Bioinspired Design and Manufacturing Strategies for next Generation Medical Implants: Trends and Challenges

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Keywords: Bioinspiration & Biomimetics, Medical Devices, Engineering Design, Additive Manufacturing.

Abstract: Bioinspired design and manufacturing strategies are enabling radical innovations in healthcare and medical devices. The complex, functionally graded, fractal, multifunctional geometries and structures of nature are inspiring for conceiving highly transformative biomedical engineering solutions, but highly challenging to replicate. Decades (if not centuries) of research, together with a convergent collection of recently developed and emergent software and hardware resources, empower our biomimetic design and manufacturing abilities and render truly bioinspired solutions feasible. Such convergence is analyzed in this study and connected with the engineering of next generation implants, characterized for their life-like features or even with quasi-living behaviors. Synergic design and manufacturing technologies with remarkable impact in implants innovation, tissue engineering, biofabrication and engineered living materials are presented and illustrated by means of different case studies. Current research trends and challenges are discussed.

1 INTRODUCTION

The complex geometries of nature (Mandelbrot, 1983, Place, 2009), characterized by functionally graded structures, hierarchical features, multi-material extracellular matrices, dynamic tissues and living cells within, lead to highly precious features from an engineering point of view. Indeed, natural living entities stand out for being remarkably lightweight, self-regulated, stimuli-responsive (or even smart), eco-efficient and truly multifunctional, which inspires designers (Benyus, 2002).

Achieving some of the mentioned characteristics has been a long-held dream for many scientists and technology developers and has made of biomimetics a fruitful area of study (Bar-Cohen, 2006). The impact of bioinspiration in healthcare is outstanding and has led to the birth of research fields like tissue engineering, biofabrication and, more recently, engineered living materials (ELMs).

In our experience, traditional implants usually lack carefully conceived biomimetic design features. Besides, they do not frequently benefit from recent and ongoing advances in the computational modelling of complex-shaped objects and fractal, hierarchical or multi-scale geometries. Seldom are they manufactured as patient-specific or personalized medical solutions, as mass-production is currently the industrial standard. In consequence, the potential benefits of employing additive manufacturing technologies (AMTs), also known as solid freeform fabrication resources, are frequently discarded.

The limited personalization and the shortage of biomimetic design strategies lead to suboptimal implants in terms of biomechanical performance. All kinds of articular implants, acting like thick bulk metallic nails anchored to the remaining bone, suffer from dramatic stress shielding phenomena due to the mechanical mismatches between employed alloys and bones.

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Lantada, A., Cendrero, A., Martínez, F., Martínez, R., Vega, C., Solórzano-Requejo, W. and Blas De Miguel, A.
Bioinspired Design and Manufacturing Strategies for next Generation Medical Implants: Trends and Challenges.
DOI: 10.5220/0012363800003657

In *Proceedings of the 17th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2024) - Volume 1*, pages 42-53
ISBN: 978-989-758-688-0; ISSN: 2184-4305

The compact structures employed for state-of-the-art implants have nothing to do with the porous, vascularized, functionally graded and multi-material tissues present in bones and joints. Compliant regions, such as those involving cartilage or transitions between bones and ligaments or bones and tendons are extremely complex to repair with mono-material mass production techniques. In the cardiovascular and neurological fields, it is common to find stiff metallic implants interacting with very soft tissues, which also generates undesired biomechanical mismatches (Liverani, 2021). In general, the bulk properties of synthetic materials cannot match the combination of strength and flexibility from natural ones. Derived synthetic structures for potential biomedical implants are either too stiff or lacking in strength.

Consequently, alternative biomimetic design and manufacturing technologies are required for modulating the stiffness of biomedical materials usable for creating implants, without dramatically affecting their strength and durability. This has been a matter for research in the tissue engineering field for more than two decades now and has been also addressed, more recently, by the development and application of biofabrication techniques. Important advances have been achieved in terms of biomimetic solutions, but their clinical impact is still very limited.

Next generation medical implants should be conceived and developed according to new strategies taking benefit of advanced design and manufacturing technologies for enhanced biomimetics. In many ways, these technologies transcend the classical Bauhaus principle of "*form follows function*" (Droste, 2019), enabling a new engineering design paradigm. In this reformulated approach, geometry, structure, material and function are bound together, become integral aspects of the same entity, thanks to the freeform design input and the use of special manufacturing resources that allow for a precise definition of matter in three or even four dimensions. Accordingly, the classical frontiers between geometry, structure, material and function dissolve, exactly as in natural living entities, which is also pursued for next generation implants.

The following section presents some of the most relevant bioinspired design features for next generation implants. Subsequently, different design strategies are presented, and synergic families of manufacturing technologies discussed through use cases. These involve AMTs, micro- and nano-manufacturing resources, robotic technologies and emergent synthetic biology related techniques.

2 DESIRED FEATURES FOR "NEXT-GEN" IMPLANTS

2.1 Lightweight and Compliant

Natural materials and structures are consequence of multi-objective optimizations achieved through evolution and responses to environmental cues. The structure of large bones in mammals, with the typical external cortical region, inner trabecular core and curvature (Bertram, 1988), are optimized for a combination of bending and dynamic loads varying in direction and constitute examples of lightweight structures. In birds, skeletons have gone through continuous adaptations to minimize the metabolic cost of flight (Dumont, 2010). At the same time, vertebrates count with different means for rendering their bodies and biological structures compliant for a better interaction with the external environment. Kinematic chains of bones connected through ligaments, like the spine and extremities, or the cushion-like features of cartilage contribute to such compliance. However, the medical device industry has traditionally relied on highly stiff materials, like steel or titanium alloys, and used mainly 100% compact structures. These lack the desired lightweight properties and compliance that biological structures exhibit. Hence, innovative design and manufacturing approaches are needed.

2.2 Functionally Graded

Biological structures also stand out for their usual functional gradients of properties. The already mentioned cortical-trabecular structure of bone is an example of density, stiffness and strength gradients, which also renders bone multifunctional by enabling vascularization. Entheses, connective tissues between tendon or ligament and bone, modulate stiffness through functionally graded structures and by combining different fibres, arrangements of extra-cellular matrices and cells. Functional gradients of properties are also found in synthetic biomechanical replacements and are normally achieved by wise geometrical designs, combinations of materials or through functional coatings (Leong, 2008, Phillips, 2008). However, in order to perfectly mimic the functionally gradients of biological materials and structures, additional research is required. Taking mechanobiology into account (Boccaccio, 2016, Perier-Metz, 2022) constitutes a relevant design trend for improved results.

2.3 Multi-Scale and Multi-Material

Essential functional gradients are also achieved in nature thanks to the hierarchical, multi-scale or fractal geometry that characterizes living tissues, organs and systems. Our cells decode and transcribe DNA, our lungs perform gas exchange, and our fingers play an electric guitar or a piano thanks to the hierarchical organization of our body. Nevertheless, multi-scale features are not so common in classical medical implants, apart from their increasingly frequent hierarchical surfaces that lead to enhanced biological interactions. These features indicate an interesting path for bioinspired implant development.

At the same time, composites are very common in biological structures. In the case of the human body, ceramics and polymers co-exist in bones, whose ceramic structure is interpenetrated by a polymeric vascular network, and joints, with their osteochondral transitions, to mention a couple of examples. Multi-material articular prostheses, with ultra-high molecular weight polyethylene capsules in between metallic components, are common but their structures and radical transitions not yet truly biomimetic.

2.4 Multifunctional and Smart

Functional gradients, combinations of constructive building blocks and hierarchical structures render biological systems multifunctional and smart, in the sense of adequately responding or adapting to external stimuli. Tissues perform several functions at the same time: structural support, thermal stability, energetic management, self-sensing, information processing, acting, among others. These features are seldom found in biomechanical replacements like prostheses or orthoses. In fact, biological multi-scaling and multifunctionality allows both for "*plenty of room at the bottom*" (Feynman, 1959) and for "*plenty of room right here*" (Bongard, 2023).

2.5 Dynamic and Living

Possibly the most challenging bioinspired properties for next generation or "next-gen" implants are the dynamism and liveness of biological entities. The self-healing properties of biological structures, based on extremely complex surveillance and repair strategies; the natural mechanisms of growth and biodegradation, which would be fundamental for paediatric biomedical prostheses; the reconfigurable and shape-morphing nature of several organs, to cite a few, feature dynamism and liveliness. Still, they prove extremely challenging to replicate.

3 BIOINSPIRED DEVELOPMENT STRATEGIES

3.1 Lattices, Meshes and Woven Structures

Straightforward combinations of computer-aided design operations can rapidly lead to biomimetic geometrical complexity built upon simple geometries like cylindric trusses, square-section bars, spheric pores, among others. Extrusions, lofts along splines, Boolean and matrix-based design tools let us achieve lattices, meshes and woven structures that imitate the porous and compliant structures of several tissues. In many cases, these geometries can be employed as load bearing scaffolds for tissue repair, which have set the foundations of tissue engineering and biofabrication (Hutmacher, 2000, Harley, 2021). The scaffolds, being porous, should allow for three-dimensional cell culture, access to nutrients in vitro, elimination of debris and vascularization in vivo. In general, meshes and woven structures may be usable for soft tissue repair, while lattices, depending on the properties of raw materials employed, may lead to advanced multipurpose implants.

3.2 FGMs and Hierarchical Structures

Despite the benefits of quasi-periodic repetitions for easily designing biomedical constructs with some biomimetic features, in many cases an additional level of complexity involving hierarchical and functionally graded materials (FGMs) can lead to enhanced biomechanical and biological performance. Progressively, along the last decade, CAD modelling resources have been complemented with specific modules or with dedicated packages aimed at performing very relevant design operations from a biomimetic point of view. Nowadays, topology optimization resources, conformal lattice design tools, algorithmic CAD modelling software, to cite some options, enable the generation of networks and porous structures within computational models, the application of lattices to desired working volumes and the use of recursive approaches to reach multi-scale hierarchical structures. These are already making a remarkable impact in biomedical implants innovation (Wang, 2016). In parallel, classical CAD modelling and methodical procedures can also lead to multi-scale features. Some examples of lattices and meshes with functional gradients and hierarchical structures are shown in figure 1 to illustrate the already achievable geometrical complexity.

3.3 Metamaterials and Metasurfaces

The unconventional properties of biological materials (stress-stiffening behaviours, unusual Poisson ratios, stimuli-responsive abilities…) are challenging to replicate with traditional materials. Metamaterials and metasurfaces, thanks to their microstructures being designed on purpose to achieve very unique structural properties or surface interactions, constitute an emergent path for creating biomimetic biodevices. Their properties depend on their CAD-modelled designed features more than on the raw materials employed, which is remarkable. The advent of high-performance AMTs is enabling their conceptual application to healthcare (Zadpoor, 2019, 2020).

3.4 Composites, Digital Materials and Voxelated Matter

Composite materials are also being reinvented by computational design and manufacturing means, which has led to concepts like digital materials and voxelated matter (Bader, 2018, Skylar-Scott, 2019), in which both structure and chemical composition are precisely defined in 3D or 4D. Consequently, relevant opportunities arise for biomedical implants better imitating the composite and intricate structures and compositions of living tissues.

3.5 Smart Materials and Structures

Smart materials and structures contribute to the final biomimetic performance through enhanced multi-functionality. In fact, smart, stimuli-responsive or multi-functional materials incorporated to advanced implants, may act as transducers for enabling self-sensing and acting abilities. The possibility of processing many of these families, such as shape-memory polymers and alloys, piezoelectric materials, electroactive polymers…, using solid freeform fabrication technologies is bound to make their incorporation to biodevices quite direct (Gardan, 2019).

3.6 Engineered Living Materials

Probably the ultimate degree of biomimicry may only be achieved by resorting to biohybrid solutions, in which synthetic materials, biological extracellular matrices and living cells synergize, as in the case of tissue engineering scaffolds, biofabricated constructs and emergent engineered living materials (ELMs) (Nguyen, 2018, Srubar III, 2020, Díaz Lantada, 2022).

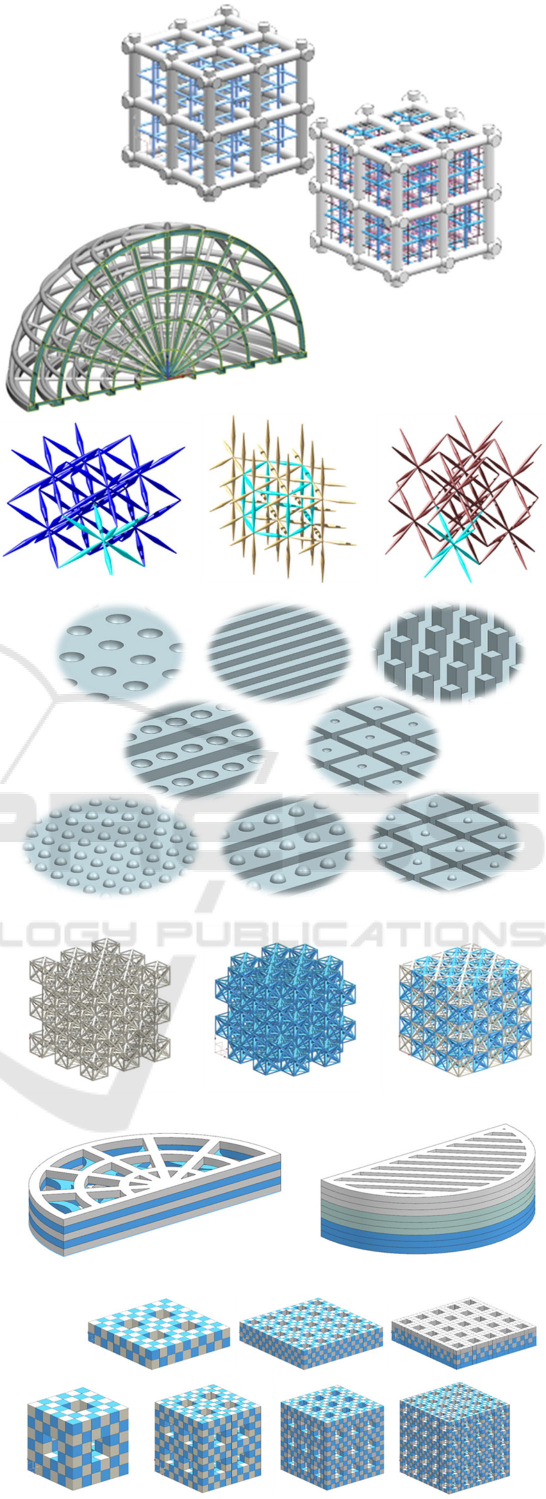


Figure 1: Examples of CAD models showcasing different bioinspired design strategies: multi-material and multi-scale lattices, functionally graded structures, mechanical metamaterials, microtextured biointerfaces, interwoven and layered materials and voxelated matter.

4 ADVANCED COMPUTATIONAL RESOURCES

4.1 CAD Modelling and Simulations

The bioinspired development strategies from section 3, as regards advanced computational resources for design purposes, are illustrated in this section and exemplified through different examples connected to the design, simulation and optimization of different biomedical implants. To start with, CAD modelling supported by simulations constitutes the *statu quo* for designing and optimizing engineering components. Geometries from implants can be designed, even in personalized ways using input from patients' medical images, and their biomechanical performance evaluated by simulations. Figure 2 presents examples of the finite element method applied to assessing and validating *in silico* different designs, before eventual *in vitro* or *ex vivo* trials. These have been performed with NX (Siemens PLM Solutions) as computational modelling software. In fact, *in silico* methods (i.e. simulations, digital twins…) are becoming more and more relevant as an alternative to *in vivo* testing, even for certification purposes, in a clear alignment with the 3Rs principles (Tannenbaum, 2015).

4.2 Topology and Topography Optimization

For an increased degree of biomimicry, the porous intricate networks that conform human tissues and their functional surface topographies should be taken into account. To this end, topology and topography optimization resources, such as n-Topology and 3D Coat, are a right choice. For instance, n-Topology (n-Top) is applied to obtain the functionally graded and bioinspired porous scaffolds designs of figure 3.

4.3 Math-Based Designs and Algorithmic CAD

In a complementary way, math-based designs and algorithmic CAD modelling are also usable for achieving lattices, meshes, woven structures, textures and metamaterials with biomimetic features. These methods also apply to rapidly modifying parametric designs for personalization purposes. By means of example, figure 3 includes the algorithmic design of a woven mesh for a stent-like device, while figure 4 presents the math-based design of innovative biointerfaces (Franco Martínez, 2023).

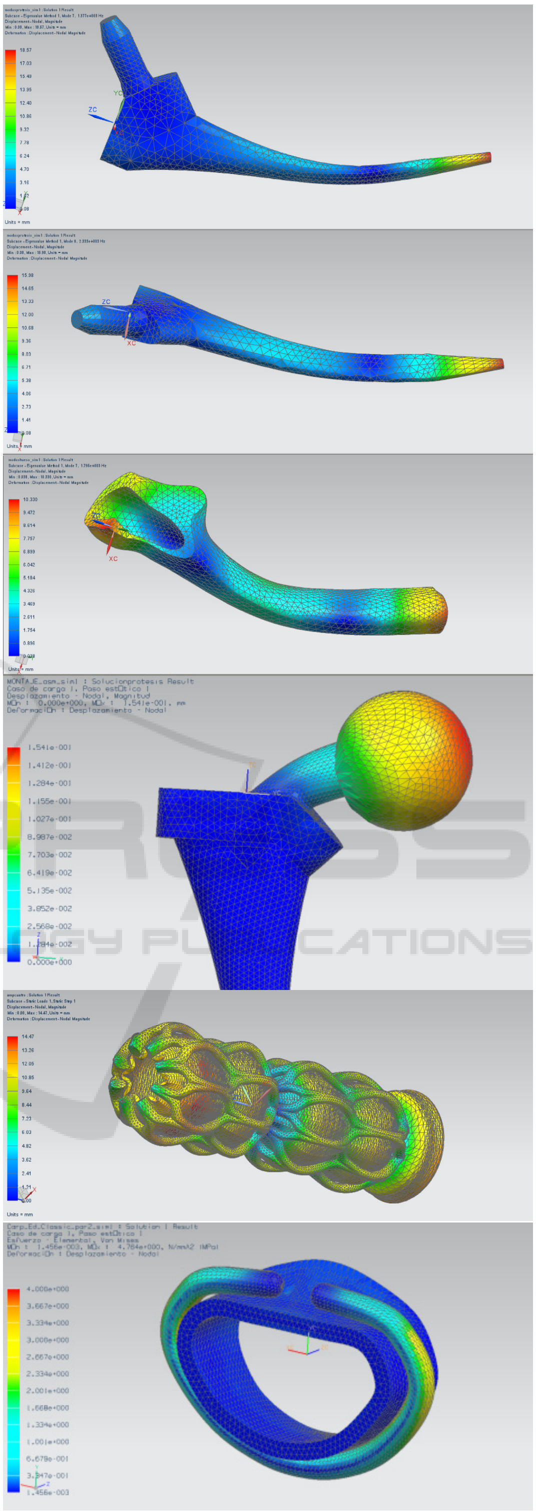


Figure 2: FEM simulations upon CAD models (adapted from Díaz Lantada, 2013): study of resonances in hip prosthesis and femur, biomechanical performance of hip replacement, interactions between transcatheter stent, annuloplasty ring and surrounding tissues.

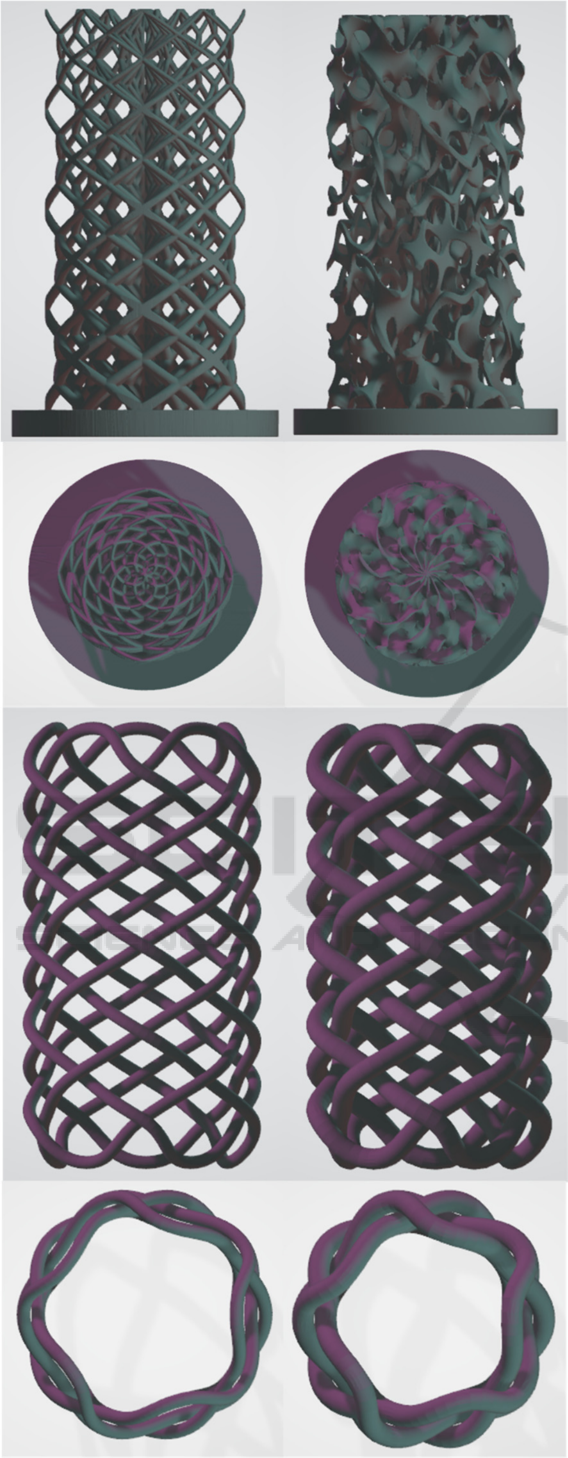


Figure 3: Topology optimized and functionally graded tissue engineering scaffolds (upper images). Algorithmic design of woven meshes for stent-like medical devices with improved mechanical compliance (lower images).

4.4 Agents Based Modelling and AI-Based Approaches

The hierarchical fractal features of the extracellular matrices, the presence of living entities in biological structures and their particular responses to a myriad of environmental cues lead to irregular and random features, which are almost impossible to imitate with classical design software. To account for these particular characteristics, the employment of agents-based modelling -in which cells, pixels or voxels iteratively and autonomously evolve in a sort of "*game of life*"- adequately integrated with CAD modelling and artificial intelligence (AI) methods, can be an interesting solution (Von Neumann, 1966, Gardner, 1970).

As an example, figure 5a presents the cellular automata-based modelling (Matlab, The Mathworks Inc.) of cells colonizing a 3D scaffolding structure, an approach that can be applied with some modifications to the modelling of porous networks and biomimetic structures for biomedical devices (Díaz Lantada, 2023). Through this approach, it is possible to model the influence of cell-material interactions and predict aspects related to cellular colonization of scaffolds, vascularization within porous implants, eventual biodegradation of the implanted structures, among other issues relevant for predicting the long-term biocompatibility and understanding the interactions between the abiotic structures and the living cells.

Another case study is presented in Figure 5b, which illustrates the automated design of a porous scaffolding structure employing cellular automata. It has been programmed using Python and interactions 1 to 10 are presented. Initial seeds, iteration by iteration, thanks to the defined growth rules, lead to a voxelated structure. Different biomimetic properties like porosity, functional gradients of stiffness, eventual outer textures… can be achieved by minor modifications of the growth rules.

A relevant aspect of these agents-based methods is their adequacy for mimicking the randomness of nature and their applicability to designing self-similar fractured fractal geometries common in nature. Once connected to artificial intelligence methods, which are capable of screening biomechanical properties and biointerfaces performance from the design stage (Bermejillo Barrera 2021, Díaz Lantada, 2020), automated design and optimization procedures can be implemented.

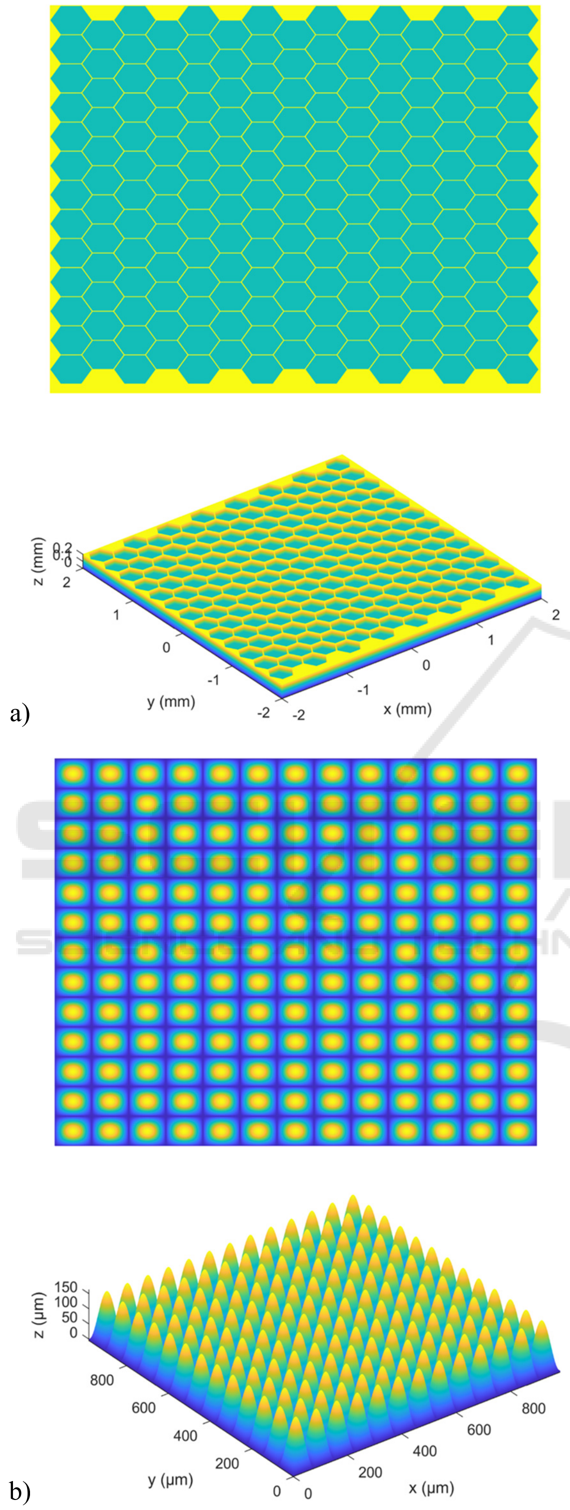


Figure 4: a-b) Math-based design of micro- and nano-textured biointerfaces for special cellular interactions (adapted from Franco Martínez, 2023). Top and isometric views. a) Hexagonal-based texture and b) lotus flower leave-like pattern.

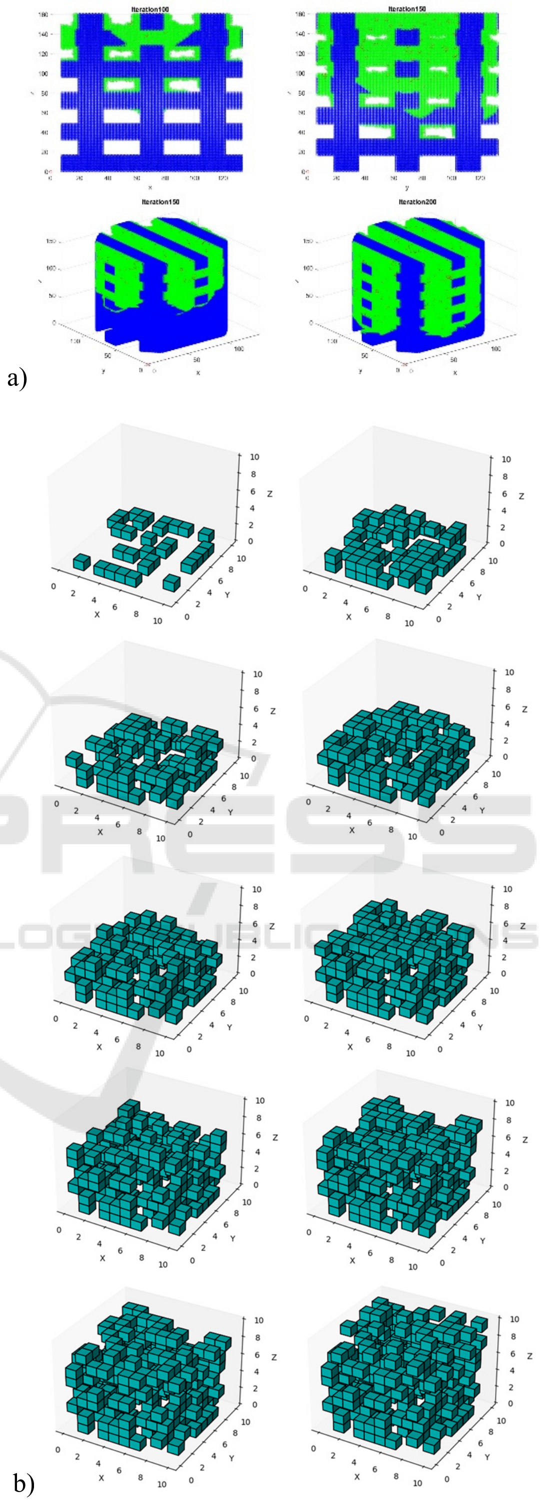


Figure 5: a) Cellular automata modelling of cells colonizing scaffolds, (adapted from: Díaz Lantada, 2023). b) Automated design of porous scaffolding structure employing cellular automata: iterations 1 to 10.

5 ADVANCED MANUFACTURING RESOURCES

5.1 Additive Manufacturing Technologies

The degree of geometrical complexity achieved with advanced computational resources can only be materialized thanks to the advent of some special families of manufacturing technologies analyzed in this section and schematically illustrated in figure 6.

Among these advanced resources, additive manufacturing technologies, most of them invented during the 1980s and 1990s, and importantly improved in terms of resolution, precision and processable materials along the first two decades of the 21st Century, stand out for the freedom of creation they enable. Indeed, AMTs (a.k.a. 3D printing technologies) usually work on a layer-by-layer fashion, depositing or changing the physical/chemical state of the raw materials being processed, employing written lines, pixels or voxels as building blocks. In a way, material, structure and product are being created at the same time, which leads on many occasions to an integration of functions through geometrical complexity. The additive approach enables the creation of meshes, lattices, porous structures, interwoven geometries, metamaterials, common in nature, but impossible or very challenging to achieve with traditional methods. An additional benefit of AMTs is the autonomous processing directly from the computational models.

From the very beginning, AMTs were applied to the biomedical field. At first, they were used for creating surgical training and planning models, and as a complement to medical diagnostic technologies, but progressively also for the direct fabrication of orthoses and prostheses (Díaz Lantada, 2012). Nevertheless, the expansion of their materials portfolio, especially the increasing possibility of manufacturing with a wide set of biomedical materials including polymers, metals and ceramics, has recently led to very relevant transformations in the medical industry. Among them, the increase of personalized implants is a clear industrial trend. Furthermore, AMTs have helped to set the foundations of biomedical research fields like tissue engineering and biofabrication, which are radically reformulating the therapeutic strategies for biomechanical tissue repair and regeneration (Hutmacher, 2000, Harley, 2021).

5.2 Robotic-Assisted Manufacturing

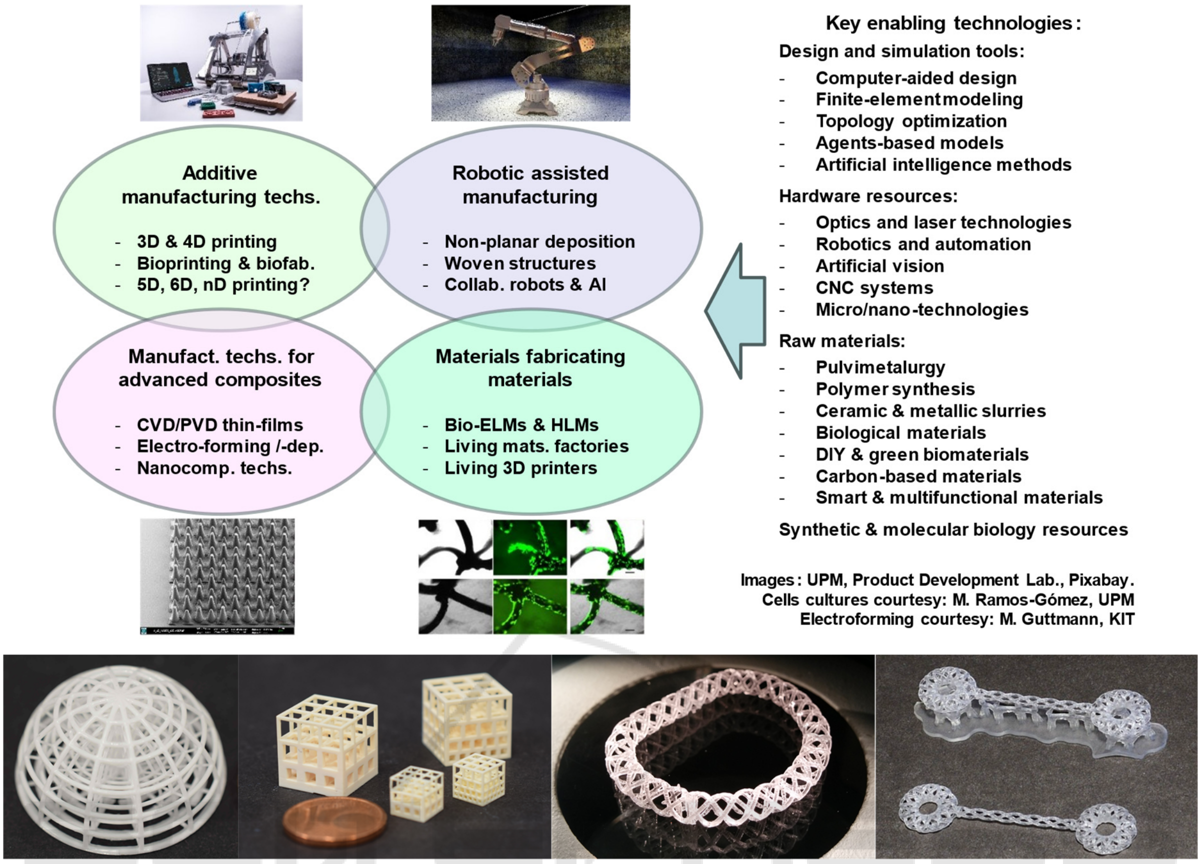
Progresses in robotics synergize with AMTs and contribute to healthcare innovation. 5-axis, 6-axis, 7-axis robots, with the possibility of moving along the x, y, z axes and performing additional movements, like roll, pitch and yaw, and of being mounted upon linear paths in production facilities, may outperform AMTs in some aspects. The use of robots for freeform fabrication by deposition of material, taking inspiration from 3D printing, has led to the concepts of "5D-, 6D-, 7D-printing", depending on the number of axes employed (Haleem, 2019, Vasiliadis, 2022). Biomedical applications are indeed being explored, especially in fields like tissue engineering and biofabrication, in which non-planar deposition paths may be biomechanically remarkable compared to those achievable by 3D printing.

5.3 Manufacturing of Advanced Micro/Nano-Composites

Micro and nanomanufacturing technologies, such as chemical and physical vapour deposition, UV-photo-lithography, electrochemical deposition, to cite a few, synergize with the aforementioned technologies in the quest for enhanced implants. As advanced, most tissues have a functionally graded and composite nature, for which the synthetic creation of graded, multi-layered and composite materials and structures is fundamental. Functionalized biomaterials that can be additively processed to achieve micro/nano-composites and the use of multi-material printing technologies creating voxelated composites are also becoming relevant for smart implants (Velu, 2019).

5.4 Synthetic Biology, Tissue Engineering, Biofabrication

Last but not least, methods from synthetic biology, tissue engineering and biofabrication enable the processing of living cells and their employment, together with biomaterials, as building blocks for highly innovative healthcare products. Scaffolds with cells are advanced medicinal products, not just medical devices, and enter the realm of engineered living materials (ELMs) (Srubar III, 2020, Díaz Lantada, 2022). The boundaries of biomimicry are hence expanded and may even lead to living biomaterials as biomaterials factories (Niemeyer, 2018, Nguyen, 2018).



a) b) c) d)

Figure 6: Schematic representation of synergic families of advanced manufacturing technologies enabling the engineering of biomimetic biodevices: additive manufacturing technologies, robotic assisted manufacturing, technologies for advanced composites and micro-/nano-composites and resources derived from synthetic biology. Key enabling technologies and raw materials for these families of advanced manufacturing technologies are also presented. Illustrative examples of achievable complexity include prototypes of: b) functionally graded tissue engineering ceramic scaffolds (courtesy of Lithoz GmbH, Tomax project), c) concepts for annuloplasty reconstruction and d) tendon repair lattices (UPM, Product Development Lab).

6 APPLICATION CASES

6.1 Bioinspired Hip Prosthesis

Two conceptual application cases are presented in this section to illustrate synergies between varied design strategies aiming at enhanced biomimicry.

First, a bioinspired hip prothesis stem is designed, as schematically shown in figure 7. The design stands out for combining: 1) a biomechanical short structure for minimizing stress-shielding; 2) a topology optimization for achieving a graded network that mimics the trabecular and cortical regions; and 3) a selective application of bioinspired biointerfaces to different regions, in which osseointegration and vascularization should be selectively promoted.

6.2 Bioinspired Vascular Stent

Second, a bioinspired vascular stent is designed, as illustrated in figure 8. Its compliant mesh is surface functionalized by means of two microtextures. The external one is aimed at the improved interaction with the endothelial cells by using a pattern that imitates the extracellular matrix of the blood vessels. The internal biointerface is conceived for simultaneously promoting blood flow and minimizing blood clotting by employing a bioinspired shark skin design.

In both cases, materialization of the presented designs would rely on ultra high-performance AMTs capable of processing the adequate biomedical materials with the desired precision, which is still a current challenge, as happens with *in vitro* validation.

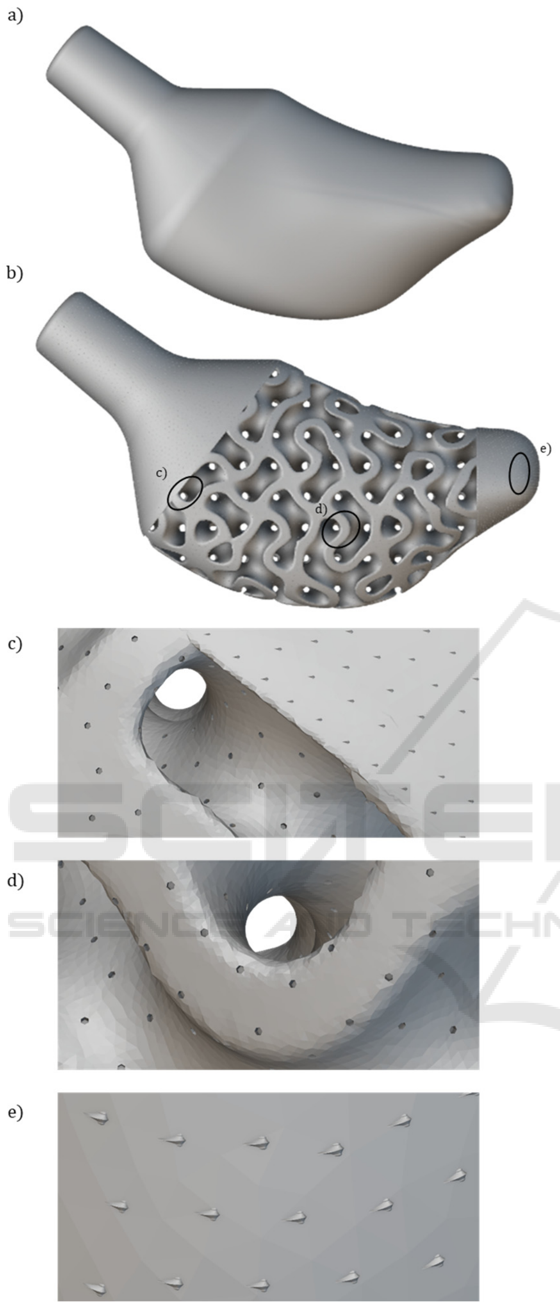


Figure 7: Multifunctional topography optimization of a short stem hip prosthesis. a) Biomechanically optimized short stem for femoral implantation. The conceptual design counts with different biointerfaces defined from the design stage according to desired biological features. b) Topology and topography-optimized solution. c-e) Topography optimization with textures mimicking the shark skin in regions where different flow orientations would be desired. d) Bone-like surface topography for enhanced osseointegration and increased primary stability.

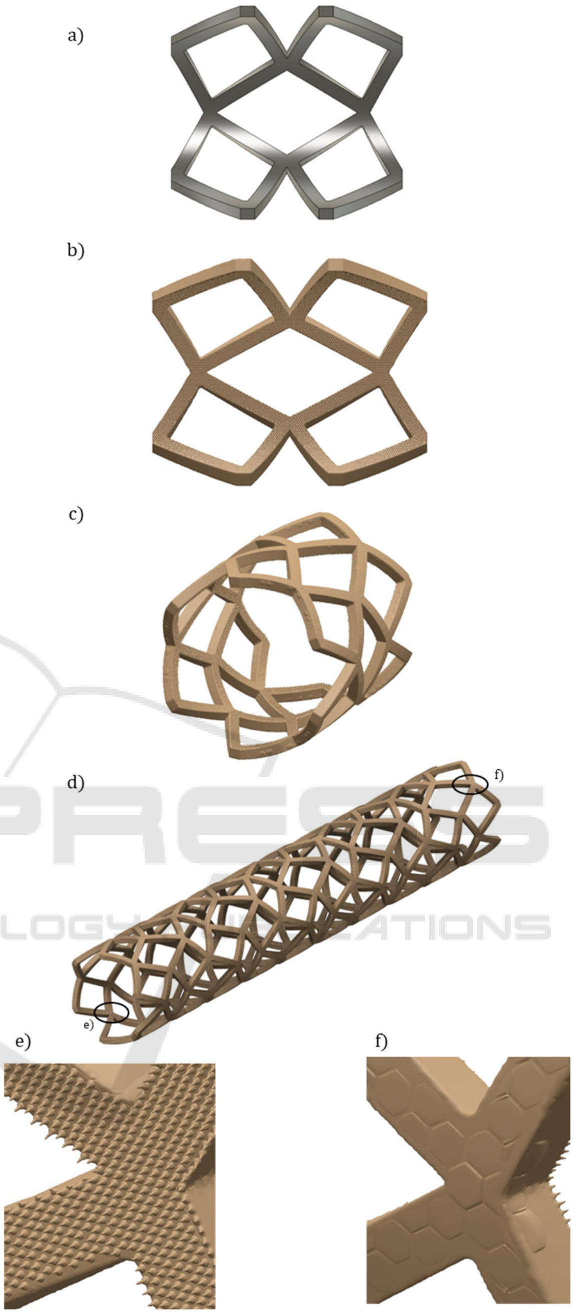


Figure 8: Innovative design for vascular stent with bioinspired surface topographies. The design process includes: a) Creation of unit cell. b) Application of topography optimizations. c) Design of basic ring. d) Replication towards complete stent. e) Detailed inner texture imitating shark skin for enhanced hemodynamics. f) Detailed external texture in contact with arterial wall for improved adhesion and long-term stability of the stent (avoiding slippery and preventing migration).

7 CONCLUSIONS

The geometrical and material complexity of living biological structures has been traditionally extremely challenging to imitate, which used to derive in suboptimal biomedical devices and implants, whose biomechanical behavior and biological interaction properties were not truly biomimetic.

Fortunately, bioinspired development strategies and advanced computational and manufacturing resources, as explained and exemplified in this study, are already synergizing in a highly stimulating way to solve the riddles of natural materials and biological structures. The quest for next generation bioinspired implants is just starting and requires integrative research efforts from as many fields as possible.

Towards the future, further expanding the biomaterials portfolio of advanced manufacturing technologies and exploring new ways of jointly processing biomaterials and living entities like cells and bacteria, in clear alignment with the nascent field of engineered living materials, can contribute to bringing biomimicry a step beyond.

In addition, if the implants of the future may rely on biohybrid solutions, there is a need for updated regulations and standards. In the European Union, to take an example, implants and tissue engineering scaffolds without cells are usually Class III medical devices, according to the Medical Device Regulation 2017/745, while scaffolds with cells are still considered advanced therapy medicinal products according to regulation 1394/2007. Further efforts in regulation and standardization harmonization are needed in this continuously evolving field.

Arguably, through expanded bioinspired and biomimetic development strategies and technological capabilities the biomedical implants of the future will importantly outperform the state-of-the-art and, hopefully, become the perfect solutions for users' biological structures needing repair or regeneration.

ACKNOWLEDGEMENTS

The research presented has been supported by the following research and innovation projects: "**iMPLANTS-CM**", from the "Convocatoria 2020 de ayudas para la realización de proyectos sinérgicos de I+D" funded by Comunidad Autónoma de Madrid (reference: Y2020/BIO-6756). "**INKplant**" funded by the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No. 953134.

REFERENCES

Bader, C. et al. (2018) 'Making data matter: Voxel printing for the digital fabrication of data across scales and domains', Science Advances, 4(5), p. eaas8652.

Bar-Cohen, Y. (2006) 'Biomimetics--using nature to inspire human innovation', Bioinspiration & Biomimetics, 1(1), pp. 1–12.

Benyus, J.M. (2002) 'Biomimicry: innovation inspired by nature', Harper Perennial, Harper Collins, New York, USA.

Bermejillo Barrera, M.D., Franco-Martínez, F., Díaz Lantada, A. (2021) 'Artificial Intelligence Aided Design of Tissue Engineering Scaffolds Employing Virtual Tomography and 3D Convolutional Neural Networks'. Materials, 14(18), 5278.

Bertram, J.E. and Biewener, A.A. (1988) 'Bone curvature: sacrificing strength for load predictability?', Journal of Theoretical Biology, 131(1), pp. 75–92.

Boccaccio, A. et al. (2016) 'Geometry Design Optimization of Functionally Graded Scaffolds for Bone Tissue Engineering: A Mechanobiological Approach', PLOS ONE, 11(1), p. e0146935.

Bongard, J. and Levin, M. (2023) 'There's Plenty of Room Right Here: Biological Systems as Evolved, Overloaded, Multi-Scale Machines', Biomimetics, 8(1), p. 110.

Dumont, E.R. (2010) 'Bone density and the lightweight skeletons of birds', Proceedings of the Royal Society B: Biological Sciences, 277(1691), pp. 2193–2198.

Díaz Lantada, A. (ed.) (2013) Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices. Boston, MA: Springer US.

Díaz Lantada, A., Franco-Martínez, F., Hengsbach, S., Rupp, F., Thelen, R., Bade, K. (2020) Artificial Intelligence Aided Design of Microtextured Surfaces: Application to Controlling Wettability. Nanomaterials, 10(11), 2287.

Díaz Lantada, A., Korvink, J.G. and Islam, M. (2022) 'Taxonomy for engineered living materials', Cell Reports Physical Science, 3(4), p. 100807.

Díaz Lantada, A. and Morgado, P.L. (2012) 'Rapid Prototyping for Biomedical Engineering: Current Capabilities and Challenges', Annual Review of Biomedical Engineering, 14(1), pp. 73–96.

Díaz Lantada, A., Sánchez, M.U. and Fernández, D.F. (2023) 'In silico Tissue Engineering and Cancer Treatment Using Cellular Automata and Hybrid Cellular Automata-Finite Element Models', in. 16th International Conference on Biomedical Electronics and Devices, pp. 56–63.

Droste, M. (2019) 'Bauhaus 1919-1933. Updated Edition'. Taschen, commemorative edition for the 100th anniversary of Bauhaus.

Feynman, R.P. (1959) 'Plenty of Room at the Bottom'. Lecture at the annual American Physical Society meeting at Caltech.

Franco Martínez, F. (2022) 'Artificial intelligence aided design of microstructured surfaces for tribology and biointerfaces engineering', PhD thesis, Universidad Politécnica de Madrid.

Gardan, J. (2019) 'Smart materials in additive manufacturing: state of the art and trends', Virtual and Physical Prototyping, 14(1), pp. 1–18.

Gardner, M. (no date) 'Conway's Game of Life: Scientific American, October 1970', Scientific American, 223, pp. 120–123.

Haleem, A., Javaid, M. and Vaishya, R. (2019) '5D printing and its expected applications in Orthopaedics', Journal of Clinical Orthopaedics and Trauma, 10(4), pp. 809–810.

Harley, W.S. et al. (2021) 'Advances in biofabrication techniques toward functional bioprinted heterogeneous engineered tissues: A comprehensive review', Bioprinting, 23, p. e00147.

Hutmacher, D.W. (2000) 'Scaffolds in tissue engineering bone and cartilage', Biomaterials, 21(24), pp. 2529–2543.

Leong, K.F. et al. (2008) 'Engineering functionally graded tissue engineering scaffolds', Journal of the Mechanical Behavior of Biomedical Materials, 1(2), pp. 140–152.

Liverani, E., Rogati, G., Pagani, S., Brogini, S., Fortunato, A. and Caravaggi, P. (2021) 'Mechanical interaction between additive-manufactured metal lattice structures and bone in compression: implications for stress shielding of orthopaedic implants', Journal of the Mechanical Behavior of Biomedical Materials, 121, 104608.

Mandelbrot, B.B. (1983) The Fractal Geometry of Nature. Henry Holt and Company.

Neumann, J.V. and Burks, A.W. (1966) Theory of Self-Reproducing Automata. USA: University of Illinois Press.

Nguyen, P.Q. et al. (2018) 'Engineered Living Materials: Prospects and Challenges for Using Biological Systems to Direct the Assembly of Smart Materials', Advanced Materials (Deerfield Beach, Fla.), 30(19), p. e1704847.

Niemeyer, C.M. et al. (2018) 'White Paper on the Biologization of Materials Research'. Preprints.

Perier-Metz, C., Duda, G.N. and Checa, S. (2022) 'A mechanobiological computer optimization framework to design scaffolds to enhance bone regeneration', Frontiers in Bioengineering and Biotechnology, 10.

Phillips, J.E. et al. (2008) 'Engineering graded tissue interfaces', Proceedings of the National Academy of Sciences, 105(34), pp. 12170–12175.

Place, E.S., Evans, N.D. and Stevens, M.M. (2009) 'Complexity in biomaterials for tissue engineering', Nature Materials, 8(6), pp. 457–470.

Skylar-Scott, M.A. et al. (2019) 'Voxelated soft matter via multimaterial multinozzle 3D printing', Nature, 575(7782), pp. 330–335.

Srubar III, W.V. (2020) 'Engineered living materials: taxonomies and emerging trends', Trends in Biotechnology, 39(6), pp. 574-583.

Tannenbaum, J. and Bennett, B.T. (2015) 'Russell and Burch's 3Rs Then and Now: The Need for Clarity in Definition and Purpose', Journal of the American Association for Laboratory Animal Science, 54(2).

Vasiliadis, A.V., Koukoulias, N. and Katakalos, K. (2022) 'From Three-Dimensional (3D)- to 6D-Printing Technology in Orthopedics: Science Fiction or Scientific Reality?', Journal of Functional Biomaterials, 13(3), p. 101.

Velu, R. et al. (2019) 'A Comprehensive Review on Bio-Nanomaterials for Medical Implants and Feasibility Studies on Fabrication of Such Implants by Additive Manufacturing Technique', Materials, 13(1), p. 92.

Wang, X. et al. (2016) 'Topological design and additive manufacturing of porous metals for bone scaffolds and orthopaedic implants: A review', Biomaterials, 83, pp. 127–141.

Zadpoor, A.A. (2019) 'Mechanical performance of additively manufactured meta-biomaterials', Acta Biomaterialia, 85, pp. 41–59.

Zadpoor, A.A. (2020) 'Meta-biomaterials', Biomaterials Science, 8(1), pp. 18–38.