"Stimuli-Responsive Pharmaceuticals: The Next Dimension with 4D Printing"

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Abstract-

4D printing (4DP) is an innovative advancement of 3D printing that adds a time-dependent functionality to printed objects. Introduced in 2013, 4DP enables the creation of structures that can transform their shape or behavior when exposed to external stimuli such as heat, light, pH, moisture, or magnetic fields. This is achieved by incorporating smart materials like Shape Memory Polymers (SMPs) and hydrogels into the printing process. SMPs allow objects to return to a pre-defined shape in response to environmental changes, while hydrogels—responsive to temperature, water, or light—are especially useful in biomedical applications like controlled drug delivery.The roots of additive manufacturing trace back to Chuck Hull's invention of stereolithography (SLA) in 1986. Since then, the field has evolved significantly, and 4DP marks a transformative leap. It has found applications in diverse sectors such as aerospace (deployable satellites, morphing wings), biomedicine (self-expanding stents, personalized implants), pharmaceuticals (targeted drug release), soft robotics, and tissue engineering. In tissue engineering, for instance, 4DP is used to develop scaffolds that adapt to the body's conditions, aiding in regeneration. Technologies like machine learning (ML), finite element analysis (FEA), and computer-aided drug design (CADD) are enhancing 4DP through smarter modeling and predictive design. 4D bioprinting, an extension of this concept, introduces responsiveness into biological structures, improving therapeutic precision and customization. Despite its vast potential, 4DP still faces challenges including limited material availability, slow response times, and the complexity of integrating multiple materials. Specialized software and hardware are also required. However, with ongoing research and innovation, the technology holds promising future applications in space manufacturing, wound care, and even 5D/6D printing. With the global market expected to grow from USD 207.4 million in 2024 to over USD 4.44 billion by 2034, 4DP is poised to revolutionize adaptive and intelligent manufacturing.

Keywords- 4D printing, smart materials, shape memory polymers, hydrogels, drug delivery, bioprinting, adaptive structures, tissue engineering, self-assembly.

Introduction

In 1986, Chuck Hull introduced the concept of three-dimensional (3D) systems for stereolithography (SLA), a breakthrough that captured global interest and is widely regarded as a foundational moment in the development of 3D printing technology.[1]Since the late 1980s, additive manufacturing (AM), also known as 3D printing or fast prototyping, has steadily gained popularity.[2,3,4]At the moment, there are two primary types of additive manufacturing for four-dimensional (4D) printing: vat photopolymerization techniques and extrusion-based techniques [5,6].Because 3D printing can quickly prototype complexly shaped 3D goods, it has found widespread use in biomedicine, polymer science, space research, and other domains.[7-11].Depending on how these materials function, 3D microstructures made of intelligent materials may undergo specific changes over time. Because of this, a new term, "4D printing," has surfaced. [12]. In 2013, Professor Tibbits introduced the idea of 4D printing [13].This marked the beginning of the 4D printing concept. At first, 4D printing was explained with the formula “4D printing = 3D printing + time,” highlighting how a 3D-printed object can change its shape, structure, or function over time.[14–16]. 4D printing is an advanced manufacturing technology that builds on 3D printing by adding the dimension of time, enabling printed objects to change their shape, properties, or functionality after fabrication in response to environmental stimuli such as heat, light, moisture, or pressure. advancement of 3D printing that introduces capabilities such as self-assembly, shape transformation, and self-repair by improving the printed object's form, structure, and function. 4D printing focuses on embedding flexible smart materials into the product design, allowing microstructures to change according to a pre-defined pattern when exposed to specific conditions or stimuli over time. Currently, 4D printing can produce dynamic, responsive objects that traditional 3D printing cannot, due to its ability to incorporate time-dependent transformations.[17-18],volume [19], and shape [20],Compared to traditional manufacturing, 4D printing provides enhanced material adaptability, allowing for precise responsiveness to environmental changes, and has already been successfully applied in several fields—for instance, in bioprinting, which enables the creation of 3D structures made from living biological components such as tissues, organs, cells, and nutrients.[21–23]. 4D bioprinting, as a next-generation emerging technology, has the potential to revolutionize fields like regenerative medicine, materials science, chemistry, and computer science,[24-26] with its key advantage being the ability of printed biological structures to alter their functions over time in response to specific stimuli. [27]. This review begins by presenting additive manufacturing techniques relevant to 4D printing, outlining the advantages and limitations of the resulting products, and explaining the concept of 4D printing is first introduced, followed by an exploration of various implementation strategies. The discussion then categorizes and reviews the types of stimuli that activate responses in 4D-printed objects. It also examines commonly used smart materials in 4D printing, such as shape memory polymers (SMPs) and hydrogels. Finally, the review highlights major applications and outlines future prospects and developments in this rapidly evolving field.

4D Printing Market Size and Forecast (2025–2034)

The global 4D printing market is projected to be worth approximately USD 281.73 million in 2025 and is expected to grow significantly, reaching around USD 4,436.96 million by 2034. This growth reflects a strong compound annual growth rate (CAGR) of 35.84% during the forecast period. The North American market is anticipated to reach USD 102.24 million by 2025 and is set to record the highest CAGR of 35.85%, underscoring the region’s leading role in the adoption and development of 4D printing technologies.

4D Printing Market Size and Forecast (2025 to 2034) – USD Million

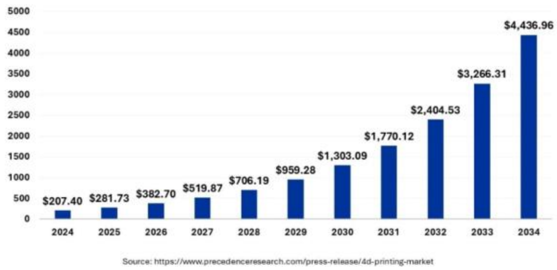

Table no.1 4D Printing Market Size and Forecast (2025 to 2034) – USD Million

Year	Market Size (USD Million)
2025	281.73
2026	~382.53
2027	~519.24
2028	~704.68
2029	~956.81
2030	~1,298.40
2031	~1,762.83
2032	~2,392.79
2033	~3,248.33
2034	4,436.96

Market Overview:

4D printing, also referred to as 4D bioprinting, shape-morphing systems, or active origami, is an advanced evolution of 3D printing that utilizes specialized materials to create objects capable of changing shape over time. This innovation is driven by the need to reduce manufacturing costs, and the 4D printing market is expected to experience significant growth as a result. Unlike traditional 3D printing, where materials are deposited layer by layer, 4D printing introduces a new dimension, allowing the object to transform in response to environmental stimuli such as heat, moisture, or pressure. For example, ventilators were quickly produced using 3D printing techniques, with parts rapidly combined to meet the high demand during the crisis.[28] progress has been made in the development of 4D-printed drug delivery systems. Melocchi et al. [29]Additionally, Uboldi et al.further contributed to advancements in this field.[30]. Additionally, Uboldi et al. [31] emphasized the use of film coating techniques in developing a 4D-printed slow-release system intended for organ retention.

Aim of the Review

This review examines the emerging field of 4D-printed drug delivery systems (DDS), focusing on the integration of smart materials and stimuli-responsive mechanisms that enable temporal shape and functional transformations in drug delivery devices. It discusses potential biomedical applications such as targeted therapy, controlled release, and minimally invasive administration, while also addressing challenges like material limitations, biocompatibility, regulatory hurdles,and manufacturing scalability. Finally, the paper provides insights into future directions and research opportunities that could facilitate the advancement and broader adoption of 4D printing in personalized medicine and precision drug delivery.[32,33,34]

1 .Materials for 4D Printing in Drug Delivery-

1.1 Shape memory materials (SMMs)

They have the unique ability to return to their original form after undergoing quasi-plastic deformation when exposed to an appropriate stimulus, a behavior known as the shape memory effect (SME). Shape memory polymers (SMPs) exhibit this capability by transitioning between their printed configuration and a predefined shape in response to external triggers. In a study by Xie et al., a shape memory polymer was created using a light-curing technique, demonstrating structural transformation when exposed to water. Additionally, SMPs can be activated through magnetic induction by embedding nanoparticles within thermoplastic materials. Various external stimuli, such as heat, can trigger these transformations in SMPs. [35,36,37], light [38,39], electricity [40-46], magnetic fields [47,48] chemical stimulus (pH changes) [49,50], humidity [51] etc.

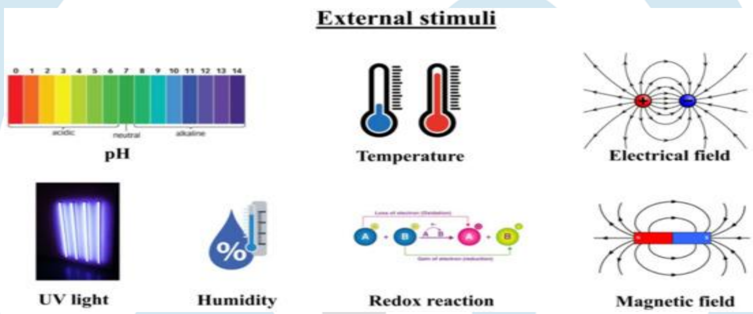

Figure 1. External stimuli for activation of polymer actuators. [52]

SMP resins exhibit greater brittleness and lower impact resistance compared to other SMPs [52], primarily due to their high crosslinking density under large strain conditions.

1.2 Hydrogels: Hydrogels are 3D crosslinked polymer networks capable of absorbing and retaining substantial amounts of water while maintaining their shape. They can be categorized in various ways: by polymer origin as natural or synthetic; by crosslinking type as physical or chemical; by electrical charge as ionic or non-ionic; by pore size as nanoporous or microporous; by size as nano-, micro-, or macro-gels; and by responsiveness to external stimuli as either conventional or smart hydrogels.[53]

1.2.1 Thermo-Responsive Hydrogels:Thermo-responsive hydrogels show phase changes that depend on temperature and are capable of rapidly transitioning between sol and gel states at a specific critical temperature [54,55,56].

1.2.2 Magnetic Responsive Hydrogels: To impart magnetic responsiveness to hydrogels, external materials such as paramagnetic or ferromagnetic substances are integrated into the polymer network, enabling quick and significant actuation when exposed to magnetic fields [57] These magnetic components ranging from metal alloys like iron-neodymium, to metal oxides such as magnetite, and surface-modified magnetic nanoparticles can be incorporated into polymers like pNIPAM, pAAm, and gelatin through either chemical or physical crosslinking, resulting in smart hydrogels that respond to magnetic stimuli [58,59,60].

1.2.3 Photo Responsive Hydrogels: Light serves as a highly beneficial stimulus for remotely triggering the expansion and contraction of 4D-printed hydrogels, enabling precise control over the release of therapeutic agents. The two main mechanisms driving the response in photo-sensitive hydrogels are 6 reversible crosslinking and photothermal activation [61].

1.2.4 Ion-Responsive Hydrogels: Ion-responsive hydrogels utilize ionizable components in their structure to enable adaptable behavior. These electrically charged hydrogels undergo volume changes when the salt concentration in their environment changes. An example of an ion-responsive hydrogel includes those containing carboxyl groups, such as sodium alginate (SA)(62), alginate(63), and poly(acrylic acid) (PAA)(64).

1.2.5 Water-Responsive Hydrogels: Water-responsive hydrogels, Water-responsive hydrogels, also known as superabsorbent polymers, are materials that can absorb and retain large amounts of water, leading to significant swelling and changes in their physical properties when exposed to moisture,are three-dimensional crosslinked macromolecular networks with a remarkable ability to swell by absorbing large amounts of liquid..

2. Applications of 4D Printing:

2.1. Aerospace and Automotive: Adaptive structures, the design phase poses significant challenges for engineers due to the demanding aircraft specifications and performance requirements. To achieve optimal aircraft design, reshaping structural members (SMs) plays a key role, particularly in enhancing wing structures to perform efficiently under various flight conditions [65]. By 2025, 4DP technology in the aviation industry is projected to hold over 25% of the market share, ranking just behind the military and defense sectors [66].

2.2.Biomedical: The properties of shape memory materials (SMMs) are advantageous in A wide range of biomedical applications, including drug delivery systems, self-expanding stents, implanted devices, catheters, guidewires, atrial occlusion tools, and thrombectomy devices [67].Four-dimensional printing (4DP) enhances the potential for personalized medical treatments.The advancement of smart medical devices is closely tied to the improved capabilities offered by shape memory materials (SMMs), including features like self-healing [68].These devices are expected to improve pathological outcomes and facilitate less invasive surgical procedures, allowing implants to be placed in regions that are typically difficult to access [69]

2.3. Soft Robotics: 4D printing technology offers not only the ability to process complex structural components with flexibility but also imparts unique intelligence to the material structure, enabling the integration of both structure and functionality [70]. Additionally, the use of multi-material 4DP allows soft robots to integrate sensing and actuation functions during the manufacturing process [71].Precisely engineered microstructural architectures have shown enhanced performance compared to traditional materials, due to their deliberately designed micro- or nanoscale structures that provide novel optical, mechanical, or electrical properties [72].A bioinspired microstructure was developed and manufactured as A high-efficiency integrated sensor-actuator [73].

2.4. Pharmaceuticals: According to Basit and Gaisford, 4D printing is currently in the early stages of development and requires further research before it can be used for manufacturing ingestible drugs. [74].Melocchi et al. supported the previous viewpoint, suggesting that significant efforts will be directed toward exploring materials, production methods, and functional behaviors in this field [75].Numerous SMP research efforts in the pharmaceutical industry have focused on investigating polymer chemical structures for use in consumable medications [76].

2.5.Tissue Engineering: The sophisticated functionalities of 4D printing technology is still in its infancy and requires more research before it can be used for producing ingestible drugs. offer potential solutions to these challenges. These include, among others, the capability to position implants in hard-to-reach areas [77] and facilitate Minimally invasive surgeries. [78].Luo et al. developed a 4D structure loaded with cells that preserved strong cell viability for a minimum of after two weeks, they discovered that NIR laser exposure had no noticeable impact on the embedded cells [80]. Lai, Li, and Wang introduced an innovative strategy to advance The area of tissue engineering.[81,82].

Advantages Over Traditional System:

I. 4D printing (4DP) enables the creation of flexible structures that can undergo geometric transformations when exposed to specific environmental stimuli, reflecting the inherent responsive behavior of the materials used [83].

II. The 4DP structures' self-operational properties—such as self-assembly, self-adaptability, and self-repair—have improved their feasibility in a range of applications.[84]

III. By offering adaptable equipment and preventing the need for resupply from Earth, it enables the reduction of launch expenses.[85]
IV. Additionally, the aerospace sector can use 4DP to build self-deploying devices and elements related to engine cooling, air control, and other applications because components can self-assemble in space.[86]
V. However, the potential applications of 4DP in a variety of industries will become.[87]
VI. Furthermore, 4D printing technology could be transformative as the next generation of additive manufacturing.[88]
VII. Furthermore, in manufacturing applications,4D printing method to helps to cut down on waste, mistakes, and product loss.[89]

Challenges and Limitations:

Challenges:

I. The main obstacle is that the intended shape or property transformation places limitations on the mechanical characteristics of 4D-printed structures.[90]
II. Significant advancements have been made in developing smart printable materials with a range of mechanical properties, and this research is essential for advancing 4D printing.[91-93]
III. Since most shape memory materials (SMMs) support only one-way shape transformation, they pose a challenge for designing dynamic or reconfigurable structures.[84]
IV. While various biomaterials, including metals and polymers, and ceramics have potential as smart materials, currently only smart polymers have proven effective for use in 4D printing.[94]
V. One of the key challenges in the field of 4D printing is the creation of smart components.[93]
VI. Some of the challenges associated with the properties of smart materials include oxidation, alterations in phase transformation behaviour, microstructural flaws, rapid solidification, and directional cooling.[94]

Limitations:

I. The current methods for 3D/4D printing are limited in their ability to produce complex shapes.[86]
II. The technology in question needs further enhancement to create more highly precise medical devices.
III. Although 4D materials have been used to create tissues with intricate structures, their full potential in clinical applications has not yet been realized due to incomplete tissue maturation and the absence of clinical trial evidence.[95]
IV. The complex physiological conditions of the human body are complex.are maintained through a variety of regulatory processes.[96]
V. However, It is crucial to emphasize that the laser-assisted method is costly and restricts researchers to using only single-material as printer ink.
VI. To overcome these challenges, future research could utilize Internet of Things (IoT) and Artificial Intelligence (AI) systems.[97]

Future Prospective Of 4D Printing

4D printing is an interdisciplinary field that merges art, science, and engineering, enabling the creation of structures that change over time in response to external stimuli. It relies on advancements in smart materials, such as shape memory polymers and hydrogels, and employs mathematical modeling to predict and control these transformations.[98]. Furthermore, 4DP is seen as a potential advancement in the evolution of lean manufacturing.[99]Advancements in 5D[100]and 6D printing[101] technologies could further enhance the capabilities of 4D printing, enabling more complex and adaptable structures. A notable Implementation is in space manufacturing. NASA, in collaboration with Made In Space, Inc., has demonstrated the feasibility of 3D printing aboard the International Space Station (ISS). This technology enables the in-orbit fabrication and deployment of CubeSats, which can significantly reduce the reliance on rocket resources, fuel, and scheduling time. However, these light-responsive materials could be harnessed to develop solar panels that continuously follow the sun's movement, ensuring a consistent power supply and potentially minimizing the size and power demands of onboard batteries[102].While a range of materials—such as shape memory polymers and stimulus-responsive hydrogels have been successfully explored, their slow response times and limited efficiency continue to hinder further progress in the field[103]. Moreover, 6D printing merges the responsive behavior of 4D printing with the complex geometries achievable through 5D printing, allowing the creation of smart-material structures with intricate curved designs. Together, these innovations pave the way for new possibilities in advanced manufacturing.[104]. 4D printing enables the development of adaptive wound dressings that conform to wound contours and function as drug delivery systems, facilitating targeted medication release at the site. Future research focuses on creating self-folding, protein-based structures and capsules capable of adjusting their drug release profiles autonomously. [105]

Conclusion: 4D printing is a groundbreaking advancement in additive manufacturing, integrating time-dependent, self-transforming structures with smart materials that react to external stimuli. This technology has the potential to revolutionize industries like biomedicine, aerospace, soft robotics, and pharmaceuticals by enabling the creation of adaptive, functional objects that can change shape or behavior in response to environmental factors. Despite challenges like material constraints, slow response times, and the complexity of multi-material integration, 4D printing's transformative potential in creating personalized medical devices, responsive scaffolds, and dynamic structures remains immense, paving the way for future innovations in engineering and healthcare applications.

References:

1. Guzmangonzalez, J.V.; Saldanamartinez, M.I.; Barajasgonzalez, O.G.; Guzmanramos, V.;Garciagarza, A.K.; Francoherrada, M.G.; Aguilar, R.J.S.; Garciaramirez, M.A. Multifunctional cube-like system for biomedical applications featuring 3D printing by dual deposition, scanner, and UV engraving. *Proc. SPIE* **2017**, *10095*, 1009511.
2. Wong, K.; Hernandez, A. A Review of Additive Manufacturing. *Int. Sch. Res. Not.* **2012**, *2012*, 1–10. [CrossRef]
3. Loterie, D.; Delrot, P.; Moser, C. High-resolution tomographic volumetric additive manufacturing. *Nat. Commun.* **2020**,*11*, 1–6. [CrossRef] [PubMed]
4. 4.Ragelle, H.; Tibbitt, M.W.; Wu, S.; Castillo, M.A.; Cheng, G.; Gangadharan, S.P.; Anderson, D.; Cima, M.J.; Langer, R. Surface tension-assisted additive manufacturing. *Nat. Commun.* **2018**, *9*, 1184. [CrossRef]
5. Zein, I.; Hutmacher, D.W.; Tan, K.C.; Teoh, S.H. Fused deposition modeling of novel scaffold architectures for tissue engineering applications. *Biomaterials* **2002**, *23*, 1169–1185. [CrossRef]
6. Melchels, F.P.W.; Feijen, J.; Grijpma, D.W. A review on stereolithography and its applications in biomedical engineering. *Biomaterials* **2010**, *31*, 6121–6130. [CrossRef]
7. Gao, W.; Zhang, Y.; Ramanujan, D.; Ramani, K.; Chen, Y.; Williams, C.B.; Wang, C.C.L.; Shin, Y.C.; Zhang, S.; Zavattieri, P.D. The status, challenges, and future of additive manufacturing in engineering. *Comput.-Aided Des.* **2015**, *69*, 65–89. [CrossRef]
8. Chia, H.N.; Wu, B.M. Recent advances in 3D printing of biomaterials. *J. Biol. Eng.* **2015**, *9*, 4. [CrossRef]
9. Wallin, T.J.; Pikul, J.H.; Shepherd, R.F. 3D printing of soft robotic systems. *Nat. Rev. Mater.* **2018**, *3*, 84–100. [CrossRef]
10. Jia, Y.; He, H.; Geng, Y.; Huang, B.; Peng, X. High through-plane thermal conductivity of polymer based product with vertical alignment of graphite flakes achieved via 3D printing. *Compos. Sci. Technol.* **2017**, *145*, 55–61. [CrossRef]
11. Dimitrov, D.; Schreve, K.; De Beer, N. Advances in three dimensional printing—State of the art and future perspectives. *Rapid Prototyp. J.* **2006**, *12*, 136–147. [CrossRef]
12. Tofail, S.A.M.; Koumoulos, E.P.; Bandyopadhyay, A.; Bose, S.; Odonoghue, L.; Charitidis, C.A. Additive manufacturing: Scientific and technological challenges, market uptake and opportunities. *Mater. Today* **2017**, *21*, 22–37. [CrossRef]

13. Raviv, D.; Zhao, W.; McKnelly, C.; Papadopoulou, A.; Kadambi, A.; Shi, B.; Hirsch, S.; Dikovsky, D.; Zyracki, M.; Olguin, C.; et al. Active Printed Materials for Complex Self-Evolving Deformations. *Sci. Rep.* **2014**, *4*, 7422. [CrossRef] [PubMed]
14. Tibbits, S. 4D Printing: Multi-Material Shape Change. Archit. Des. **2014**, 84, 116–121. [CrossRef]
15. Momeni, F.; Liu, X.; Ni, J. A review of 4D printing. Mater. Des. **2017**, 122, 42–79. [CrossRef]
16. Leist, S.K.; Zhou, J. Current status of 4D printing technology and the potential of light-reactive smart materials as 4D printable materials. Virtual Phys. Prototyp. **2016**, 11, 249–262. [CrossRef]
17. Gladman, A.S.; Matsumoto, E.A.; Nuzzo, R.G.; Mahadevan, L.; Lewis, J.A. Biomimetic 4D printing. Nat. Mater.**2016**, 15, 413–418. [CrossRef]
18. Wang, J.; Wang, Z.; Song, Z.; Ren, L.; Liu, Q.; Ren, L. Biomimetic Shape–Color Double-Responsive 4D Printing. Adv. Mater. Technol. **2019**, 4, 1900293. [CrossRef]
19. He, C.; Zhang, M.; Guo, C. 4D printing of mashed potato/purple sweet potato puree with spontaneous color change. Innov. Food Sci. Emerg. Technol. **2020**, 59, 102250. [CrossRef]
20. Kang, M.K.; Pyo, Y.; Jang, J.Y.; Park, Y.; Son, Y.; Choi, M.; Ha, J.W.; Chang, Y.; Lee, C.S. Design of a shape memory composite (SMC) using 4D printing technology. Sens. Actuators A-Phys. **2018**, 283, 187–195.[CrossRef]
21. Bodaghi, M.; Noroozi, R.; Zolfagharian, A.; Fotouhi, M.; Norouzi, S. 4D Printing Self-Morphing Structures.Materials **2019**, 12, 1353. [CrossRef] [PubMed]
22. Jessop, Z.M.; Alsabah, A.; Gardiner, M.D.; Combellack, E.J.; Hawkins, K.; Whitaker, I.S. 3D bioprinting for reconstructive surgery: Principles, applications and challenges. J. Plast. Reconstr. Aesthet. Surg. **2017**, 70,1155–1170. [CrossRef] [PubMed]
23. Seliktar, D.; Dikovsky, D.; Napadensky, E. Bioprinting and Tissue Engineering: Recent Advances and Future Perspectives. Isr. J. Chem. **2013**, 53, 795–804. [CrossRef]
24. Murphy, S.V.; Atala, A. 3D bioprinting of tissues and organs. Nat. Biotechnol. **2014**, 32, 773–785. [CrossRef][PubMed]
25. Li, Y.; Zhang, Y.S.; Akpek, A.; Shin, S.R.; Khademhosseini, A. 4D bioprinting: The next-generation technology for biofabrication enabled by stimuli-responsive materials. Biofabrication **2016**, 9, 012001. [CrossRef]
26. Yang, G.H.; Yeo, M.; Koo, Y.W.; Kim, G. 4D Bioprinting: Technological Advances in Biofabrication. Macromol. Biosci. **2019**, 19, 1800441. [CrossRef]
27. Yang, Q.; Gao, B.; Xu, F. Recent Advances in 4D Bioprinting. Biotechnol. J. **2020**, 15, 1900086. [CrossRef]
28. Ozbolat, I.T.; Yu, Y. Bioprinting Toward Organ Fabrication: Challenges and Future Trends. IEEE Trans. Biomed. Eng. **2013**, 60, 691–699. [CrossRef]
29. An, J.; Chua, C.K.; Mironov, V. A Perspective on 4D Bioprinting. Int. J. Bioprint. **2016**, 2, 3. [CrossRef]
30. https://www.precedenceresearch.com/4d-printing-market
31. Baniasadi M, Yarali E, Foyouzat A, Baghani M. Crack self-healing of thermo- responsive shape memory polymers with application to control valves, filtration, and drug delivery capsule. Eur J Mech Solids. 2021;85:104093. [Google Scholar]
32. Melocchi A, Inverardi N, Uboldi M, Baldi F, Maroni A, Pandini S, Briatico-Vangosa F, Zema L, Gazzaniga A. Retentive device for intravesical drug delivery based on water-induced shape memory response of poly(vinyl alcohol): design concept and 4D printing feasibility. Int J Pharm. 2019;559:299–311. [DOI] [PubMed] [Google Scholar]
33. Uboldi M, Melocchi A, Moutaharrik S, Cerea M, Gazzaniga A, Zema L. Dataset on a small-scale film-coating process developed for self-expanding 4D printed drug delivery devices. Coatings. 2021;11(10):2. [Google Scholar]
34. Miao, S., Zhu, W., Castro, N. J., Nowicki, M., Zhou, X., Cui, H., ... & Zhang, L. G. (2016). 4D printing smart biomedical scaffolds with stimuli-responsive biomaterials. Biotechnology Journal, 11(10), 1378–1387. https://doi.org/10.1002/biot.201600104
35. Wang, Y., Wu, D., Ye, C., & Zhang, Y. S. (2021). 4D printing for biomedical applications. Materials Today, 41, 33-51. https://doi.org/10.1016/j.mattod.2020.10.002
36. Tasoglu, S., & Demirci, U. (2013). Bioprinting for stem cell research. Trends in Biotechnology, 31(1), 10–19. https://doi.org/10.1016/j.tibtech.2012.10.005

37. W. M. Huang, "Shape memory materials," Materials today, vol. 13, no. 7, pp. 54-61, 2010.
38. Lendlein, A.; Kelch, S. Shape-memory polymers. Angew. Chem. Int. Ed. 2002, 41, 2034–2057. [Google Scholar] [CrossRef]
39. Liu, C.; Qin, H.; Mather, P.T. Review of progress in shape-memory polymers. J. Mater. Chem. 2007, 17, 1543–1558. [Google Scholar] [CrossRef]
40. Everhart, M.C.; Nickerson, D.M.; Hreha, R.D. High-temperature reusable shape memory polymer mandrels. In Smart Structures and Materials 2006: Industrial and Commercial Applications of Smart Structures Technologies; White, E.V., Ed.; SPIE: San Diego, CA, USA, 2006; Volume 6171. [Google Scholar] [CrossRef]
41. Lendlein, A.; Jiang, H.Y.; Junger, O.; Langer, R. Light-induced shape-memory polymers. Nature 2005, 434, 879–882. [Google Scholar] [CrossRef]
42. Jiang, H.y.; Kelch, S.; Lendlein, A. Polymers move in response to light. Adv. Mater. 2006, 18, 1471–1476. [Google Scholar] [CrossRef]
43. Paik, I.H.; Goo, N.S.; Jung, Y.C.; Cho, J.W. Development and application of conducting shape memory polyurethane actuators. Smart Mater. Struct. 2006, 15, 1476–1482. [Google Scholar] [CrossRef]
44. Leng, J.S.; Lv, H.B.; Liu, Y.J.; Du, S.Y. Electroactivate shape-memory polymer filled with nanocarbon particles and short carbon fibers. Appl. Phys. Lett. 2007, 1, 144105. [Google Scholar] [CrossRef]
45. Schmidt, A.M. Electromagnetic activation of shape memory polymer networks containing magnetic nanoparticles. Macromol. Rapid Commun. 2006, 27, 1168–1172. [Google Scholar] [CrossRef]
46. Koerner, H.; Price, G.; Pearce, N.; Alexander, M.; Vaia, R.A. Remotely actuated polymer nanocomposites-stress-recovery of carbon-nanotube-filled thermoplastic elastomers. Nat. Mater. 2004, 3, 115–120. [Google Scholar] [CrossRef]
47. Buckley, P.R.; Mckinley, G.H.; Wilson, T.S.; Small, W.; Benett, W.J.; Bearinger, J.P.; Mcelfresh, M.W.; Maitland, D.J. Inductively heated shape memory polymer for the magnetic actuation of medical devices. IEEE Trans. Biomed. Eng. 2006, 53, 2075–2083. [Google Scholar] [CrossRef]
48. Leng, J.S.; Lan, X.; Liu, Y.J.; Du, S.Y.; Huang, W.M.; Liu, N.; Phee, S.J.; Yuan, Q. Electrical conductivity of thermoresponsive shape-memory polymer with embedded micron sized Ni powder chains. Appl. Phys. Lett. 2008, 92, 014104. [Google Scholar] [CrossRef]
49. Tan, R.Y.H.; Lee, C.S.; Pichika, M.R.; Cheng, S.F.; Lam, K.Y. PH Responsive Polyurethane for the Advancement of Biomedical and Drug Delivery. Polymers 2022, 14, 1672. [Google Scholar] [CrossRef]
50. Li, J.; Hu, W.; Zhang, Y.; Tan, H.; Yan, X.; Zhao, L.; Liang, H. pH and glucose dually responsive injectable hydrogel prepared by in situ crosslinking of phenylboronic modified chitosan and oxidized dextran. J. Polym. Sci. Part A Polym. Chem. 2015, 53, 1235–1244. [Google Scholar] [CrossRef]
51. Agarwal, S.; Jiang, S.; Chen, Y. Progress in the Field of Water- and/or Temperature-Triggered Polymer Actuators. Macromol. Mater. Eng. 2018, 304, 1800548. [Google Scholar] [CrossRef]
52. Zhao T, Yu R,LiX, ChengB,ZhangY, YangX, Zhao X, Zhao Y,Huang W (2018) 4D printing of shape memory polyurethane via stereolithography. EurPolym J 101:120–126
53. Ullah, F.; Othman, M.B.H.; Javed, F.; Ahmad, Z.; Akil, H.M. Classification, processing and application of hydrogels: A review. Mater. Sci. Eng. C 2015, 57, 414–433. [Google Scholar] [CrossRef]
54. Andersson, M.; Axelsson, A.; Zacchi, G. Swelling kinetics of poly (N-isopropylacrylamide) gel. J. Control. Release 1998, 50, 273–281. [Google Scholar] [CrossRef]
55. Bischofberger, I.; Trappe, V. New aspects in the phase behaviour of poly-N-isopropyl acrylamide: Systematic temperature dependent shrinking of PNiPAM assemblies well beyond the LCST. Sci. Rep. 2015, 5, 15520. [Google Scholar] [CrossRef] [Green Version]
56. Li, Z.; Shen, J.; Ma, H.; Lu, X.; Shi, M.; Li, N.; Ye, M. Preparation and characterization of pH-and temperature-responsive nanocomposite double network hydrogels. Mater. Sci. Eng. C 2013, 33, 1951–1957. [Google Scholar] [CrossRef]
57. Ding, M.; Jing, L.; Yang, H.; Machnicki, C.; Fu, X.; Li, K.; Wong, I.; Chen, P.-Y. Multifunctional soft machines based on stimuli-responsive hydrogels: From freestanding hydrogels to smart integrated systems. Mater. Today Adv. 2020, 8, 100088. [Google Scholar] [CrossRef]
58. Shankar, A.; Safronov, A.P.; Mikhnevich, E.A.; Beketov, I.V. Multidomain iron nanoparticles for the preparation of polyacrylamide ferrogels. J. Magn. Magn. Mater. 2017, 431, 134–137. [Google Scholar] [CrossRef]

59. Zrínyi, M.; Barsi, L.; Büki, A. Deformation of ferrogels induced by nonuniform magnetic fields. J. Chem. Phys. 1996, 104, 8750–8756. [Google Scholar] [CrossRef]
60. Messing, R.; Frickel, N.; Belkoura, L.; Strey, R.; Rahn, H.; Odenbach, S.; Schmidt, A.M. Cobalt ferrite nanoparticles as multifunctional crosslinkers in PAAmferrohydrogels. Macromolecules 2011, 44, 2990–2999. [Google Scholar] [CrossRef]
61. Li, L.; Scheiger, J.M.; Levkin, P.A. Design and applications of photoresponsive hydrogels. Adv. Mater. 2019, 31, 1807333. [Google Scholar] [CrossRef] [Green Version]
62. ao, P., L. Tao, J. Gong, T. Wang, Q. Wang, J. Ju, et al. 4D printing of a sodium alginate hydrogel with step-wise shape deformationbased on variation of crosslinking density. ACS Applied Polymer Materials, Vol. 3, No. 12, 2021, pp. 6167–6175.
63. Lai, J., X. Ye, J. Liu, C. Wang, J. Li, X. Wang, et al. 4D printing of highly printable and shape morphing hydrogels composed of alginate and methylcellulose. Materials Design, Vol. 205, 2021,id. 109699.
64. Valentin, T. M., E. M. DuBois, C. E. Machnicki, D. Bhaskar, F. R. Cui,and I. Y. Wong. 3D printed self-adhesive PEGDA-PAA hydrogels as modular components for soft actuators and microfluidics.Polymer Chemistry, Vol. 10, No. 16, 2019, pp. 2015–2028.
65. Narayana, H.; Hu, J.; Kumar, B.; Shang, S.; Han, J.; Liu, P.; Lin, T.; Ji, F.; Zhu, Y. Stress-memory polymeric filaments for advanced compression therapy. J. Mater. Chem. B 2017, 5, 1905–1916. [CrossRef] [PubMed]
66. Vatanparast, S., Boschetto, A., Bottini, L., &Gaudenzi, P. (2023). New trends in 4D printing: a critical review. Applied Sciences, 13(13), 7744.
67. Malekmohammadi, S.; SedghiAminabad, N.; Sabzi, A.; Zarebkohan, A.; Razavi, M.; Vosough, M.; Bodaghi, M.; Maleki, H. Smart and Biomimetic 3D and 4D Printed Composite Hydrogels: Opportunities for Different Biomedical Applications. Biomedicines 2021, 9, 1537. [CrossRef] [PubMed]
68. Sadasivuni, K.; Deshmukh, K.; Al-Maadeed, M.; Sadasivuni, K.K. Introduction to 3D and 4D printing technology: State of the art and recent trends. In 3D and 4D Printing of Polymer Nanocomposite Materials; Elsevier: Amsterdam, The Netherlands, 2020; pp.1–21.
69. Narupai, B.; Smith, P.T.; Nelson, A. 4D Printing of Multi-Stimuli Responsive Protein-Based Hydrogels for Autonomous Shape Transformations. Adv. Funct. Mater. 2021, 31, 2011012. [CrossRef]
70. Davari, N.; Bakhtiary, N.; Khajehmohammadi, M.; Sarkari, S.; Tolabi, H.; Ghorbani, F.; Ghalandari, B. Protein-Based Hydrogels: Promising Materials for Tissue Engineering. Polymers 2022, 14, 986. [CrossRef]
71. Tamay, D.G.; Usal, T.D.; Alagoz, A.; Yucel, D.; Hasirci, N.; Hasirci, V. 3D and 4D Printing of Polymers for Tissue Engineering Applications. Front. Bioeng. Biotechnol. 2019, 7, 164. [CrossRef]
72. Narayana, H.; Hu, J.; Kumar, B.; Shang, S.; Han, J.; Liu, P.; Lin, T.; Ji, F.; Zhu, Y. Stress-memory polymeric filaments for advanced compression therapy. J. Mater. Chem. B 2017, 5, 1905–1916. [CrossRef] [PubMed]
73. Dimassi, S.; Demoly, F.; Cruz, C.; Qi, H.J.; Kim, K.Y.; André, J.C.; Gomes, S. An ontology-based framework to formalize and represent 4D printing knowledge in design. Comput. Ind. 2021, 126, 103374. [CrossRef]
74. Lei, D.; Yang, Y.; Liu, Z.; Chen, S.; Song, B.; Shen, A.; Yang, B.; Li, S.; Yuan, Z.; Qi, Q. A general strategy of 3D printing thermosets for diverse applications. Mater. Horiz. 2019, 6, 394–404. [CrossRef]
75. Melocchi, A.; Uboldi, M.; Cerea, M.; Foppoli, A.; Maroni, A.; Moutaharrik, S.; Palugan, L.; Zema, L.; Gazzaniga, A. Shape memory materials and 4D printing in pharmaceutics. Adv. Drug Deliv. Rev. 2021, 17, 216–237. [CrossRef]
76. Zarek, M.; Layani, M.; Cooperstein, I.; Sachyani, E.; Cohn, D.; Magdassi, S. 3D Printing of Shape Memory Polymers for Flexible Electronic Devices. Adv. Mater. 2016, 28, 4449–4454. [CrossRef]
77. Yang, X.; Lu, Z.; Wu, H.; Li, W.; Zheng, L.; Zhao, J. Collagen-alginate as bioink for three-dimensional (3D) cell printing based cartilage tissue engineering. Mater. Sci. Eng. C 2018, 83, 195–201. [CrossRef]
78. Wan, X.; Luo, L.; Liu, Y.; Leng, J. Direct Ink Writing Based 4D Printing of Materials and Their Applications. Adv. Sci. 2020, 7, 2001000. [CrossRef]
79. Lai, J.; Li, J.; Wang, M. 3D Printed porous tissue engineering scaffolds with the self-folding ability and controlled release of growth factor. MRS Commun. 2020, 10, 579–586. [CrossR

80. Mechanical and Aerospace Engineering Department, Sapienza University of Rome, Via Eudossiana 18,00184 Rome,Italy;somayeh.vatanparast@uniroma1.it (S.V.); alberto.boschetto@uniroma1.it (A.B.);paolo.gaudenzi@uniroma1.it (P.G.)
81. Gayan A. Appuhamillage [1*], Sankalya S. Ambagaspitiya [2], Rohan S. Dassanayake [2*], Achintha Wijenayake [1] Explor Med. 2024;5:17–47 DOI: https://doi.org/10.37349/emed.2024.00203 Received: September 30, 2023 Accepted: November 15, 2023 Published: February 06, 2024 Academic Editor: Nermeen A. Elkasabgy, Cairo University Faculty of Pharmacy, Egypt
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83. Wenxian Zhou Department of Orthopaedics, Bioprinting Research Group, Zhejiang Provincial Key Laboratory of Orthopaedics, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, China More by Wenxian Zhou View Biography Zhiguang QiaoEhsan Nazarzadeh ZareJinfeng HuangXuanqi ZhengXiaolei SunMinmin ShaoHui WangXiaoyan WangDong ChenJing ZhengShan FangYan Michael LiXiaolei ZhangLei YangPooyan Makvandi*Aimin Wu* Aimin Wu
84. Razzaq, M.Y.; Gonzalez-Gutierrez, J.; Mertz, G.; Ruch, D.; Schmidt, D.;Westermann, S. 4D Printing of Multicomponent Shape-Memory Polymer Formulations. Appl. Sci. 2022, 12, 7880. [CrossRef]
85. Xin, X.; Liu, L.; Liu, Y.; Leng, J. 4D Printing Auxetic Metamaterials with Tunable, Programmable, and Reconfigurable Mechanical Properties. Adv. Funct. Mater. 2020, 30, 200–226. [CrossRef]
86. Haleem, A.; Javaid, M.; Singh, R.P.; Suman, R. Significant roles of 4D printing using smart materials in the field of manufacturing. Adv. Ind. Eng. Polym. Res. 2021, 4, 301–311. [CrossRef]
87. Kuang, X.; Chen, K.; Dunn, C.K.;Wu, J.; Li, V.W.; Qi, H.R. 3D Printing of Highly Stretchable, Shape-Memory, and Self-Healing Elastomer toward Novel 4D Printing. ACS Appl. Mater. Interfaces 2018, 10, 7381–7388. [CrossRef] [PubMed]
88. Yamamura, S.; Iwase, E. Hybrid hinge structure with elastic hinge on self-folding of 4D printing using a fused deposition modeling 3D printer. Mater. Des. 2021, 203, 109605. (CrossRef)
89. Duigou, A.L.; Correa, D.; Ueda, M.; Matsuzaki, R.; Castro, M. A review of 3D and 4D printing of natural fibre biocomposites. Mater. Des. 2020, 194, 108911. [CrossRef]
90. Mulakkal, M.C.; Trask, R.S.; Ting, V.P.; Seddon, A.M. Responsive cellulose-hydrogel composite ink for 4D printing. *Mater. Des.* 2018, *160*, 108–118. https://doi.org/10.1016/j.matdes.2018.09.009.
91. Akbari, S.; Sakhaei, A.H.; Kowsari, K.; Yang, B.; Serjouei, A.; Yuanfang, Z.; Ge, Q. Enhanced multimaterial 4D printing with active hinges. *Smart Mater. Struct*. 2018, 27, 065027.
92. Miao, S.; Zhu, W.; Castro, N.J.; Nowicki, M.; Zhou, X.; Cui, H.; Fisher, J.P.; Zhang, L.G. 4D printing smart biomedical scaffolds with novel soybean oil epoxidized acrylate. *Sci. Rep*. 2016, 6, 27226.
93. J.Guo, R. Zhang, L. Zhang, and X. Cao, 4D printing of robust hydrogels consisted of agarose nanofibers and polyacrylamide, ACS Macro Lett. 7 (4) (2018), pp. 442–446. doi:10.1021/acsmacrolett.7b00957.
94. X. Kuang, K. Chen, C.K. Dunn, J. Wu, V.C.F. Li, and H.J. Qi, 3D printing of highly stretchable, shape-memory, and self-healing elastomer toward novel 4D printing, ACS Appl. Mater. Interfaces 10 (8) (2018), pp. 7381–7388. doi:10.1021/acsami.7b17082.
95. Pingale, P.; Dawre, S.; Dhapte-Pawar, V.; Dhas, N.; Rajput, A. Advances in 4D printing: From stimulation to simulation. Drug Deliv. Transl. Res. 2023, 13, 164–188. [CrossRef]
96. Ilami, M.; Bagheri, H.; Ahmed, R.; Skowronek, E.O.; Marvi, H. Materials, Actuators, and Sensors for Soft Bioinspired Robots. Adv. Mater. 2021, 33, 2003139. [CrossRef] [PubMed]
97. Ghi, A.; Rossetti, F. 4D Printing: An Emerging Technology in Manufacturing? In Lecture Notes in Information Systems and Organisation; Springer International Publishing: Berlin/Heidelberg, Germany, 2016; pp. 171–178
98. Yu, Q.; Zhang, M.; Bhandari, B.; Li, J. Future perspective of additive manufacturing of food for children. Trends Food Sci. Technol. 2023, 136, 120–134. [CrossRef]
99. Wu, C.; Xu, F.; Wang, H.; Liu, H.; Yan, F.; Ma, C. Manufacturing Technologies of Polymer Composites—A Review. Polymers 2023, 15, 712. [CrossRef] [PubMed]

100. Georgantzinos, S.; Giannopoulos, G.; Bakalis, P. Additive Manufacturing for Effective Smart Structures: The Idea of 6D Printing. J. Compos. Sci. 2021, 5, 119. [CrossRef]
101. Farid, M.I.; Wu, W.; Guiwei, L.; Yu, Z. Research on imminent enlargements of smart materials and structures towards novel 4D printing (4DP: SMs-SSs). Int. J. Adv. Manuf. Technol. 2023, 126, 2803–2823. [CrossRef]
102. Leist SK, Zhou J. Current status of 4D printing technology and the potential of light-reactive smart materials as 4D printable materials. Virtual and Physical Prototyping. 2016 Oct 1;11(4):24962.
103. Chu H, Yang W, Sun L, Cai S, Yang R, Liang W, Yu H, Liu L. 4D printing: a review on recent progresses. Micromachines. 2020 Aug 22;11(9):796.
104. Aldawood FK. A comprehensive review of 4D printing: state of the arts, opportunities, and challenges. InActuators 2023 Feb 25 (Vol. 12, No. 3, p. 101). MDPI.
105. T. S. Tran, R. Balu, S. Mettu, N. R Choudhury, N. K. Dutta, *Pharmaceuticals* 2022, **15**, 1282.