other structures i.e., ureter. The normal function of a stent is to hold up the hollow structure open [78]. Stents are often used to treat narrowed coronary arteries that supply the heart with oxygen-rich blood.

4D bioprinting has shown the latest way to fabricate stents with stimulus-responsive materials in a comparably compact size. Several 4D bioprinting methods and materials have been developed for stents. After transplantation, the stimuli are imposed, and stents would self-deform proper size and shape. Hence, invading in medical surgeries could be decreased. Ionov et al. developed an advanced 4D bio-fabrication method for hollow self-folding tubes with the minimum diameters of 20 µm using shape morphing biopolymer hydrogels [80]. The reversible shape transformations of the polymer as a response occurs with a change in Ca^{2+} ions concentration [80]. This process does not pose any negative effect on the viability of the printed cells, and the self-folded hydrogel-based tubes support cell survival for at least 7 d without any decrease in cell viability [80]. Liao et al. developed self-expanding and self-shrinking biofabricated structures that change with temperature. The proposed tubular lattice with a self-expanding/shrinking mechanism can serve as tubular stents and grippers for bio-medical or piping applications [10]. Ge et al. [50] printed high-resolution shape-memory stents with hardly any restriction of geometric complexity. After transplanted into the vessel, the stent can be heated and recover into its original shape with a larger diameter [50]. Leng et al. bioprinted 4D shape-changing objects by UV crosslinking between Fe_3O_4 particles and poly (lactic acid) that were remotely operated and had magnetically guidable properties [81]. Zarek et al. bioprinted a thermally operated endoluminal device that can transform into a tracheal stent with an increase in temperature (Figure 12A). This device with a customised design can reduce migrations (a frequent cause of tracheal stent failure), and the low profile of the shrunk shape-memory polymers (SMP) structure enables a less injurious deployment. The ability of SMPs to recover their original shapes will be advantageous for a broad range of applications, especially for stents. The two challenges still needed to overcome by 4D bioprinted stents are biocompatibility and meeting the biological characteristics of the human body. They have printed an SMP bioink made from methacrylated polycaprolactone precursor to form a tracheal stent with shape memory behaviour [8].

The stent can be deformed into its temporary smaller shape, inserted into the body, and return to its original shape upon a localised temperature increase once in the correct position, as highlighted in Figure 13.

This study further details the potential for 3D printed personalised medical devices with shape-memory behaviour. The fabricated structures are customisable to each patient's anatomy to match the trachea dimensions and arrangement of the cartilaginous rings. Consequently, the stent will provide an almost perfect fit, and there is a reduced risk of movement from the intended location, a common reason for tracheal stent failure. Furthermore, the ability to reduce the size of the stent for deployment is desirable as it makes the surgical procedure less invasive for the patient and improves recovery times [4]. The success of this study exemplifies the ability of 4D printing as a solution to the issues associated with current tracheal stent performance.

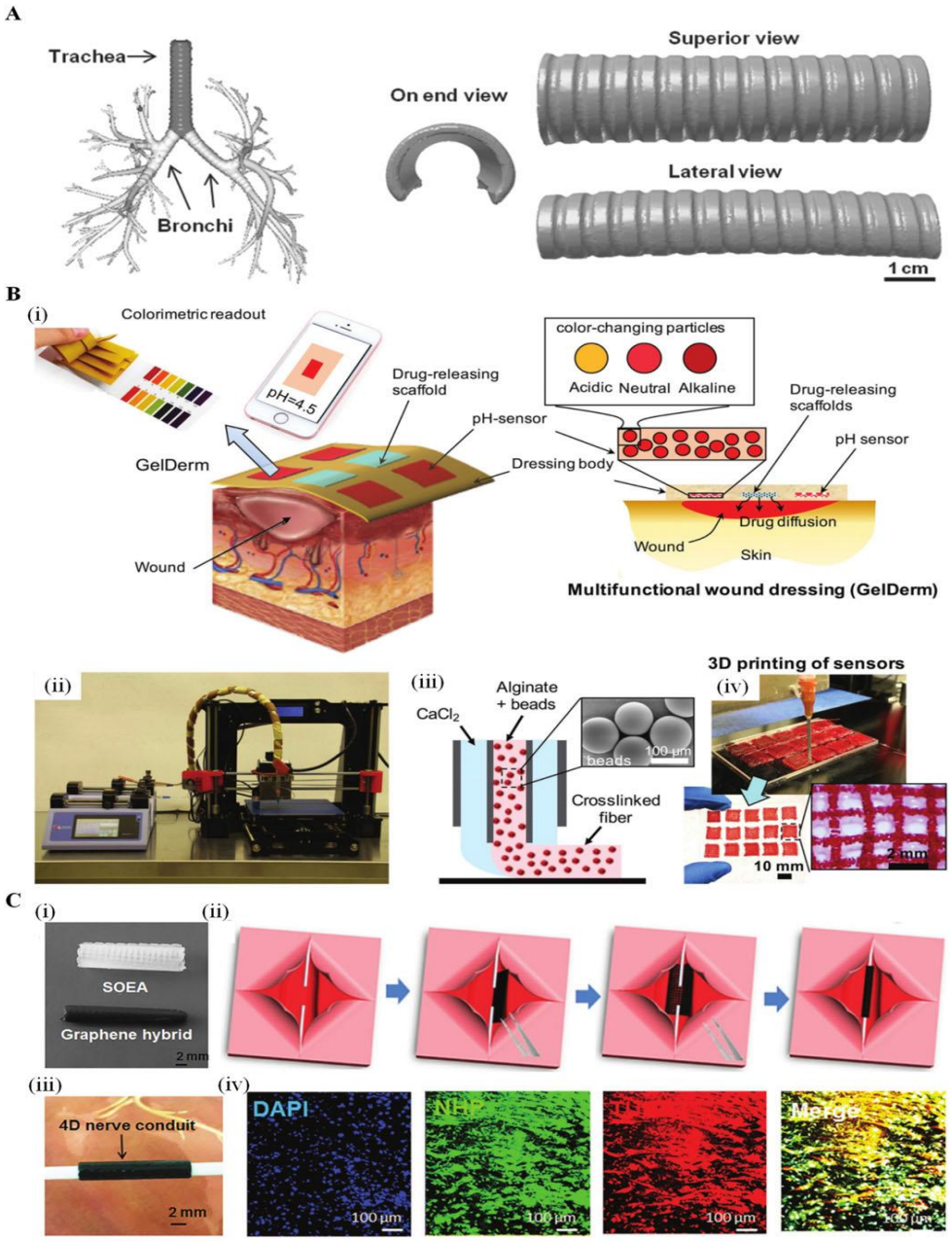

Figure 12. Applications of 4D bioprinting in biomedical fields. (**A**) 4D printed tracheal stent with thermal responsive shape memory material. The stent was initially an open duct and then evolved into a closed one after transplanted into the body. Reproduced with permission [8]. (**B**) Wound therapy by the printed medical device. The device includes sensors to detect bacterial infection by measuring the pH value. Once the infection was detected, drug-releasing process would be triggered (i). The used printer, materials, and printing process were illustrated in (ii)–(iv). Reproduced with permission [82]. (**C**) Nerve conduit by 4D bioprinting. The used material was a composite of soybean oil epoxidized acrylate (SOEA) and graphene (i). The process of nerve conduit entubulation is illustrated in (ii). The damaged nerve was represented by two stumps, and a printed flat plate was placed under the damaged nerve. As a response to body temperature, the conduit evolved into a tube and wrapped the nerve (iii). In vitro cell experiments demonstrated that mesenchymal stem cells (hMSCs) could differentiate into nerve cells when cultured on the conduit (iv) [78].

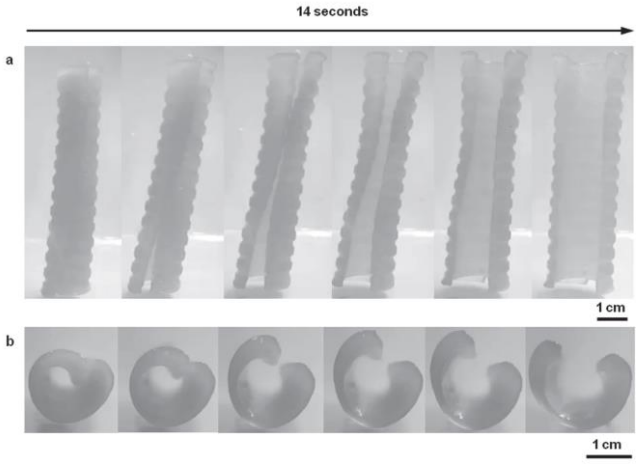

Figure 13. 4D-printed tracheal stent. (**a**) Side-view; (**b**) cross-section. Taken from [8].

4.1.5. Nerves

The peripheral nervous system (PNS) comprises nerve in an enclosed bundle of nerve fibres, i.e., axons. The nerve is the basic unit of PNS, and its function is to transmit electrical impulses. The fantastic idea is to repair the damaged nerves by 4D bioprinting. Zhang et al. fabricated an initially closed conduit that could be temporarily opened and fixed, facilitating the surgical operation on conduit implantation. Moreover, the printed material is chosen as graphene mixed soybean oil epoxidized acrylate, which shows a good electrical conductivity and enhances nerve regeneration [83]. The 4D printed conduits provide excellent physical and chemical signals for nerve regeneration, and the cultured human mesenchymal stem cells can differentiate into neural cells. The performance of nerve conduits shows us the potential ability of self-enturbulation for dynamic and seamless integration [14]. The above works give us some inspirations for wound repair from different aspects. These innovations give us a further understanding of the 4D bioprinting concept. Nerve guides are commercially available for clinical use, and research continues in this field, highlighting the immediate need for improved PNS nerve repair solutions [84]. Once bioprinting technology overcomes fabrication limitations, regulatory hurdles, and production costs, the development of a bioprinted clinical solution for PNS repair is a realistic goal.

4.2. Drug Delivery Systems (DDS)

Drug delivery is another promising application for 4D printing technology, receiving growing interest in recent years. By tuning the SME transition point of thermo-responsive materials close to physiological temperature and achieving a broad transition temperature range, localised drug release can be achieved within the body [54]. Porous polymers are favourable as drug carriers due to their light weight and increased surface area [76]. Moisture-responsive materials that could be actuated by fluids within the body are also a desirable research area. Mirani et al. developed a directly activated drug delivery system by 4D bioprinting (Figure 12B) [82].

PCL is a widely reported SMP that has been used in biomedical applications for many years due to its low melting point, high drug permeability, and low degradation rate in vivo [51]. Sidler et al. have reported a new 4D printing technology, MADAME, as discussed in Section 2.4, which they suggest can be used to fabricate drug delivery patches, prosthetic body parts, and smart wound dressings [12]. This report claims their new technology would be capable of producing wearable wound dresses for the treatment of burns as well as other injuries. Shishkovsky et al. have shown the potential for self-initiating/fixing SMAs using SLM technology with potential applications as sensors, implants, and DDSs by 4D printing the alloys Ni-Ti (Nitinol) and Cu-Al-Ni. The researchers propose that the strains/stresses evolving from the austenite-martensite transformation of the SMAs would allow drug release from the material's pores due to displacements and resultant forces [40].

The use of hydrogels as drug delivery carriers has been widely reported as they can be embedded with pharmaceuticals, antibodies, and other biological components [18,85]. For example, Vehse et al. used micro-stereolithography to produce poly (ethylene glycol) diacrylate (PEGDA) scaffolds with potential application as drug release forms (Figure 14) [29]. Diode laser curing was identified as a potential method for drug-loading the scaffolds, and the drug acetylsalicylic acid was added to the liquid PEGDA before printing. Different specimens were printed containing varying concentrations of the drug. While the drug did not denature upon exposure to UV light, its addition disrupted the polymer chain network as the compressive strength of the printed structure was reduced compared with a pure PEGDA printed scaffold [29].

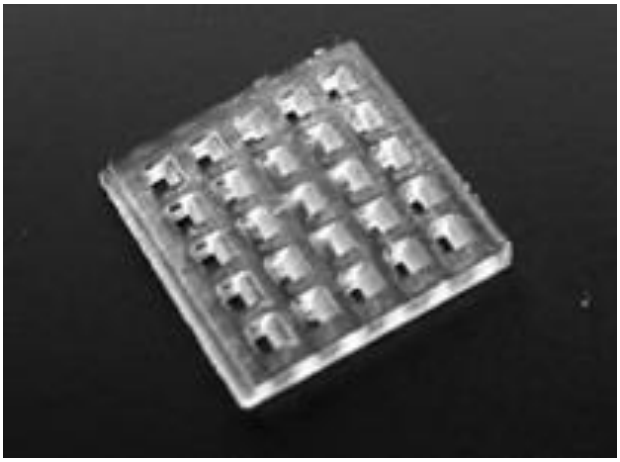

Figure 14. Micro-SLA Printed poly (ethylene glycol) diacrylate (PEGDA) scaffold. Taken from [29].

The examples given above indicate the potential of 4D printing to fabricate drug delivery systems that respond to human body temperature or moisture. Gioumouxouzis et al. report the suitability of polylactic acid (PLA), polyvinyl alcohol (PVA), and polyacrylics (Eudragit®) as biocompatible SMPs with the potential to create pharmaceutically active structures for drug delivery systems [21]. In this study, FDM was used to print a filament mixture of PVA, mannitol, and the drug hydrochlorothiazide (HCTZ)—creating a controlled release drug delivery system [21]. The drug could be incorporated into the polymeric filament either by hot-melt extrusion or by immersing the filament in solutions of the required drug. The printed structure showed zero-order release kinetics with up to 95.25% of the drug dissolving within 240 min compared with a marketed product showing near-full release within 10 min [46]. This indicates the potential for controlled release dosage within drug delivery systems and suggests FDM as a suitable AM technique.

4.3. Minimally Invasive Surgeries

The shape memory behaviour exhibited by 4D printed structures makes them attractive for use in personalised medical devices. Printed surgical implants, which can be deformed into a small temporary shape before being deployed into the body and actuated in an otherwise unreachable location, would provide minimally invasive surgeries and reduce patient recovery times [18]. To be used as minimally invasive surgical devices, 4D printed structures must either be capable of local actuation by a patient's body temperature, pH, or moisture or have the ability to be stimulated without direct contact from the stimulus externally, e.g., by magnets or an electric charge [46].

Kashyap et al. printed a radiopaque and porous SMP foam using semi-crystalline thermoplastic shape memory polyurethane (SMPU) with potential for use in Endovascular embolization (EE). EE is a surgical procedure used to treat abnormal blood vessels within the brain and other parts of the body by preventing blood flow to a specified region [42]. For example, endovascular coiling can be used in the treatment of aneurysms or in certain cancer treatments to starve tumour cells by blocking the blood

flow. Further exploration into the biomedical applications of porous SMP printed scaffolds is required to determine the full potential of the technology [42].

Porous SMP foams show greater advantages in this field due to their greater volumetric expansion, low weight, and increased surface area compared with traditional solid SMPs [64]. Mu et al. report that tuning a thermo-responsive SMPs to respond to physiological temperature (≈37 °C) can be achieved by using in-direct doping materials [46]. Yang et al. fabricated an initially closed conduit that could be temporarily opened and fixed, facilitating the surgical operation on conduit implantation (Figure 12C) [78].

The implementation of 4D printed surgical devices could reduce the risks associated with complex surgeries due to reduced incision sizes from minimally invasive implantable devices and the associated improvement in recovery times. The overall reduction in operation and surgical complications would improve the general patient experience.

5. Potential Future Applications

The following section describes some potential applications of 4D printing dependent on further research and evolution within the field. Recent developments outside of the biomedical field have highlighted the potential of 4D printing within aerospace, manufacturing, and robotics. If further advancements can be made to reduce printing times, prevent structural degradation, and find more smart materials with an improved performance, the future applications of this technology are seemingly unbounded. If further developments can be made to reduce fabrication costs, 4D printed objects could find a place within the home.

This technology shows interesting applications within the field of retail and e-commerce. Devices could be deformed into their temporary state, stored, and transported in their smaller configurations, and actuated by the customer on delivery. This could significantly reduce supply chain costs. 4D printing may also find its way into mainstream art and design. Certain SMPs exhibit colour change on actuation, this could be used to create highly intricate children's toys which change shape in the bath.

4D printing shows potential in the fabrication of actuators and sensors for engineering applications. One potential use may be to fabricate plugs for process lines. These could be printed as cylindrical devices smaller than the cross-section of the required pipeline and thermo-mechanically trained to ensure shape memory in the radial direction. The structure would be fixed at a certain point within the pipe and expand in response to the presence of a chemical, pH, or temperature. This could act as a safety valve to respond to changes in operating conditions where downstream exposure to certain chemicals or conditions would otherwise cause a safety issue. For example, the presence of water when processing alkali metals such as potassium and sodium must be avoided completely. Needless to say, this would require extensive review to determine a way to fix the device at a particular point within the pipe, ensure complete shape recovery to avoid failure of the device, and relies on the development of devices with extremely fast response times.

4D printing also shows potential for use within the field of smart textiles such as orthopaedic casts. For example, if a patient has broken their arm, the cast could be 3D printed from an X-ray in a large enough size that it can be loosely placed over the arm and actuated in a way that it shrinks to fit the patient and provide the best support for the broken bone. Similarly, this technology could be used to create wearable technologies for activewear. This could provide aerodynamic sportswear customised to each athlete's body for enhanced performance. The recent excitement around the sportswear company Nike's "Back to the Future"-inspired self-lacing shoes shows potential for smart-textiles to succeed in the retail market. Perhaps we will all be wearing 4D printed clothes one day giving the term "one size fits all" a completely new meaning.

6. Limitations and Future Outlook

6.1. Materials Availability

One of the major limitations of this technology is the limited number of smart materials suitable for printing and especially those which are biocompatible and hence suitable for biomedical applications. As discussed earlier, light-curable printing techniques require the use of liquid photopolymerisable resins, which can be hardened upon exposure to UV light, and powder-solidification methods experience difficulties extruding SMPs with low glass transition temperatures. One solution to aid in the fabrication of 4D structures from otherwise unprintable polymer materials is the use of sacrificial moulds. The mould is 3D printed using sacrificial materials and filled with the liquid monomers of the unprintable material. Curing is used to polymerise the material, and after removing the mould, the solid 3D structure is formed [18]. This provides a relatively effective solution, while further advancements are undertaken to develop materials with improved printability. A commonly reported issue during small-scale operation is the difficulty in achieving high-resolution feature design details. This is a problem when fabricating nano/micro-scale devices and hence remains a current limitation of this technology in the biomedical field.

6.2. Cost and Research Limitations

The cost of 3D printing technologies has significantly reduced in recent years, with commercial FDM printers now costing from $150 USD [38]. 4D printing is a new and emerging area of technology, so while developments have reduced the cost of AM printers, extensive investment in research is required before 4D printed structures can be introduced into the clinical environment [10]. Understanding the nonlinear, time-dependent behaviour of 4D-printed architectures requires the use of complex simulations [49]. This is a limitation in terms of time and costs due to the required investment in research. The various studies discussed in this review are based on small-scale experiments. Before 4D printed biomedical devices can be used by patients, extensive clinical trials will be required [37]. In addition, due to the novelty of the technology, it is unclear if authority legislation will be enforced when real-life implementation becomes feasible. Hence, we are far away from the stage of clinical application of 4D printed biomedical devices. While certain biomedical applications of 3D printing have been well-reported, the incorporation of smart materials is significantly less developed. Research into the field has vastly increased since its introduction in 2015. With continued development, this generation may see the implementation of 4D printed objects in our everyday lives.

6.3. Practicality and Technical Limitations

While extensive research is being made to improve the costs and quality of 3D printed structures, slow printing speeds remain a major drawback of AM techniques. While the ultrafast printing techniques developed by Huang et al. [2].show potential for improvements, the viability of scale-up has not yet been considered, and further research is required. While notable improvements have been made, the difficulty in producing accurate feature details by 3DP techniques persists, and it is common for printed structures to deviate from the 3D CAD model. This can occur when attempting to print small-scale structures using SLA [32]. Biomedical devices often require design features on micro/nanoscale, so further developments are required to improve accuracy before mass scale-up can be achieved. Continued actuation between configurations has been shown to cause degradation of the printed structures; hence further developments are required to improve the durability and life-span of these structures [7].

7. Conclusions

4D printing is making its mark as an additive manufacturing technique with the capability to create dynamic structures. While 3D printing has shown great potential in solid freeform fabrication, the restriction of printing only rigid structures can be overcome by the incorporation of time-responsive

materials in 4D printing. This provides a solution to some of the societal and economic challenges of an ageing population by providing a potentially inexpensive and scale-able method for manufacturing personalised medical devices. Some of the various applications proposed for this technology include tissue engineering and regenerative medicines where synthetic tissues can be fabricated for skin grafts, bone reconstructions, and organ transplants. The reported cytocompatibility and strength of these scaffolds from various studies highlight the potential of this field to address medical issues for current and future generations.

Many additive manufacturing techniques developed for 3D printing applications have been modified for use with smart materials. The light-based methods of stereolithography and PolyJet, which concern the sequential UV curing of layers of photopolymerisable liquid resin, are attractive for biomedical application due to the high-resolution structures achievable on the micro/nano-scale. However, there are a limited number of biocompatible materials suitable for use with these techniques, and therefore further research is required to widen the available material options. The high-temperature methods required by fused deposition modelling, selective laser melting, and selective laser sintering make them unsuitable for bioprinting using cell-laden and hydrogel materials. However, these techniques show promising capabilities in other applications such as aerospace, military, and manufacturing. The shape-memory response is dependent on both the smart materials and AM techniques used, however, further developments are required to deepen our understanding and maximise the potential of this technology.

Since the introduction of 4D printing in 2013, there have been many developments in the field of shape-memory materials. Most notably, these include shape-memory polymers (SMPs), which exhibit low density, biocompatibility, and biodegradability, shape-memory alloys (SMAs) with increased mechanical strength and ability to fabricate large structures, and hydrogels which can be printed to create biomimetic structures. However, the inherent limitations of printing singular materials such as SMPs or SMAs have led to the development of tailorable SMCs. These composite materials can overcome the physical property limitations of individual materials and expand the capabilities of 3D printed structures.

A desirable characteristic of printed structures is hierarchical shape memory to create self-deforming structures. This can be achieved either by printing a combination of active and inactive materials in different areas of a structure to produce differential strain upon exposure to the stimulus or by multi-material printing to create multi-SME. This can be used to fabricate detailed structures with complex shape-morphing capabilities and tailorable stimuli responses.

The successes of 3D printed medical devices have been established in several reports. Utilising X-ray, MRI, or CT scans as a basis for the 3D CAD model can allow complex medical devices to be fabricated which are tailored to a patient's anatomy. Consequently, incorporating smart materials into this process shows potential for 4D printing to fabricate implants that can be autonomously deployed inside the human body. A further focus of material science research lies in tuning the shape memory response around a specific level of stimulus. For example, for an autonomous response, personalised medical devices must be able to respond to temperature or moisture levels within the human body. While there have been some successes, further research into the tuning of SME initiation for these devices is required before clinical application.

Reports of ultrafast printing techniques and renewable printing resins made from soybeans are evidence to the progress of this technology. As 4D printing is evolving because of these world-wide scientific efforts, production costs are decreasing, and the achievable quality of printed structures is improving. It is expected that future generations may be able to obtain 4D printed customisable dressings, drug delivery systems, or even personalised implants from their local surgery. However, further research and development into technologies and materials are required before 4D printing of biomedical devices becomes a viable option for real-world application.

Author Contributions: Conceptualization, A.B. (Ankur Bajpai), A.B. (Anna Baigent), and N.R.; writing—original draft preparation, A.B. (Ankur Bajpai), A.B. (Anna Baigent), and S.R.; reference management, A.B. (Ankur Bajpai) and A.B. (Anna Baigent); writing—review and editing; C.Ó.B., V.K., and N.R.; supervision, C.Ó.B., V.K., and N.R. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AM	Additive manufacturing
DDS	Drug delivery system
SMP	Shape memory polymer
SMA	Shape memory alloy
SMC	Shape memory composite
3D	Three-dimensional
DIW	Direct ink writing
4D	Four-dimensional
SLA	Stereolithography apparatus
FDM	Fused deposition modelling
SLM	Selective laser melting
DLP	Direct laser printing
SLS	Selective laser sintering
PolyJet	Photopolymer Inkjet
SME	Shape memory effect
MME	Melt material extrusion
T_g	Glass transition temperature

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