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4D Printing: A Snapshot on an Evolving Field

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Three-dimensional (3D) printing, or more formally Additive Manufacturing (AM), was introduced in the mid-80s and since then it has had a great impact on virtually all industry, market, and research areas, from automotive to healthcare, enabling the fabrication of complex structures with precise control on both internal and external geometries[1-3]. After about 30 years, in 2013, Tibbits *et al.*[4] proposed the term "four-dimensional (4D) printing" to denote the fabrication via AM of structures with the capability to shape transform over time, the "fourth dimension", under a predefined stimulus.

Shape-changing, self-repairing, self-assembly, are some of the characteristics today associated with 4D printed objects, highlighting that these are no longer static objects but programmable active structures that accomplish their function thanks to their architecture and composition[5-8].

Indeed, "smart" or "responsive" materials constitute a main ingredient of 4D printing, undergoing a useful, predictive, reproducible, and macroscopic physical or chemical change as a consequence of an environmental variation. Several couples of "smart material-stimulus" could be enumerated spanning from metals to ceramics and polymers activated by both coherent and incoherent forms of energy, including electric field and heating, liquid flow, pH, magnetic field, light.[9-10]

In this context, AM acts as an enabling technology by allowing a precise deposition of an exact amount of one or more stimulus-responsive materials in predefined positions, without any constraints on the geometric complexity. In this way, tiny variations can be transformed in macroscopic movements.

Although in all classes of materials there are examples of smart materials, nevertheless smart polymers (e.g., shape memory polymers SMP, liquid crystal elastomers) have been preferred for 4D printing, given their easier processability, and the large range of applicable stimuli.

The changes that occur in a 4D printed object can be one-way or two-way[11, 12]. In a one-way change, the object transformation is irreversible and represents the target and final state of the object. Differently, in a two-way change, the transformation is reversible, and the object has two stable states. Therefore, repetitive transformation can be achieved through the application and removal of the stimulus.

Indeed, 4D printing is influenced by several variables, thus mathematical models are a very useful tool to determine their right combination for achieving the desired transformation.

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In 2018 the Gartner hype cycle, which forecasts the evolution of emerging technologies, pinpointed 4D printing as an innovation in its triggering stage, with a decade before reaching its mainstream[13]. As a matter of facts, 4D printed structures present some key advantages over static 3D printed objects: i) an easier fabrication and storage, since 4D constructs are usually fabricated as a flatted object, achieving their complex 3D shape after printing; ii) a reduction of assembling costs, being often based on compliant mechanisms; iii) exploitation of reliable alternatives to electrical actuation, with the possibility to use 4D printed structures even in a harsh environment, such as the human body; iv) capability of multi-functionality, self-assembly and self-repair.

For these reasons, since its introduction, the 4D printing approach has been in rapid expansion in several fields, including smart textiles, autonomous and soft robotics, electronics, biomedical devices and tissue engineering (TE)[14,15]. Giving a closer look at biomedicine, the use of the AM technologies to fabricate 3D constructs that are designed to interact with physiological systems at the cellular level has been referred to as Bioprinting[3]. Bioprinting is mostly used to fabricate scaffold, namely 3D and porous structures providing physical support to growing cells. Some bioprinting technologies (e.g., extrusion based bioprinting and inkjet printing) allow the direct processing of both biomaterials and living cells.

Following the logical train of thought, but also the trend, the term 4D bioprinting has appeared in literature, indicating the application of the 4D printing approach to fabricate structures that are designed to be influenced by and to have an influence on cell behavior and functions thought their property variations. In this context, traction forces generated by cells attached on the 4D printed structure can be exploited to induce the desired shape-changing property. Conversely, environment-induced shape-changing could stimulate, for example, cell differentiation or alignment.

As clearly stated, 4D printing is influenced by several variables (*e.g.*, stimulus, materials, geometries), thus mathematical models and template design strategies are a very useful tool to determine the combination of variables that leads to the maximum and desired movement of the 4D printed structures[12,16,17]. The basic mechanisms of property changing in 4D printing and 4D bioprinting can be due to: i) the direct use of a single material; ii) the combination of different materials, that are characterized by different responses to the same stimulus; iii) the exploitation of cellular activities[7,18,19]. These mechanisms can be synergistically combined to reach a more significant or a more complex change in the 4D structure[20,21] or, for example, to obtain activations at different timepoints thanks to different characteristic times of each phenomenon[22-24]. Attempts to define a taxonomy of shape-changing movements, achievable through 4D printing, have been tried[25].

When a single smart material is used, the 3D printed geometry plays an essential role to induce the object transformation. Indeed, by precisely and spatially controlling the material deposition, local anisotropy and gradients of material can be introduced in the structure by the AM fabrication process itself, which lead the structure transformation. Although some studies have presented single-material 4D-printed structures, many researchers consider 4D printing in a multi-material fashion using smart (also referred ad active) materials that are selectively arranged with conventional (also referred as passive) materials to obtain the desired property changing behavior[26]. The developments and progress in multi-material printing have boosted the progression of 4D printing[3]. Indeed, some AM technologies (e.g., FDM, EBB, PolyJet) can be used to simultaneously deposit different materials, thus creating multi-material structures with spatially controlled chemical and mechanical properties. In 4D bioprinting, cells can be exploited to generate the property change in a 3D printing structure. In this case, the material involved must be biocompatible and cell-friendly, but they do not strictly require smart properties. Living cells, that are seeded on or into the scaffolds, can act as the active part of the constructs, performing topological changes, for example through cell traction forces, that originate from actin polymerization and actomyosin interactions[27]. In this context, the use of the cell traction forces as a driving mechanism to fold 2D structures, on which they adhere, to create complex 3D structures, is named "cell origami"[28].

Using the aforementioned materials and the related stimuli for their activation, it is possible to physically program many morphological transformations enabled by the proper organization guaranteed by 3D printing. By means of this technology smart devices can be manufactured in a single fabrication step and capable of carrying out tasks as a consequence of a change, over time, of their chemical-physical properties under a predefined stimulus. These smart devices can be used by a surgeon as support during surgery or can be designed on specific patient needs[16,29]. Constructs for a controlled drug delivery or structures that self-bend in order to replace a damaged blood vessel can also be fabricated[30]. Furthermore, 4D printing has influence on other biomedical applications, such as bioactuation, biorobotics, and biosensing[31-33].

Although some progress has been made, 4D printing development is still at an early stage, and several challenges need to be addressed. The target application, the knowledge of the materials' behavior, the correct stimulus, and the printing parameters are fundamental elements to be considered, globally increasing the complexity of this fabrication process. In addition, when manual intervention is required, for example during the programming phase when using SMPs, 4D printing is not a fully automated procedure. Being many phenomena temperature-dependent, the actuation speed of the 4D printed devices is limited. The actuation process occurs slowly, requiring a long-time range for the accomplishing of the desired task. Furthermore, 4D printed devices based on polymeric matrices suffer in those applications where strength is needed.

In conclusion, 4D printing is emerging and still under-development fabrication technology that thanks to the constant progress in materials science, 3D printing and biology, is opening a new door in biomedical engineering and will serve as an enabling tool to solve problems in tissue engineering, drug delivery, and medical devices manufacturing.

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