Review Article

Applications and Future Aspects of 4D Printed Biopolymeric Scaffold Materials in Tissue Engineering: A Systematic Literature Review

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Abstract

The emergence of smart materials (stimulus-responsive materials) and cells enables 4D printing to enhance printed structures dynamically. By undergoing controlled morphological changes, engineered tissues may be made using these dynamic scaffolds. This article provides an overview of the use of stimuli-responsive biomaterials in tissue engineering and several 4D printing methodologies based on the functional change of printed objects. This review also goes through the existing and future prospects for using 4D printing in bone tissue engineering and the limitations in this field. Using a variety of stimuli-responsive biomaterials and 4D printing techniques, the form or function of these objects might evolve. These novel technologies have the potential to meet unmet medical needs, as shown by a recent review that summarised the use of 4D printing in bone tissue engineering. This current review is about the potential of this cutting-edge technology for tissue engineering in the biomedical area by delving further into the ongoing conversations regarding future issues and perspectives.

Keywords: 4D printing, Biomaterials, Biomedical, Multifunctional materials, Tissue engineering

1 Introduction

The extraordinary advancement of 3D printing technology and materials science over the last couple of decades has piqued interest in stimuli-responsive biomaterials. Various research has been done to develop a new age of 4D printing. Even though 4D printing is still a relatively young technology, it has already substantially influenced several areas within the healthcare and pharmaceutical industries [1]–[5]. The term "4D printing" refers to the practice of creating objects from 3D printed material that can autonomously and programmable respond to external stimuli, such as tension, light, liquids, temperature changes, magnetic fields, gas pressure, embedded electronics, or a combination thereof to alter their shape or function. The applications of 4D printing include tissue regeneration, medical device creation, and medicine administration. Potential medicinal uses of the dynamic 4D-printed material discussed in this study are outlined [6].

First, the technology behind 4D printing is in its infancy. Indeed, there is not yet a 4D printer on the market. The accompanying technology must be progressively refined to create new, ultra-precise medical tools [7]. The key potential applications for different thrust areas in 4D printing are depicted in Figure 1. A systematic literature review method has been adopted to collect and segregate the work effectively to provide thoughts and concepts. The systematic

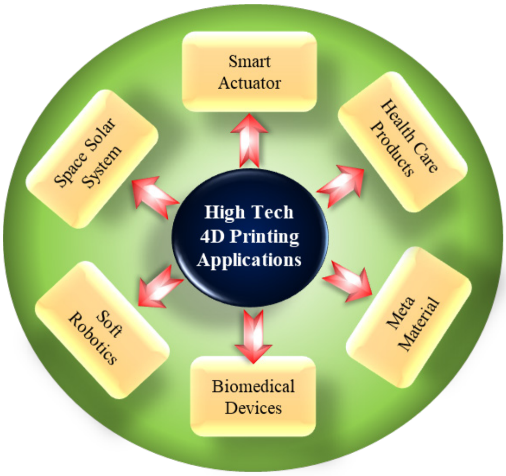

Figure 1: The key potential applications for different thrust areas in 4D printing.

literature review technique has been adopted to review recent research on the application of 4D printing and materials used in 4D printing, the systematic literature review technique has been adopted. Each stage and research article's collection and selection criteria for including the research article for review purposes are all explained in Figure 2. Unfortunately, the present state of printing accuracy and material performance does not allow it to fulfill this standard. Second, each person's natural setting is unique in complexity and volatility. When using 4D printing in biomedicine, the printed objects should be tailored to the organism's microenvironment via microfluidic devices. Microfluidic systems control small volumes of fluid (often between 106 and 1015 mL) by passing them through a network of channels and chambers with diameters on the order of tens of micrometers [8]–[12]. Compared to 3D printing methods, 4D printing has superior quality, precision, accuracy, and performance capabilities and can produce any complicated object utilizing various materials. The type of materials used in bioprinters should be carefully considered, as should their nature [13]. In multiple academic and industrial settings, including the biological one, 4DP has been applied. 4D Printing needs smart materials and smart designs to accomplish stimuli-responsive behaviors. In terms of clever designs, it is crucial to properly pre-program 4D printed structures in computer-aided design (CAD) by accounting for the time-dependent deformation of 3D objects [14]–[18]. Microfluidic devices, with their biomimetic microenvironments, provide a platform well-suited for realizing the biological potential of cells to generate functional tissue. An example of a 3D-printed material that reacts to tension, light, liquids, temperature changes, magnetic fields, gas pressure, embedded electronics, or any combination of these stimuli to autonomously and programmable modify its configuration or function the process known as 4D printing. In 2014, a multi-material thread was folded into the letter "MIT" as the first show of the strength of 4D printing. Several polymers, metals, and ceramics have been created for 4D AM (Additive Manufacturing)

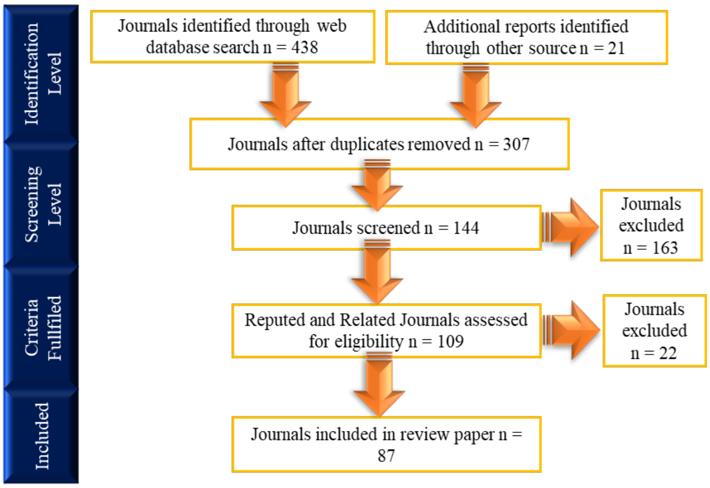

Figure 2: Systematic literature survey of the current review process selection including identification level, screening level, criteria selection process, and final selected journals inclusion process.

[19]. Drug administration and stent placement are examples of how the shape-shifting properties of 4D AM materials might be employed in dynamic and adaptable human contexts. The evolution of 4D AM techniques is influenced by the capabilities of geometrics possessed by the relevant 4D AM materials. For the design and production of 4D smart structural materials, such as soft robotics, controlled grippers, programmable shape change patterns, and many more, many fascinating possibilities may be explored [20]. Numerous heat-responsive 4D materials, such as hydrogels, SMAs (Shape Memory Alloys), and SMPs (Shape Memory Polymers), have been described, making heat the most widely used relatively inexpensive stimulus for 4D printing.

1.1 *Influence of 4D process parameters*

1.1.1 Printing speed

Since the material is stretched more during rapid extrusion, the resulting residual stresses are greater when the material is deposited at higher rates. The results show that the printing speed has a direct correlation to the level of residual tensions. Thinner layers may have significantly less of an impact on the printing pace. If the printing speed remains the same and just the layer height is altered, less PLA material will be extruded through the nozzle and stored as stresses when using thinner layers.

1.1.2 Build plate temperature

The effect of the build plate temperature on the efficiency of the shape-changing process is also studied. A greater degree of distortion of the printed structures was predicted as a result of the deposited layers if the build plate was kept at a lower temperature during printing. By lowering the temperature rapidly, we can decrease the chain mobility of the polymer and potentially maintain higher residual stresses in the layers. This would lead to a permanent hardening of the macroscopic form, eliminating any possibility of stress relief. Thinner structures (those made up of a smaller number of layers) should be more sensitive to variations in build plate temperature since this temperature largely affects the first layer. The second layer would be extruded onto the first, keeping the former's hotter upper surface in place since the layers are stacked one on top of the other.

1.1.3 Number of active layers

The strain and bending angle produced by single-layer PLA specimens are the lowest. Since there is just one layer of PLA in the construction, it cannot flex enough (has fewer residual stresses stored in the material) to cause significant bending. The 2-, 3-, and 4-layer constructions, on the other hand, curved to a greater extent, but they did so at relatively comparable angles, and the results overlapped somewhat. This phenomenon is thought to originate from a rotation of the neutral axis. The neutral axis lies nearly at the geometric center of all active layers in 2-, 3-, and 4-layer systems. If one assumes that one set of active layers is compensating for another set, then one may draw this conclusion.

However, in that case, the structure should not sag in any way. It is speculated that the most residual stresses are retained in the initial layer of active material printed immediately onto the build plate. Yet, their poor reaction time overshadows the widespread use of heat-driven 4D printing technology [30]. This work mainly focused on the 4D printing materials in the biomedical scaffold applications in the developing 4D printing technology, and addressed the prospects of 4D printing in precise. Hence, this review could communicate the aspects of 4D printing materials for bone scaffolds and tissue engineering along with future perspectives.

2 Material Systems Used in 4D Printing

Adding the fourth dimension of time, 4D printing methods differentiate themselves from traditional 3D printing, which is used to make static structures. When using 4D printing, a 3D-printed object may evolve its form and function over time due to anthropogenic factors, including temperature, light, water, pH, etc. 4D printing has become a promising area of additive manufacturing, garnering tremendous interest among researchers and professionals across various fields. The input type and outputs for different 4D printing materials with multiple applications are listed in Table 1.

The main concept is to alter materials on the nano and micro scale such that they may be 3D printed

Table 1: Applications, input type, and the response of different materials used in the 4D printing

Stimulus	Materials/Methods	Application	Output Advantages	Ref.
pH	Chitosan-based polymers	Bone regenerating drugs	Tunable mechanical characteristics; controlled medication release	[21]
Light	Photoinitiators (benzophenone)	Photo-curing and cell delivery	Excellent form fidelity; Absolute stability	[22]
Light	coumarin, o-nitrobenzyl ether	3D vascular networks	Cytocompatibility Multistage lighting program	[23]
Temperature	poly(N-isopropylacrylamide) (pNIPAM)	Soft tissue cell-filled bilayers	Temperature-sensitive; easily accessible	[24]
Humidity	Poly-ethylene glycol (PEG)	Bilayers packed with cells	Sustained Biocompatibility	[25]
Humidity	Cellulose stearoyl esters	Bioactuators/ Biosensors	High level of biocompatibility	[26]
Magnetic field	Gadolinium (Gd^{3+})	Spheroids Cancer treatment	Less toxic effect; lack of an invasive nature	[27]
Biological	Polypeptides, Polynucleotides	Programmable cell adhesion matrices, shape memory hydrogels	Improved biodegradability	[28]
Electric field	Polyaniline, polythiophene	Biomimicry	Conductivity improved	[29]

into components that can undergo structural changes on a molecular scale over time [31]. Nano- to macro-scale 3D printed products, such as smart devices, and metamaterials, may be created with 4D printing for various applications in prototypes, aerospace, medicine, and more.

If a polymer is subjected to cyclic stresses (deformations) with an amplitude less than its ultimate strength, its frictional surface will eventually wear down and become damaged. Polymer fatigue failure always results from either a buildup of damage or the expansion of a flaw to a critical size. Physical qualities, ambient circumstances, and mechanical loading variables all significantly affect the fatigue behavior of polymeric materials.

Yield strength, ultimate tensile strength, and uniform elongation all fall before increasing as the strain rate rises. Increasing a polymer's strain rate causes the modulus, yield stress, and flow stress all to increase. At higher strain rates, polymers generally have a greater strain rate sensitivity.

2.1 *4D Printing by multi-materials and composites*

Some of the most often used multi-material systems in 4D printing include fiber-reinforced or bilayer SMP composites, multi-material SMPs, and desolvation-induced multi-materials [32]. When it comes to the latter, it is possible to manipulate the form by taking advantage of the volume loss caused by the desolvation of the remaining unreacted component.

In a multi-material structure, eigenstrains caused by environmental stimuli may drive the structure's shape change depending on the positions and volumes of the different materials [33].

2.2 *4D Printing of multifunctional materials*

A more futuristic development in 4D printing is the extension of its original definition beyond changing shapes to shifting functions and properties. For satisfactory 4D printing, like 4D printing or Conscience materials that can be printed using 3D printing technology might be a game-changer [34]. The shape-shifting capabilities of 4D printing have been used to print functional products like electrical devices.

Tissue engineering, medication delivery, and the construction of transplantable and regenerative organs are just a few promising future biomedical uses of 4D printing. Research on self-healing materials for 3D printing has also been conducted to boost the reliability and durability of material systems by allowing for structural repair and functional recovery of materials after printing [35].

Optical and electrical properties, for example, may be influenced by form modification during functional 4D printing. Many people now refer to the process that results when 3D printing is fused with

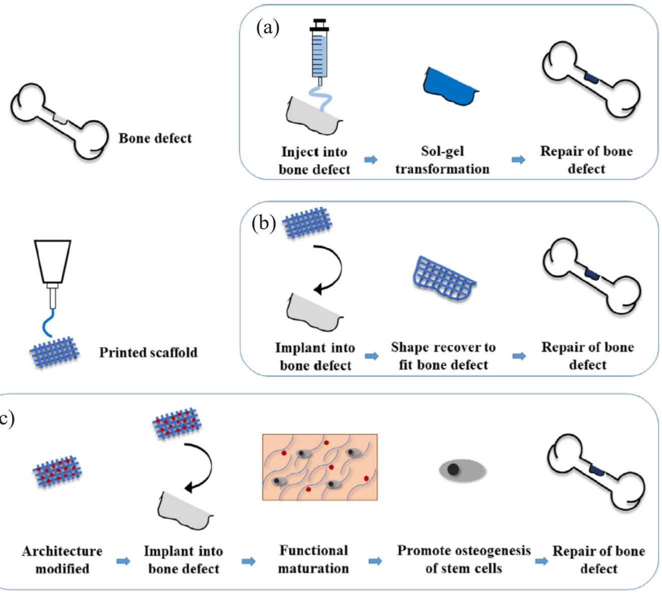

Figure 3: Bone repair process in tissue engineering using 4D printing technology (a) Hydrogels that respond to temperature, which may be injected, have been shown to promote 4D bone tissue regeneration, (b) Shape-shifting mechanism-based 4D printing of bone tissue, (c) Biomimetic microenvironment-based, 4D printing of bone tissue [41].

functional elements that vary over time. 4D printing refers to printing objects with unique properties, such as the capacity to change shape, size, color, or other attributes, such as the development of tissues [36], [37]. 4D printing, 3D biocompatible printing, and the printing of living organisms are all methods that gradually evolved. Similar to 2D printing, 4D printing uses 3D printing to combine the morphology of biomaterials with the development of synthetic tissue structures. An example of the bone repair process in tissue engineering is illustrated in Figure 3.

2.3 *4D printing materials for bioimplants*

4D printing technique described in which the orientation of embedding non-swelling cellulose fibers was carefully engineered to produce anisotropic swelling behavior. This method allowed for the design and realization of elaborately formed overall structures with a combination of straight and curved Gaussian components. SMPs and their composites are other commonly used 4D AM polymers. These materials have several benefits, including massive deformation, multi-stimulus response, biocompatibility, lightweight, and cheap cost. The multi-material printing method was used to create printed active composite materials. Origami designs might be thermo-mechanically programmed using composite materials driven by shape-morphing behavior thanks to printed SMPs fibers in an elastomer matrix [16]. To create permanent programmed forms, Ding *et al.* developed a direct 4D printing approach that included the programming processes in the 3D printing process. To enable wireless operation of 4D-printed medical equipment, including magnetic granules, into an SMPs matrix.

A novel 4D AM polymer based on hydrogel and SMPs was suggested. The use of ultrafast digital printing eliminated the need for layer-by-layer printing in the vertical dimension and line-by-line printing in the planar dimension, therefore overcoming the limitations imposed by AM on print speed. Ni-Mn-Ga SMAs printed with a binder jetting printer and NiTi alloys printed using selective laser melting (SLM) techniques are two examples of shape memory alloys (SMAs) that show promise as future 4D AM metallic materials. 3D-printed shape-memory alloys (SMAs) in these works display shape-memory characteristics due to martensitic transition at different temperatures.

To make use of the shape-changing potential of the appropriate 4D AM materials, new 4D AM methods are being developed. Opportunities exist for creating and producing 4D intelligent structural materials, such as soft robotics, controlled grippers, and programmable shape change patterns. Numerous heat-responsive 4D materials, such as hydrogels, SMAs and SMPs, have been described, making heat the most widely used and readily available stimulus for 4D printing. Heat-driven 4D printing methods have the potential for wide-ranging applications, but their poor reaction time is a fundamental drawback. Due to its many desirable qualities, including rapid reaction, wireless control, pinpoint focusing, and eco-friendliness, light-driven 4D technology has garnered a lot of interest.

Light-triggered 4D systems employ graphene, carbon nanotube, liquid crystal elastomer, monolayers, and hydrogels. Light-responsive micro-swimmers were reported. Actuators made using 4D printing technology have been shaped by humidity.

A humidity stimulus produced a hydrophilic/hydrophobic bilayer with potential use in soft actuators [38]. Magnetic fields are also significant in creating 4D materials because of the favorable circumstances for their help in biomedicine and treatment, including their finely tunable nature and a high degree of biocompatibility with living beings. DIW printed a magnetic butterfly framework and a magnetic actuator in the shape of a flower. Biomimetic 4D structures inspired by organisms as diverse as spirulina cells, caterpillars, starfish, and jellyfish are responsive to magnetic fields. In addition to these methods, researchers have examined tension, electrical, and gas-driven 4D printing systems.

These 4D-driven technologies have made considerable strides lately. Still, most currently available smart 4D structures only respond to a single stimulus, severely limiting their potential to interact with their environments and adapt to various inputs. Innovations in 4D printing have led to the emergence of a new class of printed structures in multi-responsive materials and technologies, such as light-thermal dual-responsive hydrogels, electrothermal and electrochemical actuation materials, magnetic-photo/thermal dual stimuli actuators, temperature-pH sensitive fluorescence bilayer actuators, and light-humidity-temperature-pH sensitive hydrogels. A biomimetic 4D composite with shape and color responsiveness was developed using FDM. These thermochromic pigments and SMPs were used to create it. Meanwhile, there are still hurdles to jump when it comes to 4D AM methods, such as the limitations imposed by light's wavelength and its biological toxicity, worries about the reactive nature of the method, and the difficulty of controlling the frequency of a magnetic field [39].

2.4 *Recovery performance of the material*

Extreme deformations do not affect the ability of shape memory materials (SMMs) to restore their original shape after being stimulated. This behavior may be understood for shape memory polymers (SMP). To prevent the chains from sliding out of place when the component is bent like a spiderweb, SMP should incorporate net points as the rigid segments that hold the original shape. Instead, the soft segments are in charge of the transition from rigid to soft, fixing the applied deformation and recovering the applied strain through a softening transition.

Chemical or physical crosslinks, such as crystalline or molecular entanglements, make up the challenging phase. The entropic elasticity of amorphous chains reveals a remarkable elastic deformation capacity in the soft phase. By crystallization, glass transition, or reversible crosslinks, a soft-to-rigid transition can restore the original shape of a distorted chain. Calculating the recovery rate of 4D-printed materials requires only an Equation (1),

$$SRR\ (\%) = \frac{recovered\ deflection}{recorded\ deflection} \tag{1}$$

Where, SRR- Shape Recovery Rate.

2.5 *Asymmetric behavior of the polymeric material*

The primary focus of the previous works is the static compressive response of cellular materials. Because the body's muscles may keep the bone and, by extension, the prosthesis compressed under perfect implantation conditions, this is crucial in biomedical contexts. Failure assessments of joint prostheses that broke unexpectedly showed that tensile stresses lead to failure due to patient weight, activity levels, lack of skeletal support, and implant mispositioning or loosening.

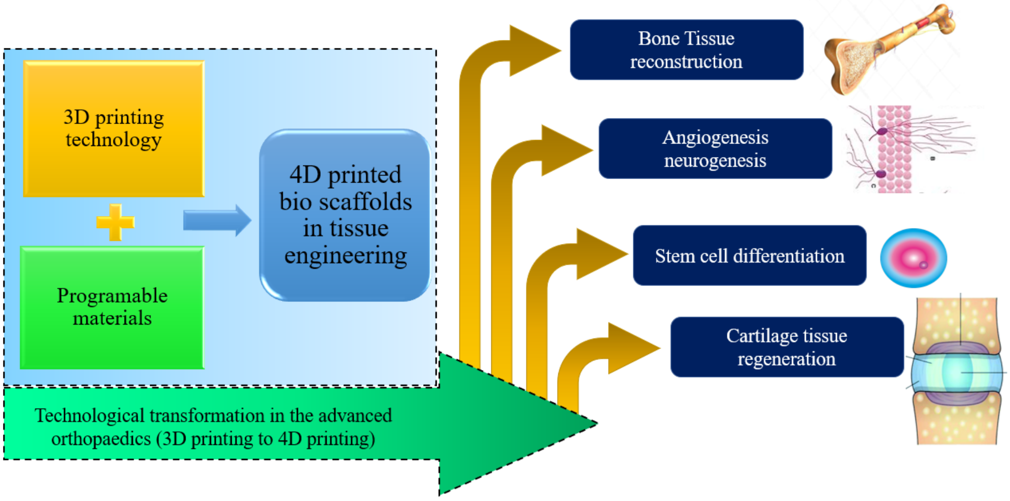

Figure 4: The technological transformation of 3D printing to 4D printing for producing scaffolds and the application of 4D printing in orthopaedics.

3 Potential Applications of 4D Printing in Tissue Engineering

3.1 *Skin*

Skin tissues from patients are obtained by skin biopsy. After being cultured in vitro to produce adequate cells, the cultured skin cells are transported to a bioprinter to create personalized skin. The skin is the body's biggest organ and acts as a protective barrier against invading germs and other infections. Hence, skin damage makes one more likely to get an infection. pH levels in healthy, noninfected wounds are between 5.5 and 6.5 throughout the healing process, whereas those in infected wounds are over 6.5. Thus, an alkaline wound pH is more favorable for healing than an acidic wound pH. In most cases, a bacterial infection is assumed to be present through 3D printing to create a wide variety of shapes [40]–[44]. In recent years, memory materials have been the focus of extensive research and development by many firms and academics to speed up the body’s natural ability to repair wounds. For various applications, Mirani *et al.* developed a pH-sensitive hydrogel-based bandage called GelDerm. If an infection is detected, GelDerm triggers the release of antibiotics at the wound site through a pH-dependent color change. Wounds are easier to identify and treat because of this cutting-edge [45]. Another research group has created a pH and temperature sensor-laden electronic patch that can respond to heat and cold as a drug-loaded hydrogel. Wound infection and inflammation may be monitored using pH and temperature sensors [46]. In response to temperature changes, the drug-loaded hydrogel gradually releases the medication. The preclinical test proved the promising potential of this material for wound treatment [47].

3.2 *Orthopaedics*

Though bone can heal some damage, there is a limit to how much damage can be repaired without outside help. Treating patients with abnormally large bones due to trauma, cancer, or infection remains a significant issue for modern medicine [48]. The technological transformation of 3D printing to 4D printing for producing scaffolds and the application of 4D printing in orthopaedics as shown in Figure 4.

Bio scaffolds, which attempt to imitate the structure of live tissue and promote the formation of new bone, have been developed as a potential solution to this issue. For instance, hydroxyapatite/polylactide scaffolds may undergo temporary deformation under compression but restoring their original morphologies upon heating helps shape recovery characteristics made available by the FDM process [49]. As the temperature rises over the glass transition temperature, the scaffold can return to its previous shape due to the increased entropy and mobility of the polymer chains. The quality of medical treatment is improved due to decreases in surgical wounds, patient recovery durations, and pain [50].

Scaffolds made from natural polymers, which degrade in the body, including chitosan and native starch-based enzyme-responsive implants, have also been produced. Amylase and lysozyme break down chitosan and starch in living organisms [51]. As a result of scaffold implantation, lymphocytes and macrophages will move to the location and produce lysozyme. The next step is for the body's enzymes (such as amylase and lysozyme) to begin degrading the scaffold, eventually resulting in a porous framework. Its porous nature makes it easier for cells to adhere and move around. As a result, the implant has enough mechanical strength during the implantation stage and develops porosity following the in vivo degradation through enzymes, enabling bone tissue regrowth. In vivo degradation through enzymes, allowing bone tissue regrowth. Only a few numbers of responsive materials have been created for use in tissue engineering and have been investigated for decades. These materials must serve this role and be biocompatible, noncytotoxic, and ideally biodegradable (resorbable). They also need specific mechanical strength and the ability to carry out dynamic processes in physiological environments. When applying a stimulus to the body or in the presence of cells, it must be secure and simple to control. For instance, staying away from extreme pH levels and hot temperatures is the best. Only a few dynamic polymers meet all the necessary criteria due to the demanding controls [52]. The implant successfully eliminates the porous implant's subpar mechanical properties. To some extent, the biological activity of a material may be correlated with how quickly it creates apatite when soaked in a solution simulating body fluid (SBF) [53], [54].

The production of biomaterials for use in bone tissue engineering relies heavily on the identification of bioactive materials capable of generating a surface apatite layer. Chitosan's crucial pH range is associated with a conformational shift that has been proven to influence apatite production [55]. Apatite formation is promoted by an increase in surface roughness when the surface pH is raised from acidic to neutral. Apatite synthesis requires regulation of the pH change that happens throughout the process. When a person is wounded or inflamed, the pH of the surrounding tissue changes from its normal 7.4 to roughly 5.2, becoming more essential. Surface apatite formed at pH 7.4 with a denser composition than on the SBF at pH 5.4. However this result contradicts what is anticipated for a pathological bone healing process [56]. By altering the surfaces of the materials, the biomineralization process may be controlled, and bone remodeling can be stimulated in vivo.

3.3 *Heart*

The development of atherosclerosis is a risk factor for cardiovascular disease. Heart conditions may now be treated using vascular stents. For instance, by fusing Fe_3O_4 nanoparticles with polymers, Using Direct write (DW) 4D printing has been utilized to produce a magneto-responsive material (lactic acid). The nanocomposite may be directly triggered and magnetically steered by assuming its original shape in a magnetic field, after which it can support the blood vessel [57]–[61]. Despite these benefits, the core concept involves producing heat through a magnetic field to restore the original form. When using magnetic fields in clinical medicine, it is essential to keep the frequency within a safe range of 50–100 kHz to prevent damaged neighboring tissues due to excessive warmth. Cause of mortality worldwide, and its complications, including heart failure, are among the significant causes of death worldwide [62], [63]. The current therapies cannot restore cardiac function. Bone marrow stem cell therapy for acute myocardial infarction has been shown to enhance heart function, decrease infarct size, and stop more infarcts from occurring [64]. However, a substantial number of cells will be destroyed in the process. Photolithographic methods minimize cell loss during transport to create thermally sensitive, bilayered, biodegradable polymers. Cells are cultured on a layer of nonreactive diacrylate triblock copolymer made up of polyethylene glycol and polylactic acid. The second layer comprises a stimuli-responsive polymer called poly(N-isopropyl acrylamide) (PNIPAAm). The swelling behavior is temperature-dependent, making this a valuable technique for enclosing and safeguarding cell clusters [65].

4 *Cell Viability of 4D Printed Scaffolds*

A dynamic printed scaffold's primary biological benefit is its ability to mimic the extracellular matrix and increase cellular mobility after cells have been enclosed inside it. Specifically, the secreted proteins and morphogens from the cells are determined mainly by the scaffold's structural features, which in turn distinguish the cells' migratory patterns [66]. When it comes to internal and exterior cellular signaling activities, biomaterials' molecular dynamics and orientations, as well as their geometrical properties, leave crucial footprints. Some polymer structures (like integrin and dopamine) play essential roles in cellular attachment to the matrix [67]. Ultra-viscous bioinks apply shear stress that is detrimental to cell survival. The greater the viscosity, the greater the damage to the cell membrane and the greater the likelihood of cell necrosis. Yet another desirable feature is the more outstanding quality of the printed scaffold with a higher viscosity. Moderating cellular stress, avoiding dry microenvironments, and reducing cell necrosis are all strategies for printing highly hydrated gels [68].

5 *Regenerative Medicines Using 4D Printing for Organs and Tissues*

When it comes to curing or replacing damaged or diseased tissues and organs, 3D printing has shown promising results and might one day be the solution to a global problem. The biomanufacturing potential of 3D printing is increasing rapidly. With its foundation in the cutting-edge capabilities of 3D printing, 4D printing takes the revolution in tissue/organ creation brought about by these technologies one step further by including a time-dependent dynamic process in the fabrication design. Printing structures with hundreds or thousands of interacting water droplets organized in programmed patterns allowed the fabrication of foldable synthetic tissues that can be directed from the outside using light [69]. Changing form dynamically is within the capabilities of these structures. With water flowing over the bilayers, the printed 4-petal structure of droplets of varying internal osmolarities collapsed into a hollow spherical [70]. Due to their multi-compartmental nature, ability to exchange information, and adaptability to change, these structures may more closely resemble biological ones. In addition, a light-controlled in vitro expression method might be employed to give these structures a more natural appearance. This method would enable the structures to synthesize protein from encapsulated DNA. The expression system regulates the brightness of lights. The target gene's promoter region has several biotin attachments sites [71]. To inhibit RNA polymerase from transcribing the DNA, astreptavidin–biotin complex was utilized as a steric blocker of the promoter region. Connecting the promoter to the biotins were photocleavable linkers. In this way, the expression system was initially inactive. Only after the block was removed by low-energy UV light did transcription, followed by translating the messenger RNA into a protein, culminating in a fully operational system. The highly regulated light-activated DNA (LA-DNA) promoter was created and optimized the number of biotins. The developed synthetic tissues respond to light by combining LA-DNA with stabilized aqueous droplet networks. Using an expression method regulated by the LA-DNA promoter, an a-hemolysin (aHL) pore has been integrated into the synthetic cells. The 3D-printed synthetic tissue is ineffective since no aHL was made, and there are no conductive pathways across the solidified droplet interface bilayer. By utilizing LA-DNA or focused irradiation to pattern the synthetic cells, we could create long 3D ways of cells that might produce aHL within synthetic tissues [18], [72]–[76]. Consequently, directed electrical communication triggered by light was accomplished using external electrodes. There is promising future use for these synthetic tissues in medication delivery and surgical tissue replacement.

The materials' multi-compartment architecture allows for the release of both binary and ternary agents; the components of the agents (for example, an enzyme and a substrate) are united at a specified point to generate potent effectors. Synthetic tissues might replace injured tissues, particularly for making a temporary electrical connection following nerve injury. Furthermore, employing synthetic tissues instead of therapies based on actual cells may alleviate worries about immunogenicity and uncontrolled proliferation.

6 Future Perspectives and Current Challenges

Because it adds “time” to the three existing dimensions of 3D printing, 4D printing is often regarded as the cutting edge of tissue engineering because of its potential for producing complex structures with dynamically adjustable forms and behaviors on demand. Recent years have seen a surge in interest in 4D printing

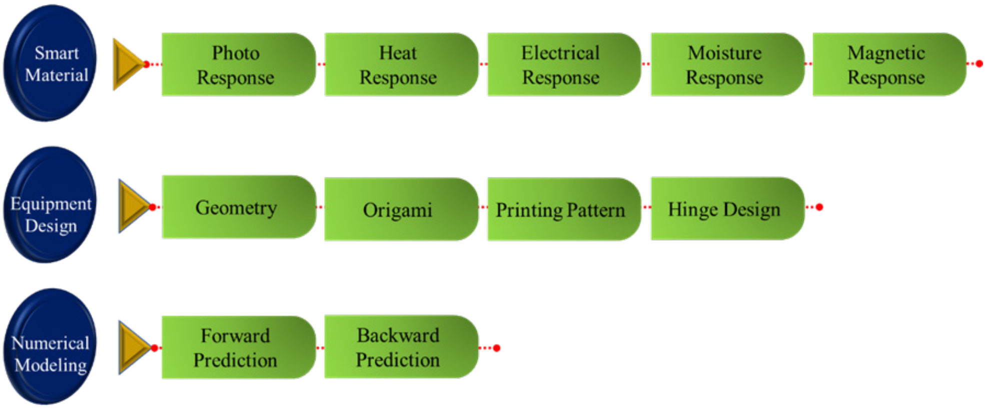

Figure 5: Major research areas in 4D printing in the future technological landscape include smart material development, experimental design, and numerical modeling of the biosystem.

technology for use in both the biomedical research community and clinical settings, thanks to advances in our understanding of tissue regeneration and the creation of stimuli-responsive biomaterials. In individualized tissue regeneration, for instance, 4D printing technology offers vast application opportunities [77]. Major research areas in 4D printing in the future technological landscape, such as smart material development, experimental design and numerical modeling of the biosystem, are shown in Figure 5. The exact geometry of the defect locations would be accommodated by the 4D-printed implantations, whose form and size would have been determined beforehand.

Biomimetic properties would emerge in the post-printing phase after implantation, allowing for more accessible tissue remodeling and maturation. Simultaneously, advances in computer model systems have opened up fresh prospects for neo-tissue growth programming in individualized tissue engineering. The ability to fabricate self-growing constructions using 4D printing transformational properties may also be helpful in the treatment of adolescents. For instance, when treating children with tracheobronchomalacia, based 4D-printed medical device tailored to the patient's specific needs was very beneficial [67]. There was evidence of self-growth in the 4D-printed PCL airway splints, with the devices demonstrating the desired mechanical and degradation characteristics over time. Advantages may be shown when using 4D-printed constructs to treat teenage patients with congenital malformation because of their ability to self-transform and self-mature [78].

Clinical applications of medication delivery and cell treatment may also benefit from stimuli-responsive cell assembly and tissue remodeling technologies. Treatments for spinal cord injuries have used a stem cell delivery method powered by magnetic forces. These stimuli-responsive cell carriers may exhibit directional migration and cell-homing capabilities in vivo, making them therapeutically useful for injury repair in a particular area [79].

In past reports, only specific 3D bioprinters may employ safe human-use polymers. These include natural and manufactured polymers, such as carbohydrate polysaccharides and acrylate-based polymers. Emerging innovations in the functionalization of existing monomers/polymers to make them printable or boost their biocompatibility may pave the way for deploying innovative devices for biomedical applications. Soybean oil epoxidized acrylate is a newly discovered material used in 4D systems [80].

Tissues with complex structures have been produced using 4D materials. Still, their widespread usage in therapeutic applications has yet to materialized due to the immaturity of the printed tissue and the absence of data from clinical studies. Consequently, post-printing procedures like cellular coating and cell self-organization must be optimized to ensure that printed tissue bio-objects mature successfully. Indeed, the possibility of generating synthetic tissue bio-objects with functional qualities equal to the original tissue is made by post-tissue maturation [3], [81]–[86]. Even with these restrictions, 4D printing still has much untapped potential. In the beginning, we can only see the tip of the proverbial iceberg regarding all the revolutionary research and methods developed. The transition from 4G to 5G in the communications sector is analogous in that most people see it merely as a faster connection and miss the commercial opportunity it presents. In addition, as engineering advances, such restrictions will vanish. Products might be made from various dynamic materials that react differently to different stimuli to adapt to the body [87]. Creating individualized medical devices from the start would assist in overcoming this constraint rather than mass production.

7 Conclusions

4D printing is introducing novel biomedical therapeutic approaches; consequently, organic and inorganic materials are becoming more friendly. After years of research and development, the 4D printing industry is starting to form. The views of experts on the growth of the sector are diverse. Though still in its infancy, 4D printing has received significant attention from industry leaders for the vast opportunities it brings.

Author Contributions

M.T.: conceptualization, reviewing, writing an original draft and editing; B.C.: research design, data analysis; P.R.: data curation, writing and editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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