Additive Manufacturing of Nitinol for Smart Personalized Medical Devices: Current Capabilities and Challenges

Andrés Díaz Lantada[1][a*], Carlos Aguilar Vega[1][b], Rodrigo Zapata Martínez[1][c], Mónica Echeverry Rendón[2], Muzi Li[2], Óscar Contreras-Almengor[2][d], Jesús Ordoño[2], William Solórzano-Requejo[1][e], Miroslav Vasic[3], Juan Manuel Munoz-Guijosa[1] and Jon Molina-Aldareguia[1,2][f**]

[1]*Department of Mechanical Engineering, ETSI Industriales, Universidad Politécnica de Madrid, Madrid, Spain*
[2]*IMDEA Materials Institute, Tecnogetafe, Getafe, Spain*
[3]*Center for Industrial Electronics, ETSI Industriales, Universidad Politécnica de Madrid, Madrid, Spain*

Keywords: Additive Manufacturing, Shape-Memory Alloys, Smart Materials and Structures, Medical Devices.

Abstract: Shape-morphing smart medical devices constitute a current research trend and are bound to transform healthcare thanks to the improved interactions with the human body they enable. 4D printing technologies facilitate the development of such devices and start to provide innovative solutions like minimally invasive surgical tools and devices, ergonomic appliances and orthoses, evolutive implants and active *in vitro* biodevices, among others. Most studies so far, dealing with 4D printed biodevices, have been focused on smart polymeric materials and structures, whose biomechanical, biochemical and biological properties cannot always match those from shape-morphing and shape-memory alloys (SMAs). Considering several recent synergic breakthroughs in the additive manufacturing of smart alloys, this study presents 4D printing with SMAs for a new generation of medical devices, illustrated through case studies by our team. The more relevant strategies under research for enhancing the performance of 4D printed NiTi are illustrated and varied foreseen directions for achieving a sustainable and equitable impact in healthcare are discussed.

1 INTRODUCTION

Additive manufacturing technologies (AMTs) have emerged in the last decades, as highly transformative resources enabling freedom of design, fostering the personalization of devices and reformulating the world of design with original design-for-additive-manufacturing (DfAM) methods (Lipson, 2011, Yang, 2015 Thompson, 2016). The additive manufacturing (AM) of lattices, porous structures, functionally graded materials and multi-material structures may bring to relevant benefits including biomimetic and biomechanical design strategies for enhanced performance through bioinspiration.

Besides, geometrical complexity can be applied to the integration of varied functionalities, to the minimization of components and to the elimination of post-production operations, hence enhancing the development lifecycle. However, in most cases, 3D printed objects are passive elements unable to interact with the environment in a dynamic way, as needed quite often for biomedical applications and healthcare products, which should often evolve according to patients' growing and healing processes. In general, passive structures require the incorporation of sensors and actuators for allowing such interactions and result suboptimal in terms of integration, direct fabrication, cost, weight and eco-impacts.

[a] https://orcid.org/0000-0002-0358-9186
[b] https://orcid.org/0000-0003-0291-3041
[c] https://orcid.org/0000-0002-2611-7050
[d] https://orcid.org/0000-0002-8166-4161
[e] https://orcid.org/0000-0002-2989-9166
[f] https://orcid.org/0000-0003-3508-6003

Lantada, A., Vega, C., Martínez, R., Rendón, M., Li, M., Contreras-Almengor, Ó., Ordoño, J., Solórzano-Requejo, W., Vasic, M., Munoz-Guijosa, J. and Molina-Aldareguia, J.
Additive Manufacturing of Nitinol for Smart Personalized Medical Devices: Current Capabilities and Challenges.
DOI: 10.5220/0012363900003657

In *Proceedings of the 17th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2024) - Volume 1*, pages 123-134
ISBN: 978-989-758-688-0; ISSN: 2184-4305

For around two decades now, the AM of shape-shifting systems or shape-morphing geometries has been a research topic that has grown in parallel to the progressive advances in AMTs and related usable materials. The processing of active, multifunctional or smart materials, capable of responding to external stimuli, employing AMTs and rapid prototyping processes, initiated a field that would be subsequently referred to as “4D printing”. Synergic integration of innovative materials, wise designs for self-assembly or improved deployment, interlocked structures, printable mechanisms and advanced manufacturing technologies promoted a steady growth of 4D printing (Tibbits, 2012, 2014, Ge, 2013, 2014).

Towards higher performance, the AM of smart alloys has been also a topic of research for more than a decade, although connections to 4D printed medical devices are much more recent.

Pioneering studies dealt with the ultrasonic AM of composites with aluminum matrices and embedded shape memory nickel-titanium (NiTi or “nitinol”) alloy, magnetostrictive galfenol and electroactive PVDF phases, approaching active and self-sensing structures (Hahnlen, 2010). Ultrasonic consolidation, a hybrid manufacturing process that embeds fibers into metal matrices, was also explored and led to NiTi shape memory alloy (SMA) fibers into aluminum (Al) matrices, mainly for structural applications (Friel, 2011).

Regarding more adequate alloys for the biomedical industry, the precise, efficient and sustainable AM of highly biocompatible shape-memory alloys from the NiTi family has been a long-held dream that is currently at hand. Indeed, in spite of the tricky processability of NiTi, different studies have demonstrated that it can be additively processed, which opens a plethora of applications (Lee, 2017). A turning point is marked by different technologies enabling the AM of NiTi, whose limits and potentials have been analyzed (Van Hunbeeck, 2018).

Healthcare stands out as an extremely interesting fields for 4D printed NiTi devices, although some limitations still need to be addressed. Among them, the finding of final medical applications, in which the benefits of AMTs combined with the smartness of NiTi can be exploited, for outperforming the current gold standards, is also essential.

Accordingly, as presented in this study, exploring new concepts for personalized, shape-morphing, minimally invasive and evolutive biomedical devices seems a very adequate strategy for taking advantage of the mentioned benefits linked to the printability of superelastic and shape-memory alloys.

Furthermore, unprecedented design and manufacturing approaches, like the combined use of both shape-memory and superelastic properties of different kinds of NiTi, the employment of special structures leading to NiTi metamaterials and the creation of interwoven and interlocked NiTi structures, to cite a few, may lead to a new generation of 4D printed high-performance medical devices.

Considering all the above, this study analyzes the current state, as regards the additive manufacturing of NiTi, and the more promising approaches to obtain 4D printed nitinol medical devices. Furthermore, different biomedical application concepts, benefiting from DfAM methods are presented and illustrated through printed prototypes. Main strategies for empowering the shape-morphing performance of these and related biodevices are also exemplified. At the end of the paper, current limitations are described in detail and a research roadmap is provided.

2 ADDITIVE MANUFACTURING OF NITINOL: CURRENT STATE

2.1 Shape-Memory and Superelastic Nitinol as Biomedical Materials

SMAs constitute a family of high-performance smart materials capable of recovering an original shape after being significantly deformed, just by heating over the transformation shape temperature (shape-memory effect). At the high temperature phase, the deformation can be recovered just by releasing the applied stress (superelasticity). Transformations between the low temperature phase (martensite) and the high temperature phase (austenite) or between austenite and stress-induced martensite are involved. NiTi, FeMnSi, CuZnAl and CuAlNi stand out as polycrystalline SMAs with the previously described transformations (Huang, 2002, De la Flor, 2005).

However, due to its special relevance, outstanding thermomechanical properties (including shape-memory and superelasticity) and biomedical aptitude, our team is focusing on the enhanced AM of the nitinol family and its application to biomedical devices. Indeed, NiTi has been widely used in healthcare, for instance in the cardiovascular field in blood-contacting devices (i.e. stents, heart valves), in orthopedics as bone substitutes and in orthodontics as orthodontic fixators, among other applications (e.g. otolaryngology, neurosurgery, ophthalmology, urology, gynecology) (Auricchio, 2021).

Growing evidence suggests that NiTi alloys are biocompatible due to the protective titanium-based oxide layer on its surface (Elsisy, 2021). Nonetheless, one major drawback impairing these alloys biocompatibility is the content of Ni that can be released from the surface into the surrounding microenvironment and their associated toxicity (Nasakina, 2019). Another concern that has been associated with the use NiTi is surface-induced thrombus formation (Gegenschatz-Schmid, 2022). In this sense, several surface treatments have been studied in order to improve NiTi biocompatibility.

The additive processability of NiTi may lead to a very promising freedom of creation for highly innovative medical devices, but necessasrily brings also new unknowns to its biocompatibility, which should be carefully addressed, as further discussed in the research outline.

Regarding biomedical applicability, both superelastic and shape-memory nitinol alloys have their own application areas:

On the one hand, thermally activated nitinol can be employed for the controlled deployment of a surgical tool that may perform mechanical and thermal ablation at the same time. Although the high activation temperature is normally inadequate in healthcare, composition modifications may lead to activations at room temperature, thus opening a wider set of applications.

On the other hand, superelastic nitinol has led to several minimally invasive procedures based on self-expanding surgical tools and implants. A current research challenge is the sensitivity of these outstanding thermomechanical properties to the actual composition and processing conditions, as described in sections 5.1 and 5.2.

2.2 Additive Manufacturing Strategies for 3D/4D Printed Nitinol Biodevices

Selective laser sintering (SLS) and selective laser melting (SLM) or laser powder bed fusion (LPBF) have transformed metals' research and enabled solid freeform fabrication with a wide set of metals and alloys and with new design metallic materials including high entropy and superalloys. For example, both shape-memory and superelastic NiTi samples have been achieved by selective laser melting (Shayesteh Moghaddam, 2019, Obeidi, 2021). Other laser-based processes such as laser engineering net shaping (LENS) and laser cladding have been also reported as options for additively processing smart alloys (Van Hunbeeck, 2018).

To some extent, other processes like electron beam melting (EBM), fused deposition modeling (FDM) and wire arc additive manufacturing (WAAM) are also applicable to the processing of smart alloys (Van Hunbeeck, 2018), yet without the achieved impact of PBLF. Recently, electron beam freeform fabrication (EBF3) has been highlighted as technology capable of mitigating some of the common challenges involved in the selective laser melting of NiTi, such as impurity pick-up (C, O and N) and part size limitation (Paiotti, 2019).

Among key enabling technologies, not yet explored for the printing of shape-memory alloys, but with remarkable potential considering their recent impact for extreme quality parts in high performance materials, it is important to highlight lithography-based methods. These lithographic techniques evolve from the widespread digital light processing (DLP) of photopolymers but employ slurries, in which a polymeric matrix additively processed includes high quantities of ceramic or metallic particles.

For instance, lithography-based ceramic manufacturing technique (LCM) provides the most remarkable precision and versatility in ceramic AM, as it can process several kinds of ceramics, including smart piezoceramics, magnetic ceramics and multi-ceramic components (Schwentenwein, 2014). The same principle is being applied to metallic slurries, as an emergent process and could prove viable for the AM of NiTi, even in the micro/nano-scale using two-photon polymerization of metal (Vyatskikh, 2018).

2.3 Other Key Enabling Technologies for 3D/4D Printed Nitinol Biodevices

There are several methods by which SMAs can be heated and activated. Among the most widely used for this purpose are: 1) Joule, resistive heating or direct Ohmic heating, 2) convective heating, and 3) inductive heating (Qiu, 2001). These methods have been validated with both conventional NiTi alloys and with additively manufactured ones, employing powder bed laser fusion, by our team.

Resistive heating is the most widely used heating methodology as SMA are conductive alloys with low resistance, but such a method is generally current-limited to small and slim geometries. It depends on the electrical resistivity of the SMA actuator. To cite a biomedical example, an artificial urethral valve was developed with NiTi wires as actuators that replace the urinary sphincter muscles and by resistive heating the opening and closing functions are controlled (Chonan, 1997).

Convective heating depends on the heat transfer coefficient of the SMA. Convective heating using water for rapid heating and cooling was applied to an artificial muscle designed based on a spring bundle actuator (Park, 2019) and to a bioinspired design of vascular “blood vessel” that includes within a wet SMA actuator (Mascaro, 2003). Microvascular actuators demonstrated adequate for the convective heating of shape-memory polymers (Díaz Lantada, 2016), which could be directly translated to SMAs, once their high-precision 3D printing is mastered.

Induction heating seems to be a very good option for the future of the medical field, since contactless heating may be accomplished. With induction heating SMA can be uniformly heated resulting in better thermal control and higher heating rate. It depends mostly on the magnetic permeability of the SMA, size of the sample and applied frequency and magnetic field intensity (Saunders, 2016). For instance, transcutaneous induction heating was used to heat an orthopedic shape memory implant within biological tissue (Pfeifer, 2013, Müller, 2014). In addition, safety studies, where stents were inducted heated, were assessed as a potentially new method to treat esophageal cancer (Zhou, 2009).

3 BIOMEDICAL APPLICATION CONCEPTS FOR 3D/4D PRINTED NITINOL

3.1 Materials

To explore the printability of NiTi and its versatility for developing innovative medical technologies, two powder compositions obtained by gas atomization were acquired (Fort Wayne Metals). Mean particle diameter was c.a. 30µm for both powders. One batch had a composition closer to the equiatomic, for achieving shape-memory properties, the other with around an additional 1% of Ni to reach superelastic properties.

3.2 Methods

Design of a collection of test probes and medical devices concepts, such as vascular stents, heart valve structures, surgical tools…, were carried out at UPM employing a combination of software resources, including: NX (Siemens PLM Solutions) for geometrical modeling and n-Topology (nTop) for topology/topography optimization.

Manufacturing of the different test probes and conceptual biodevices presented in this study was performed at IMDEA Materials Institute by laser powder bed fusion. A Renishaw AM400 was employed as additive manufacturing system. Final post-processing included cleaning and electro-polishing to achieve an adequate surface roughness, whose impact in biocompatibility is further analyzed in section 5.1. Overall, the process followed recommendations from previous studies with slight modifications due to specific software/hardware constraints (Gan, 2021, Mani, 2022).

3.3 Innovative Concepts for 3D/4D Printed Nitinol Biodevices

Figure 1 presents a collection of stents and heart valve structures with systematic variations to illustrate the viability and versatility of the additive processing of Ni-Ti alloys.

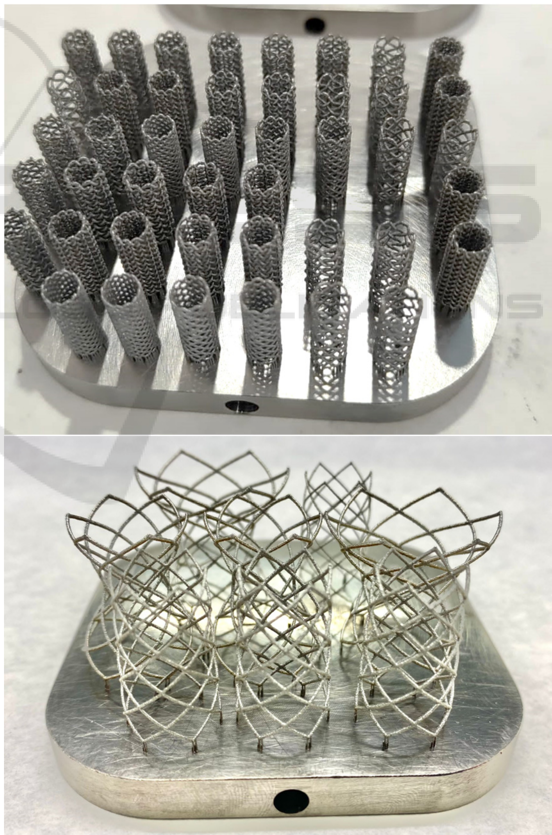

Figure 1: Collection of stents and structures for heart valve replacement obtained by LPBF of superelastic NiTi. Designs: UPM, prototypes: IMDEA Materials Institute, as in all figures presented in the study (iMPLANTS-CM “Synergy” project from Comunidad de Madrid, Spain).

Classical manufacturing processes have led to a very successful implementation of superelastic Ni-Ti in medical practice, especially for self-expandable vascular stents and valve structures. However, those mass-produced devices do not really account for some patients with unique morphological features. It is precisely in this field, in which AM Ni-Ti would prove competitive, for example for heart valve structure with slightly elliptical cross-sections to minimize perivalvular leakage or for Y-shaped stents for the treatment of aneurysms.

After demonstrating the viability of obtaining the more classical vascular devices other concepts presented below in figure 3 and in section 4 are also explored, such as: surgical manipulators or grippers, functionally graded lattices as tissue engineering scaffolds and minimally invasive kidney stone retrieval baskets.

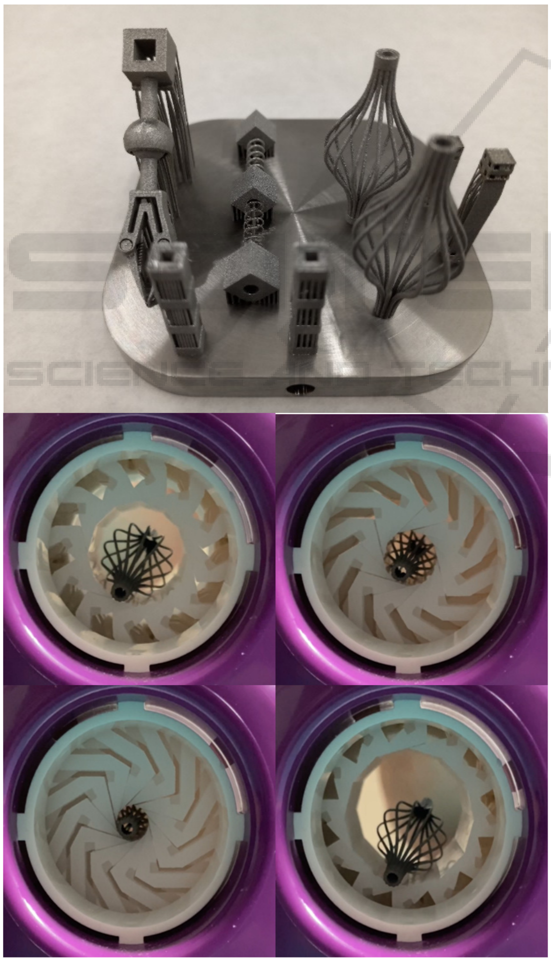

Figure 2: Proof-of-concept surgical actuators in NiTi. Crimping test of a superelastic NiTi mesh conceived as minimally invasive kidney stone retrieval basket.

4 EMPOWERING THE SHAPE-MORPHING PERFORMANCE

4.1 Overview of Strategies

Different principles applied to promoting the shape-morphing behavior of shape-memory & superelastic NiTi, are schematically presented in figure 3 and experimentally demonstrated in the supporting videos provided as companion for current paper. These will be presented in the Biodevices conference and are available for readers, on reasonable request, in case the final publication will not share them openly. In short, the supporting videos illustrate examples of 4D printed actuators related to medical devices concepts from previous section. S1 presents the successive crimping and compliant response of a 4D printed NiTi mesh, inspired by medical devices designed for extracting strange bodies from inside the organism in a minimally invasive way, such as kidney surgical baskets and thrombectomy devices (as also presented in figure 2). S2 presents a similar geometry to that of S1, but 4D printed employing shape-memory NiTi powder; the shape-memory training and recovery processes are illustrated. S3 deals with a shape-memory NiTi structure, counting with two structural cubes connected by a compliant spring, which is trained by pseudoplastic deformation and recovered through heating. Finally, S4 and S5 present scaffolds connected by compliant strips, respectively with shape-memory and superelastic properties.

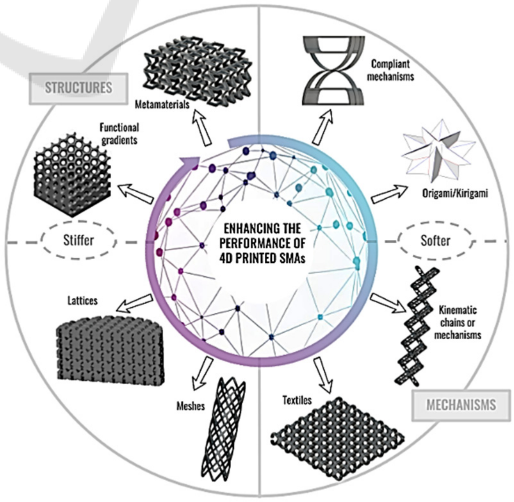

Figure 3: Examples of designed geometries, metamaterials, mechanisms, textiles and other structures for empowering the shape-memory performance of smart alloys, especially shape-memory and superelastic NiTi.

4.2 Biomechanical Metamaterials

Mechanical metamaterials, through designed microstructures and solid freeform manufacturing technologies, which are capable of defining matter in 3D, can be created with unique or exotic properties not found in traditional synthetic materials (Kadic, 2012, Frenzel, 2017). Control over the elasticity tensor, auxetics with negative Poisson ratio, atypical thermal expansion coefficients and thermal conductivity, unusual interactions with sound and shock waves, among others, can be achieved for a wide set of application fields (Kadic, 2019). Some biological and biomechanical materials' properties can be mimicked with *ad hoc* designed metamaterials and with combinations of metamaterials, lattices and porous networks, which puts forward the interest of these innovative geometries-structures-materials for the development of biomedical implants. AMTs have proven to be a fundamental booster for research in this exciting area of metamaterials, whose properties depend more on the actual designed microstructure than on the characteristics of the raw materials employed for their materialization. Interestingly, shape-memory materials may synergize with metamaterials' structures to achieve enhanced shape-morphing ability or to promote their superelastic behavior. In consequence, investigating the manufacturing of metamaterials employing SMAs is proposed, as strategy for enhancing the performance of 4D printed SMAs and devices based on them.

4.3 Origami Principles, Compliant, Bistable & Multi-Stable Structures

Obtaining deployable structures with sufficient stiffness in the deployed state is a very frequent requirement in different types of applications: they allow the transport in folded configuration of space load-bearing structures, the minimally invasive introduction by catheterization of medical devices such as stents or valves, or the change of wing geometry during the takeoff and landing of aircrafts.

Additionally, the large deflections involved in the deployment process can be used to obtain compliant actuators, very useful in applications such as robotic manipulators and surgical biodevices. The energy stored in the folding process and/or provided during deployment can also allow high actuation forces with very low control forces. Obtaining deployable structures with these features and functionality suitable for each application is based on three fundamental considerations:

First, the design of stable structures in the deployed state; second, the flexibility of the folding zones; and third, the energy supply for the deployment process. Traditionally, the physical materialization of any of these concepts has been subject to important restrictions, associated with the use of plastic deformation or subtractive processes, such as casting, folding, electrical discharge machining or chip removal. These processes are associated with important limitations for the manufacture of deployable structures and compliant actuators, both in size and geometry, being complicated to obtain structures with characteristic lengths less than 10^{-2} m, with variable thicknesses or morphological gradients, and usually being necessary the assembly of different components to reach the final system. The characteristics associated to additive manufacturing and 4D printed components make it possible to overcome the described restrictions, which expands the horizons for developing smart medical devices with unprecedented functionalities and features. In particular:

1) The manufacture of very small thickness features and continuously variable thickness elements - which allows for the tuning of the local flexural stiffness and prevents the formation of stress concentrators- which, in turn, facilitates:
    a) Integral manufacturing of high performance deployable structural concepts without the need for assembly or mechanical hinges, such as articulated, reticulated and chiral structures, based on both flexibility and bistability, with improved precision and repeatability.
    b) The optimization of flexure hinges**,** and the use of origami and auxetic geometries, that could lead to deployable structures with greater stiffness as well as a longer fatigue life.
2) The possibility of manufacturing along-the-thickness morphological gradients would allow asymmetrical sheets without the need for the use of composite materials (Riley, 2020). Those sheets, when cooled, would acquire bistable or multi-stable characteristics. The same could be achieved by using shape memory materials, which would acquire these characteristics once the transition temperature is reached.
3) The option of multi-material manufacturing would allow, for example, the integration of shape memory materials into bistable structural concepts, giving rise to low-energy activation actuators (Liu, 2019, Puthanveetil, 2022).

4.4 Functionally Graded Geometries and Structures

In connection with the above, the AM of shape-memory alloys can, not only lead to a biomimetic performance of the developed medical devices, but also help to reach singular smart properties like increased shape-morphing ability, step-by-step actuations or even quasi-autonomous responses.

Thanks to the careful design of functionally graded geometries and structures, such features are possible. For example, it is feasible to create structural and functional units in the same device, to employ topology optimization procedures to fine-tune the compliance of different regions of the device, and to use conformal lattice design methods to map different unit cells of well-know properties within the actual medical device (Feng, 2018). These methods are already impacting the field of tissue engineering with different alloys, ceramics and polymers, whose additive processing and designs including functionally graded structures lead to biomimetic structures for repairing tissues with nonhomogeneous density like bone. The processability of superelastic NiTi can provide an extra design freedom and bioinspired implants for replacing bones and bones connected to other bones through cartilaginous joints may be possible. The regeneration of the sternal-rib complex and innovative spine tissue engineering approaches can also benefit from these ongoing research directions. Besides, functionally gradients of porosity could even be applied to the creation of biomimetic microvascular structures within the smart medical devices, for enabling convective heating / cooling from within, for enhanced control of the activation, as already demonstrated with shape-memory polymer concepts for surgical devices (Díaz Lantada, 2016).

Through additive manufacturing, function and structure become more interwoven than ever before and multifunctional structures are achievable. The use of smart alloys increases the number of achievable functionalities. Thinking about the future, as discussed in section 5.2, compliant regions for biobots with active SMA wires or "muscles" integrated in their structures, may lead towards smart and living materials and structures with NiTi chassis. Related schematic concepts and prototypes for an innovative robotic hand (both showing a single finger and an index-thumb couple) are presented in figure 4.

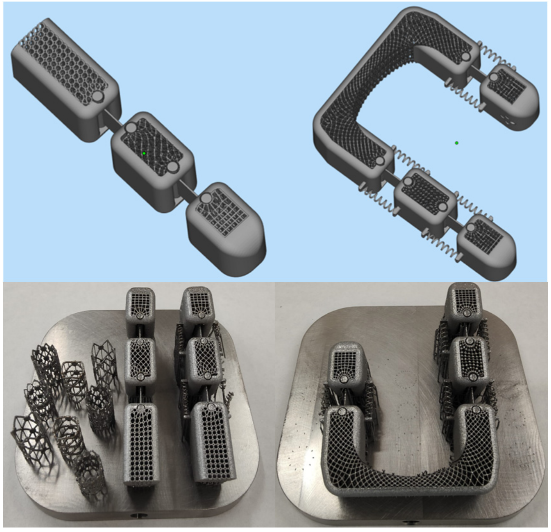

Figure 4: Innovative concepts for lightweight and smart robotic hand: CAD models and prototypes by LPBF of shape-memory NiTi. A single finger and an index-thumb couple are illustrated. Both benefit from the use of functional gradients of porosity and from the incorporation of flexible hinges between phalanxes for enhanced compliance and consequent actuation range.

4.5 Functionally Graded Alloys

Another way of achieving functional gradients, to obtain design-controlled properties at every point of a smart SMA-based biodevice, is the employment of functional gradients of composition across the structure. This leads to functionally graded alloys, which combined with functionally graded geometries and structures increase the freedom of design and actuation of smart systems based on SMAs. The potential creation of well-defined shape-memory and superelastic regions in a single device, thanks to controlling the composition of deposited NiTi powder or the processing conditions layer-by-layer, or even within each single layer, is of special relevance.

Pioneering examples have demonstrated that it is possible to modify the processing conditions of selective laser melting to obtain superelastic NiTi without postprocessing. Arguably this effect could be employed to spatially control the phases of NiTi within complex printed parts. Another option may be to resort to laser-based multiple metallic material additive manufacturing with different compositions of NiTi raw powders (Shayesteh Moghaddam, 2019, Wei, 2021).

4.6 Printed Kinematic Joints (Mechanisms) and Textiles

An additional degree of compliance can be obtained by printing mechanisms or textiles, for achieving highly deformable NiTi structures, to which active NiTi elements can be incorporated as driving actuators. Arguable this can lead to empowering the shape-morphing magnitude of the smart biodevices and promote precise micromanipulation. In this way, the traditional MEMS-related processes, applied to the creation of NiTi surgical tools and micro-manipulators, could be complemented with 3D/4D printed micro-mechanisms, having the desired number of degrees of freedom depending on the application, and aimed at providing innovative configurations for more versatile interactions with the human body. The topology optimized shape-memory NiTi actuator of figure 5, which includes a spherical joint with 3 degrees of freedom and distal grippers with revolute joints and shape-memory actuation, provides an example of the achievable complexity.

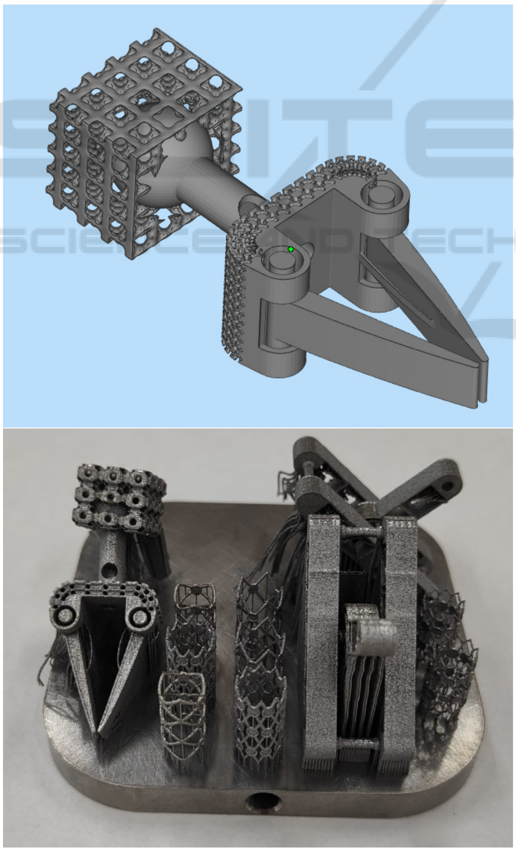

Figure 5: Design and prototype of shape-memory NiTi gripper. LPBF-printed biodevices (stents and actuarors).

Similar design principles applied to textiles can lead to innovative NiTi meshes for implants like stents, gastric bands and septal occluders. Surgical devices like thrombectomy and lithoextraction systems can also rely on SMA textiles. Interestingly, the use of woven or knitted 3D printed meshes importantly increases the compliance of superelastic biodevices, as illustrated in figure 6 with a conceptual superelastic NiTi structure mimicking an esophageal stent.

Figure 6: Prototypes of computational-driven design of a knitted mesh: LPBF-printed superelastic NiTi biodevices imitating the size and features of esophageal stents. Simple manipulation by hand illustrates the remarkable compliance of the achieved woven structure.

5 TOWARDS THE FUTURE

5.1 Current Limitations and Challenges

The potentials of AMTs for the personalization of healthcare are evident and involve varied subfields, such as patient-oriented surgical training and planning, support to personalized surgical practice, development of patient specific implants for soft and hard tissues, and personalized solutions for tissue engineering, regenerative medicine and biofabrication. However, most experiences still are experimental and rely on a written prescription, which limits their incorporation to the standard procedures at hospitals, in part due to a current lack of standardization (and almost absent regulation harmonization) surrounding patient-specific medical devices obtained additively from patients' medical images. The incorporation of active materials, such as shape-memory alloys, to patient-specific implants brings new concerns, which should be analyzed and discussed by the communities of researchers, materials and technology developers, medical devices manufacturers, healthcare practitioners, end users and patients, standardization entities, regulators and regulatory bodies. Only through the definition of shared good practices will these medical solutions, based on 4D printed smart alloys, deploy their transformative potentials. The creation of specific technical committees for standardization, the sharing of advances through open publications and the involvement of users in these biomedical transformations, are among the good practices that should be promoted.

Among technological challenges, one of the most critical for LPBF of NiTi alloys is to identify the optimum processing window for fabricating parts with desirable mechanical and functional properties. This has been widely studied in the literature. A wide range of volumetric energy densities (VED) have been reported in the literature by manipulating the input laser power, scanning velocity, hatch spacing and layer thickness to find optimal combinations, from as low as 38 J/mm^3 (Gan, 2021) to as high as 750 J/mm^3 (Zhao, 2020). Hence, due to the high sensitivity of NiTi SMAs and the possible hardware and software differences in each commercial AM system, process parameter sets generated by one group might be rendered unusable by other researchers (Xue, 2021). Nevertheless, a relatively low energy density range (between 55 and 100 J/mm^3) is commonly observed to provide the right combination of desired properties.

Furthermore, the surface finish required by most biomedical applications is another one of the critical postprocessing issues that must be faced in future. The printed parts are characterized by a rough surface, including the presence of un-melted powder particles left by LPBF. Surface modifications will be thus required both to smooth the rough finish left by LPBF and to impose the appropriate oxide layer to optimize corrosion resistance and minimize Ni release, which can be toxic, allergenic, and carcinogenic depending on the amount released and length of exposure. This is common to any manufacturing method of nitinol implantable devices and several reviews can be found in literature about finishing methods, including chemical etching, mechanical polishing, electropolishing and/or thermal treatments (Mani, 2022). However, the optimization of these surface treatments for LPBF produced parts remains a challenge that must be tackled in future.

Deepening into biocompatibility, a successful medical device should not rely on the simple use of a biocompatible material. The *in vivo* response and the success of an implant in the body depends on multiple variables, including aspects from the design, composition, microstructure, surface properties, and interaction of the material with cells and body fluids. In addition, the applications also play a crucial role in the material's performance. Static and dynamic systems, for instance, consider different variables and phenomena where mass transfer and diffusion of elements help to compensate and equilibrate the complete system.

SMAs are a promising tool to obtain engineered tissue constructs and to treat tissues with complex geometry and restricted access. However, there are still some concerns about this topic regarding the biological response (Wen, 2018). Among other biomaterial properties, cell-material interactions may be influenced by surface roughness, wettability and chemical composition, which are well known to determine the fate of cells. In any case, this will be highly dependent on the cell type and the tissue to regenerate. For instance, materials with high roughness have been reported as suitable for inducing osteointegration for bone implants since the surface area to anchor the bone is more considerable, favoring the cell adhesion. In the case of stents, roughness has greatly influenced hemocompatibility (Wang, 2010) or modulated endothelial and smooth muscle cell functions (Khang, 2010), thus arising as an important parameter to consider for the design and manufacture of vascular stents.

Another big challenge of 4D bioprinted structures is their *in situ* delivery and activation. NiTi implants activation or self-organization by external stimulus without affecting the cell environment is still a big challenge. The responsive effect of these materials to multiple physiological signals can be modified in a controlled way (inducing growth tissue or destroying it, if necessary, as in the case of tumoral tissue). The quid of the question is to identify the proper stimulus to activate the system at the right moment, precisely, and without causing acute side effects by affecting multiple physiological processes (Sinha, 2020). One promising application for these NiTi SMAs structures is as drug delivery systems (Lukin, 2019). Through these devices, it is possible to have precise control not only on the spatial distribution, by the material organization of the implant, but also on the release of drugs or cells in a programable manner.

Among other biological-related aspects, it is important to consider the ability to form complex structures with multi-materials and structures that can stimulate a stratified tissue considering the different cell groups and specifications (Ionov, 2018). Arteries and osteochondral regions are among the functionally graded tissues potentially benefiting from additively manufacturing SMAs.

Summarizing, although preliminary results are promising regarding the biocompatibility of additively processed NiTi alloys for future biomedical applications (f.e. figure 7), it is necessary to further study several aspects, as detailed below.

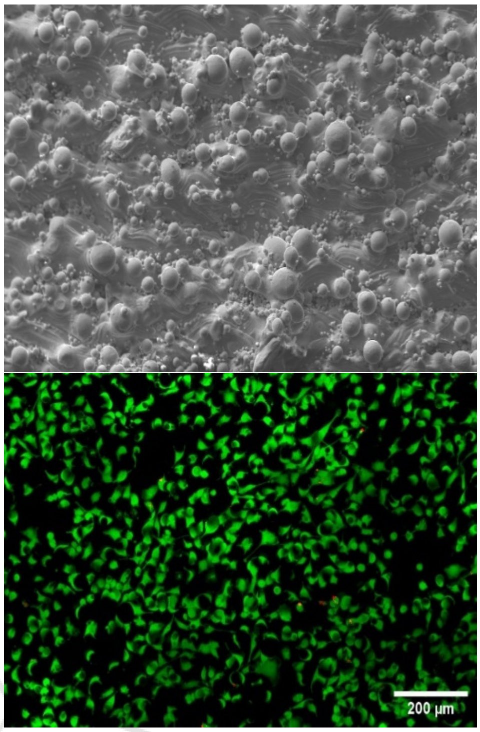

Figure 7: Direct viability test, in which endothelial cells (EA.hy926) are seeded upon a directly 3D printed surface of NiTi (SEM image). The lower image shows live cells in green and dead cells in red.

5.2 Research Perspective

AMTs are continuously advancing and are expected to lead to the processing of a wider range of NiTi compositions and other SMAs. These combinations may lead to high-performance devices, although their biomedical applicability should be cautiously analyzed, following guidelines from ISO Standard 10993.

In parallel, apart from increasing the portfolio of additively processable alloys, other interesting combinations between polymers and alloys, both with shape-memory properties, should be studied for achieving more versatile systems, capable of multiple or stepped actuations, triggered at different temperatures or by a variety of external stimuli, to reach a new generation of smarter medical devices. Among examples of the benefits of combining soft polymeric phases with embedded SMA actuators it is important to highlight the research by Akbari and cols (Akbari, 2021).

Together with the urgent need for internationally accepted standards dealing with the safe and straightforward development of high-quality personalized medical implants, other ethical, legal and social aspects demand careful attention for making 4D printed SMAs truly transformative for healthcare. Among them, healthcare technology equity is probably the most remarkable. The key question is: how do we accomplish that game-changing technologies, such as high-performance AMTs, come closer to the patients and users, in both physical and economic terms, hence ensuring accessible medical devices for all?

Challenging though it may be, some innovative and inspiring equity-fostering approaches to healthcare and production, in which additive manufacturing technologies are key players, can be highlighted. Do-it-yourself communities of “makers” have already transformed several industrial fields and their creative power, adequately canalized and mentored to comply with internationally accepted standards and applicable regulations, in connection with open-source medical device initiatives, is becoming a remarkable trend.

Thanks to open-innovation environments and to the promotion of open-source approaches, the whole development life-cycle can be arguably optimized and reach to safer products by enhanced design peer-review (De Maria, 2020). Regarding production and supply chain issues, interconnected global networks of additive manufacturing systems, working with similar quality control procedures, are bound to promote the print-on-demand of personalized medical devices and to bring the production closer to the point-of-care. As regards the accessibility of expensive AM systems, strategies for making them available to the community should be also explored.

ACKNOWLEDGEMENTS

The research presented has been supported by the following research and innovation project: "**iMPLANTS-CM**", from the "Convocatoria 2020 de ayudas para la realización de proyectos sinérgicos de I+D en nuevas y emergentes áreas científicas en la frontera de la ciencia y de naturaleza interdisciplinar" funded by Comunidad Autónoma de Madrid (reference: Y2020/BIO-6756).

REFERENCES

H. Lipson, "The Shape of Things to Come: Frontiers in Additive Manufacturing," 2011.

S. Yang and Y. F. Zhao, "Additive manufacturing-enabled design theory and methodology: a critical review," The International Journal of Advanced Manufacturing Technology, vol. 80, no. 1–4, pp. 327–342, Sep. 2015.

M. K. Thompson et al., "Design for Additive Manufacturing: Trends, opportunities, considerations, and constraints," CIRP Annals, vol. 65, no. 2, pp. 737–760, 2016.

S. Tibbits, "Design to Self-Assembly," Architectural Design, vol. 82, no. 2, pp. 68–73, Mar. 2012.

S. Tibbits and K. Cheung, "Programmable materials for architectural assembly and automation," Assembly Automation, vol. 32, no. 3, pp. 216–225, Jul. 2012.

Q. Ge, H. J. Qi, and M. L. Dunn, "Active materials by four-dimension printing," Appl Phys Lett, vol. 103, no. 13, p. 131901, Sep. 2013.

Q. Ge, C. K. Dunn, H. J. Qi, and M. L. Dunn, "Active origami by 4D printing," Smart Mater Struct, vol. 23, no. 9, p. 094007, Sep. 2014.

R. Hahnlen and M. J. Dapino, "Active metal-matrix composites with embedded smart materials by ultrasonic additive manufacturing," Mar. 2010, p. 76450O.

R. J. Friel, "Investigating the effect of ultrasonic consolidation on shape memory alloy fibres," 2011.

A. Y. Lee, J. An, and C. K. Chua, "Two-Way 4D Printing: A Review on the Reversibility of 3D-Printed Shape Memory Materials," Engineering, vol. 3, no. 5, pp. 663–674, Oct. 2017.

J. Van Humbeeck, "Additive Manufacturing of Shape Memory Alloys," Shape Memory and Superelasticity, vol. 4, no. 2, pp. 309–312, Jun. 2018.

W. Huang, "On the selection of shape memory alloys for actuators," Mater Des, vol. 23, no. 1, pp. 11–19, Feb. 2002.

S. de la Flor, "Simulación numérica y correlación experimental de las propiedades mecánicas en las aleaciones con memoria de forma.," Tesis, Universitat Politècnica de Catalunya, Barcelona, 2005.

F. Auricchio, E. Boatti, M. Conti, and S. Marconi, "SMA biomedical applications," in Shape Memory Alloy Engineering, Elsevier, 2021, pp. 627–658.

M. Elsisy, M. Shayan, Y. Chen, B. W. Tillman, C. Go, and Y. Chun, "Assessment of mechanical and biocompatible performance of ultra-large nitinol endovascular devices fabricated via a low-energy laser joining process," J Biomater Appl, vol. 36, no. 2, pp. 332–345, Aug. 2021.

Nasakina, Sudarchikova, Sergienko, Konushkin, and Sevost'yanov, "Ion Release and Surface Characterization of Nanostructured Nitinol during Long-Term Testing," Nanomaterials, vol. 9, no. 11, p. 1569, Nov. 2019.

K. Gegenschatz-Schmid et al., "Reduced thrombogenicity of surface-treated Nitinol implants steered by altered protein adsorption," Acta Biomater, vol. 137, pp. 331–345, Jan. 2022.

M. A. Obeidi et al., "Laser beam powder bed fusion of nitinol shape memory alloy (SMA)," Journal of Materials Research and Technology, vol. 14, pp. 2554–2570, Sep. 2021.

N. Shayesteh Moghaddam et al., "Achieving superelasticity in additively manufactured NiTi in compression without post-process heat treatment," Sci Rep, vol. 9, no. 1, p. 41, Dec. 2019.

R. Paiotti Marcondes Guimaraes, F. Pixner, G. Trimmel, and S. T. Amancio-Filho, "4-D Printing of NiTi Shape Memory Alloys," Sep. 2019. Accessed: Sep. 14, 2022.

M. Schwentenwein, P. Schneider, and J. Homa, "Lithography-Based Ceramic Manufacturing: A Novel Technique for Additive Manufacturing of High-Performance Ceramics," Oct. 2014, pp. 60–64.

A. Vyatskikh, S. Delalande, A. Kudo, X. Zhang, C. M. Portela, and J. R. Greer, "Additive manufacturing of 3D nano-architected metals," Nat Commun, vol. 9, no. 1, p. 593, Dec. 2018.

J. Qiu, J. Tani, D. Osanai, Y. Urushiyama, and D. Lewinnek, "High-speed response of SMA actuators," International Journal of Applied Electromagnetics and Mechanics, vol. 12, no. 1–2, pp. 87–100, Feb. 2001.

S. Chonan et al., "Development of an artificial urethral valve using SMA actuators," Smart Mater Struct, vol. 6, no. 4, p. 004, Aug. 1997.

C. H. Park, K. J. Choi, and Y. S. Son, "Shape Memory Alloy-Based Spring Bundle Actuator Controlled by

Water Temperature," IEEE/ASME Transactions on Mechatronics, vol. 24, no. 4, pp. 1798–1807, Aug. 2019.

S. A. Mascaro and H. Harry Asada, "Wet Shape Memory Alloy Actuators for Active Vasculated Robotic Flesh".

A. Díaz Lantada, A. De Blas Romero, and E. C. Tanarro, "Micro-vascular shape-memory polymer actuators with complex geometries obtained by laser stereolithography," Smart Mater Struct, vol. 25, no. 6, p. 065018, Jun. 2016.

R. Pfeifer et al., "Noninvasive induction implant heating: An approach for contactless altering of mechanical properties of shape memory implants," Med Eng Phys, vol. 35, no. 1, pp. 54–62, Jan. 2013.

C. W. Müller et al., "Transcutaneous electromagnetic induction heating of an intramedullary nickel–titanium shape memory implant," Int Orthop, vol. 38, no. 12, pp. 2551–2557, Dec. 2014.

J. Zhou et al., "Hyperthermia by a nitinol stent in an alternating magnetic field: Safety and feasibility in rabbit esophageal cancer," Progress in Natural Science, vol. 19, no. 12, pp. 1713–1719, Dec. 2009.

R. N. Saunders, J. G. Boyd, D. J. Hartl, J. K. Brown, F. T. Calkins, and D. C. Lagoudas, "A validated model for induction heating of shape memory alloy actuators," *Smart Mater Struct*, vol. 25, no. 4, p. 045022, Apr. 2016.

M. Kadic, T. Bückmann, N. Stenger, M. Thiel, and M. Wegener, "On the practicability of pentamode mechanical metamaterials," Appl Phys Lett, vol. 100, no. 19, p. 191901, May 2012.

T. Frenzel, M. Kadic, and M. Wegener, "Three-dimensional mechanical metamaterials with a twist," Science (1979), vol. 358, no. 6366, pp. 1072–1074, 2017.

M. Kadic, G. W. Milton, M. van Hecke, and M. Wegener, "3D metamaterials," Nature Reviews Physics, vol. 1, no. 3, pp. 198–210, Mar. 2019.

K. S. Riley, K. J. Ang, K. A. Martin, W. K. Chan, J. A. Faber, and A. F. Arrieta, "Encoding multiple permanent shapes in 3D printed structures," *Mater Des*, vol. 194, p. 108888, Sep. 2020.

Y. Liu et al., "Synergistic effect enhanced shape recovery behavior of metal-4D printed shape memory polymer hybrid composites," Compos B Eng, vol. 179, p. 107536, Dec. 2019.

S. Puthanveetil, W. C. Liu, K. S. Riley, A. F. Arrieta, and H. le Ferrand, "Programmable multistability for 3D printed reinforced multifunctional composites with reversible shape change," Compos Sci Technol, vol. 217, p. 109097, Jan. 2022.

J. Feng, J. Fu, Z. Lin, C. Shang, and B. Li, "A review of the design methods of complex topology structures for 3D printing", doi: 10.1186/s42492-018-0004-3.

A. Díaz Lantada, A. De, B. Romero, and E. C. Tanarro, "Micro-vascular shape-memory polymer actuators with complex geometries obtained by laser stereolithography," 2016, doi: 10.1088/0964-1726/25/6/065018.

N. Shayesteh Moghaddam et al., "Achieving superelasticity in additively manufactured NiTi in compression without post-process heat treatment," Sci Rep, vol. 9, no. 1, p. 41, Dec. 2019.

C. Wei, Z. Zhang, D. Cheng, Z. Sun, M. Zhu, and L. Li, "An overview of laser-based multiple metallic material additive manufacturing: from macro- to micro-scales," International Journal of Extreme Manufacturing, vol. 3, no. 1, p. 012003, Jan. 2021.

J. Gan et al., "Effect of laser energy density on the evolution of Ni4Ti3 precipitate and property of NiTi shape memory alloys prepared by selective laser melting," J Alloys Compd, vol. 869, p. 159338, Jul. 2021.

C. Zhao, H. Liang, S. Luo, J. Yang, and Z. Wang, "The effect of energy input on reaction, phase transition and shape memory effect of NiTi alloy by selective laser melting," *J Alloys Compd*, vol. 817, p. 153288, Mar. 2020.

L. Xue et al., "Controlling martensitic transformation characteristics in defect-free NiTi shape memory alloys fabricated using laser powder bed fusion and a process optimization framework," Acta Mater, vol. 215, p. 117017, Aug. 2021.

G. Mani, D. Porter, K. Grove, S. Collins, A. Ornberg, and R. Shulfer, "Surface finishing of Nitinol for implantable medical devices: A review," *J Biomed Mater Res B Appl Biomater*, Jun. 2022.

C. Wen et al., "Mechanical behaviors and biomedical applications of shape memory materials: A review," AIMS Mater Sci, vol. 5, no. 4, pp. 559–590, 2018.

B. L. Wang, L. Li, and Y. F. Zheng, "In vitro cytotoxicity and hemocompatibility studies of Ti-Nb, Ti-Nb-Zr and Ti-Nb-Hf biomedical shape memory alloys," Biomedical Materials, vol. 5, no. 4, p. 044102, Aug. 2010.

J. Lu, D. Khang, and T. J. Webster, "Greater endothelial cell responses on submicron and nanometer rough titanium surfaces," J Biomed Mater Res A, vol. 9999A, p. NA-NA, 2010.

S. K. Sinha, "Additive manufacturing (AM) of medical devices and scaffolds for tissue engineering based on 3D and 4D printing," in 3D and 4D Printing of Polymer Nanocomposite Materials, Elsevier, 2020, pp. 119-160.

I. Lukin et al., "Can 4D bioprinting revolutionize drug development?," Expert Opin Drug Discov, vol. 14, no. 10, pp. 953–956, Oct. 2019.

L. Ionov, "4D Biofabrication: Materials, Methods, and Applications," Adv Healthc Mater, vol. 7, no. 17, p. 1800412, Sep. 2018.

S. Akbari, A. H. Sakhaei, S. Panjwani, K. Kowsari, and Q. Ge, "Shape memory alloy based 3D printed composite actuators with variable stiffness and large reversible deformation," *Sens Actuators A Phys*, vol. 321, p. 112598, Apr. 2021.

C. de Maria, L. di Pietro, A. Ravizza, A. D. Lantada, and A. D. Ahluwalia, "Open-source medical devices: Healthcare solutions for low-, middle-, and high-resource settings," *Clinical Engineering Handbook, Second Edition*, pp. 7–14, Jan. 2020.