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A methodological approach towards the bio-inspired design of novel scaffolds for tissue engineering

Pierpaolo Fucile[1], Francesco Lamonaca[2,3], Antonio Gloria[4], Lorenzo Moroni[1]

[1] *MERLN Institute for Technology-Inspired Regenerative Medicine, Complex Tissue Regeneration Department, Maastricht University, P.O. Box 616, Maastricht, 6200MD, The Netherlands*
[2] *Department of Computer Science, Modeling, Electronics and Systems Engineering (DIMES), University of Calabria, Ponte P. Bucci, 87036, Arcavacata di Rende, Italy*
[3] *National Research Council of Italy, Institute of Nanotechnology (CNR-NANOTEC), Rende, Italy*
[4] *Department of Industrial Engineering, Fraunhofer JL IDEAS, University of Naples Federico II, P.le Tecchio 80, 80125 Naples, Italy*

ABSTRACT
The design of scaffolds for multi-tissue regeneration is very complex in terms of material and structure, as a direct consequence of hierarchical and organizational features. TRIZ represents the Russian acronym for the "Theory of Inventive Problem Solving" (TIPS). TRIZ is able to identify and codify such principles, using them to make the creative process more predictable. It is a methodology for the identification of the system conflicts and contradictions in order to solve the inventive problems. Its multidisciplinary features and the general approach to product design can make TRIZ as an intriguing starting point for the biomimetic approach in a systematic and organized way. Biomimetics aims at a complete integration between nature and technology. In this scenario, BioTRIZ shares the contradiction resolution method of the Altshuller's theory, representing a systematic biomimetic approach towards the product design. In the current study, BioTRIZ was considered to systematize the process of bio-inspired design of 3D optimized scaffolds for the regeneration of complex tissue defects. A device for the regeneration of osteochondral tissue defects was considered as a case study. The technical solutions involved the design of a two-compartment, hybrid and functionally graded scaffold.

Section: RESEARCH PAPER

Keywords: Bio-inspired design; design for additive manufacturing; BioTRIZ; scaffolds for tissue engineering

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Corresponding author: Pierpaolo Fucile, email: p.fucile@maastrichtuniversity.nl

1. INTRODUCTION

The advances in materials chemistry, technologies and design strategies have pushed the research towards the development of innovative devices for tissue engineering and replacement [1]-[6].

Biomimetics, or Biomimicry, is a quite recent formal study which takes inspiration from nature in order to copy and adapt biological mechanisms and, hence, to design new technologies or improve existing ones [7]. Although this process nowadays is carried out in a systematic way, nature emulation has always been present throughout history. For instance, Leonardo da Vinci made several studies on the flight of the birds in order to design his flying machine, whilst Velcro was invented by Georges de Mestral after analysing burrs in his dog's fur [8].

The current global situation of ecological crises and climate changes requires a different approach in terms of environmental impact, instead of the traditional engineering approach to new objects and technologies which tends to exploit resources and causes excessive pollution [9].

A general framework for natural concepts integration in the development of new technologies consisted in a literature analysis and "trial-and-error" approach, which resulted in a waste of time, materials and energy, since every new system had to start from zero for each natural mechanism analyzed and tested.

A first systematic approach to product design and problem solving was represented by the TRIZ methodology, the Russian acronym for "Teoriya Resheniya Izobretatel'skih Zadatch" (in English "Theory of Inventive Problem Solving", TIPS), which was developed by Genrich Altshuller and Rafik Shapiro in the

Soviet Union in the 1950s [10]. TRIZ is a very powerful problem solving and new product design toolkit based on the analysis of several successful patents [11]. This analysis allowed for a systematic resolution to engineering issues, granting repeatable, reliable, and predictable innovative solutions in terms of design and fabrication methods [12], as well as an easy transfer of concepts and solutions from one science field to the other [7]. The multidisciplinary features and the general approach to the product design make TRIZ a perfect starting point for a biomimetic approach in a systematic and organized way [13], [14]. It offers different methods to solve design problems which range from low to high level of complexity.

TRIZ is structured as an algorithm [15], which allows for new designs through the overcoming of a contradiction [10], meaning a trade-off that must be found between two technical features. The patents' analysis performed by Altshuller led to the definition of two types of contradictions. Technical contradictions arise when one attribute is worsened by the improvement of another one. Whilst physical contradictions represent a situation in which two opposite physical states exist. The Altshuller's Matrix of Contradictions is the main TRIZ tool used to solve the contradictions. The improving parameters are arranged on the vertical axis of the matrix, whilst the antithetic ones are put on the top row, and their combination ideally represents every potential design contradiction to be solved. In the Altshuller's algorithm, the solution to any contradiction can be found in a list of 40 Inventive Principles (IPs).

In this context, TRIZ represents a methodology that minimizes the waste of energy and time during the design phase of a new technology, through a robust definition and identification of the problem, resulting in a systematic approach which can be the starting point for a biomimetic approach.

A further step to a complete eco-friendly approach to design and problem solving was made by dr. Vincent in 2006 [7], who studied with his team several technological and natural systems, also analyzing which variable had to be used for solving problems at different size levels. It was observed a tendency in changing materials or increasing the amount of energy in technological systems, whilst for the same size levels, nature tends to exploit information and space variables. In fact, nature achieves different and complex functions through the combination of proteins and manipulation of their shape, thus avoiding a high exploitation of energy resources [9].

The algorithm introduced by Vincent was called BioTRIZ [7], as it shares the contradiction resolution method of the Altshuller's theory, representing a systematic biomimetic approach towards the product design. Over 500 biological phenomena were analyzed and about 2500 contradictions and their solution were identified in natural systems. The resulting contradiction matrix was named PRIZM ("Pravila Reshenija Izobretatel'skih Zadach Modernizirovannye", "The Rules of Inventive Problem Solving, Modernized" in English).

This matrix is a condensed version of the traditional TRIZ one, as it is a 6x6 matrix, since all parameters are grouped in 6 meta-categories (substance, structure, space, time, energy, and information) (Table 1) [7], [8], [16]. Thus, every inventive principle is generated from the conflict between two of these meta-categories (e.g., substance vs. space). Actually, two different PRIZM matrices were developed. The first one was derived from TRIZ contradiction matrix and dealt with synthetic systems, whilst the second one was the consequence of the analyses related to the contradictions resolution in natural systems. This shows how the same issue may be solved with different IPs in the two systems. In general, if different kinds of solutions to pairs of conflicts, which are arrived at in technology through classical TRIZ and in biology, are compared, it is worth stressing how the principles that technology and nature employ to solve the problems may be very different, also dealing with very similar problems.

The similarity between TRIZ and BioTRIZ matrices is only 0.12, where 1 represents the identity [7], [9].

Vincent defined the following pathway of application for BioTRIZ [7]:

1. *Define the problem in the most general, yet precise way. It is essential to avoid specific directions of thought or premature solution of the problem. Then list the desirable and undesirable properties and functions.*
2. *Analyze and understand the problem and so uncover the main conflicts or contradictions. The technical conflicts are then identified in the TRIZ matrix and listed. Find the functional analogy in biology or go to the biological conflict matrix.*
3. *Compare the solutions recommended by biology and TRIZ. Find the common solutions for biological and engineering fields. List the technical and biological principles thus recommended.*
4. *Based on these common solutions, build a bridge from natural to technical design. To make the technical and biological systems compatible, make a list of their general recommended compositions.*
5. *Create a completely new technology, add to the basic TRIZ principles some pure technical or pure biological ones.*

The idea to identify and integrate opportunities between TRIZ and biomimetics may lead to the development of a more efficient inventive design methodology for tissue engineering applications.

Tissue engineering is a multidisciplinary field of science which merges knowledge from engineering, biology, and medicine. It aims to a complete regeneration of a damaged, overcoming conventional treatments, such as prosthetics and transplants [17]-[20]. The damaged tissue regeneration is enhanced through 3D scaffolds with a fully interconnected porous structure and

Table 1. The PRIZM Matrix: BioTRIZ (adapted from [7]). The reported numbers are related to the list of 40 IPs of TRIZ.

META-CATEGORIES	SUBSTANCE	STRUCTURE	SPACE	TIME	ENERGY	INFORMATION
SUBSTANCE	13,15,17,20,31,40	1-3,15,24,26	1,5,13,15,31	15,19,27,29,30	3,6,9,25,31,35	3,25,26
STRUCTURE	1,10,15,19	1,15,19,24,34	10	1,2,4	1,2,4	1,3,4,15,19,24,25,35
SPACE	3,14,15,25	2-5,10,15,19	4,5,14,17,36	1,19,29	1,3,4,15,19	3,15,21,24
TIME	1,3,15,20,25,38	1-4,6,15,17,19	1-4,7,38	2,3,11,20,26	3,9,15,20,22,25	1-3,10,19,23
ENERGY	1,3,13,14,17,25,31	1,3,5,6,25,35,36,40	1,3,4,15,25	3,10,23,25,35	3,5,9,22,25,32,37	1,3,4,15,16,25
INFORMATION	1,6,22	1,3,6,18,22,24,32,34,40	3,20,22,25,33	2,3,9,17,22	1,3,6,22,32	3,10,16,23,25
	INVENTIVE PRINCIPLES (IPs)					

tailored architecture, as well as appropriate mechanical and biological behavior. In fact, scaffolds must have load bearing function and must mimic the tissue composition, enhancing extracellular matrix analogue deposition [17], [21], [22]. Scaffolds must satisfy several requirements [23]: (i) biocompatibility (i.e., the scaffold must not induce an inflammatory response, (ii) network of pores with high level of interconnectivity, (iii) biodegradability, with degradation times inversely proportional to tissue regeneration ones, (iv) bioresorbability, and (v) load bearing function.

Typical scaffold materials are synthetic polymers (e.g., polycaprolactone - PCL), and often polymeric matrices reinforced with inorganic nanoparticles (e.g., hydroxyapatite - HA) which are more versatile than natural materials in mechanical and functional properties. Furthermore, the same synthetic material can be used for different TE applications varying its chemical and physical properties [24], [25].

Anyway, over the past years, great efforts have been devoted to the development of devices with optimized properties for different kinds of applications, benefiting from the advances in methodologies and design strategies [20]-[23].

An example is topology optimization, which represents a mathematical method aiming to optimize the material layout within a given design space, according to the constraints, loading and boundary conditions, in order to maximize the performance of a system. With regard to scaffolds for tissue engineering applications, the objective should be to attain desired mechanical and mass transport (e.g., permeability) properties. As both mechanical and mass transport properties depend upon the porosity and architectural features of the scaffold, computational design methods have to be used for the prediction and optimization of a microstructure for achieving the desired balance.

Scaffolds for tissue engineering may be developed through advanced fabrication methods such as additive manufacturing techniques, and, in particular, 3D Fiber Deposition, which allows for a material deposition in a layer-by-layer manner and a precise control on porosity, as well as on structural features and long-range architecture, thus resulting in complex and custom-made morphologies [25], [26]. These results cannot be reached through traditional fabrication techniques, such as gas foaming, solvent casting and salt leaching [25]. In this scenario, the BioTRIZ philosophy may be employed to avoid the unnecessary waste of energy, materials, and time.

In the current study, the attention was focused on BioTRIZ to systematize the process of bio-inspired design of 3D optimized scaffolds for the regeneration of complex tissue defects.

The design of a 3D scaffold for the regeneration of osteochondral tissue defects was selected as a case study. Thus, the process had to take into account several features related to the tissue (i.e., bone and cartilage) that differ histologically, chemically and physiologically. Clearly, the concept of "one kind of scaffold per tissue" was not considered as an appropriate solution.

2. GENERATION OF NOVEL CONCEPTS

The first step of this study consisted in the identification of contradictions during the design phase of the scaffold for the osteochondral tissue regeneration. Some of these contradictions were case specific and dealt with the multi-tissue regeneration. As previously discussed, according to the BioTRIZ philosophy [7], [9], a single scaffold for multi-tissue regeneration was considered, in order to introduce an innovative device for tissue engineering applications and to avoid unnecessary waste of energy and materials at the same time. The main parameters involved in the design contradictions were the material composition (i.e., polymer matrix/filler weight ratio) and porosity values, which influence the mechanical and mass transport properties, as well as the biological performances.

The impact of porosity and lay-down pattern (i.e., fiber stacking sequence) on cell differentiation and mechanical properties has already been analyzed [20], [27]-[29].

Tissue engineering issues related to the mechanical and mass transport properties as well as to the biological performances can be solved during the design phase acting on physical, chemical and structural parameters (e.g., material composition, porosity, lay-down pattern). These issues deal with an intriguing paradigm requiring scaffolds which are able to balance temporary mechanical function with mass transport properties, also favouring biological processes. Furthermore, information about the two separate tissues and their interface must be considered as well.

The contradictions were initially solved through TRIZ methodology and the resulting inventive principles (IPs) were identified into the PRIZM matrix, and the meta-categories were compared. The best concepts, which could act as a bridge between the engineering and natural worlds [7], were generated.

Finally, novel 3D scaffolds for osteochondral tissue regeneration were designed and additively manufactured (i.e., 3D Fiber Deposition). The mechanical and mass transport properties (i.e., permeability), which generally influence the biological performances, were experimentally evaluated. 3D scaffolds for both bone and cartilage regeneration were used as controls.

3. RESULTS

The previously reported tissue engineering issues are described by the following contradictions:

1. Pores must be big enough to enhance mass transport properties, and small enough to enhance mechanical performances at the same time. This represents a physical contradiction which was solved through the "separation in time" principle [30].
2. The scaffold must sustain different loading conditions and mimic different extra-cellular environments, keeping its architecture as simple as possible.
3. Scaffold material must be easy to process and possess good mechanical properties at the same time. Plain polymers, which are easily processable, lack mechanical resistance.

Contradictions were solved through the following TRIZ features:

- 14. Strength: typical results in terms of mechanical properties must be granted in the bone and cartilage compartments of the scaffolds.
- 25. Loss of time: every waste, including time one, must be minimized, thus maximizing productivity.
- 26. Quantity of Substance: pores morphology and dimension depend on the lay-down pattern deposition, as well as on the distance between two adjacent polymeric filaments. Bigger pores result in fewer strands, and vice versa.

- 32. Ease of manufacture: in the context of Eco-engineering and positive impact on nature, scaffolds must be versatile and easy to realize, despite the multi-tissue application. This feature is related to "33. Ease of operation" as well.
- 36. Device Complexity: the osteochondral damage application requires a scaffold with different properties and function on different cross-sections.

The following inventive principles (IPs) were identified in the Altshuller's Matrix of Contradictions and compared to biological principles [7]:

- IP 3: Local Quality. *Change an object's structure from uniform to non-uniform. Use a temperature, density, or pressure gradient instead of constant temperature, density or pressure.* This is a common feature of living organisms, which are multifunctional and heterogeneous (e.g., cells).
- IP 4: Asymmetry. *Change the shape of an object from symmetrical to asymmetrical.* Almost every "biological object" is asymmetrical, since asymmetry is a response to its history and adaptation do several functions.
- IP 9: Preliminary Anti-Action. *If it will be necessary to do an action with both harmful and useful effects, this action should be replaced with anti-actions to control harmful effects.* To prevent harmful effects is a common mechanism in nature (e.g., non-woody plants are pre-stressed in tension, thus minimizing solid material in the structure, and penguins feathers which protect them from freezing temperatures). In the same way, topology optimization "protects" scaffolds from structural and functional failure by properly modifying its architecture during the design phase.
- IP 40: Composite Materials. *Change from uniform to composite (multiple) materials.* As previously said, almost every natural material is composite.

The great effort to reproduce the structure of the natural bone, which is a natural nanocomposite where crystallites of an inorganic material (hydroxyapatite) reinforce the collagen (a natural polymer) fibrils, has led to the development of biomimetic solutions. As a result, 3D hybrid constructs consisting of two distinct but integrated compartments, where a nanocomposite (PCL/HA) and a neat polymer (PCL) compartment devoted to bone and cartilage regeneration, respectively, were developed [17], [24]. The construct consisted of a functionally graded scaffold with a gradient in porosity/pore size, material composition and mechanical properties, trying to mimic the osteochondral tissue complex. The design is presented in Figure 1. In terms of material composition, the bone compartment of the scaffold was designed with a higher amount of HA nanoparticles at the first layers, which was gradually lowered till reaching the top of the structure. On the top of such structure, the optimized compartment for cartilage regeneration was additively manufactured. A system of intertwined concentric fibers, which mimicked the tidemark region, was designed to create an interlocking between the two compartments. Such multi-material structure with integrated functionalities was realized with different cartridges, containing nanocomposite material characterized by different polymer matrix/filler weight ratio and plain PCL, placed on the mobile arm of a 3D plotter. The cartridges were properly switched at specific scaffold layers. Furthermore, the bone compartment of the scaffold was characterized by a fiber diameter of 400 μm and a pore size of 300 μm, which was gradually decreased up to 100 μm in the proximity of the interface between the two designed compartments. The fiber diameter was also gradually decreased acting on the flow rate of the process. A fiber diameter of 100 μm and a pore size of 100 μm were considered for the cartilage compartment.

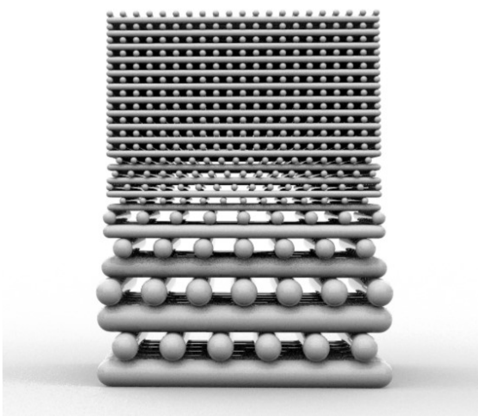

Figure 1. A representation of the two-compartment, hybrid and functionally graded scaffold in terms of fibre diameters and porosity to mimic the bone and cartilage compartments.

The result in terms of compressive mechanical properties demonstrated the load-bearing capabilities of the 3D additive manufactured hybrid construct. The overall mechanical behavior and properties of the two-compartment hybrid device were the result of the synergistic contribution of the functionally graded structure of the nanocomposite (i.e., PCL/HA) compartment and the polymeric (i.e., PCL) compartment which first deformed during compression. Anyway, also taking into account the one-compartment scaffolds selectively designed for bone and cartilage regeneration, the experimental results showed values of compressive modulus which were consistent with those reported for subchondral bone (e.g., 98–270 MPa) [31] and for cartilage (e.g., 2–20 MPa) [32]. Anyway, it is worth remembering that in the native osteochondral tissues the mechanical properties depend upon the patient's activity, age, and location in the body.

4. CONCLUSIONS

The need to minimize the impact of technology on nature has led to the development of design and fabrication methodologies which enhance eco-innovation, mimicking natural processes and systems. Biomimetics aims to inspire creative design promoting the synergy between artificial and natural systems, and BioTRIZ has made this process systematic, thanks to the "thesis-antithesis" structure, which is typical of the TRIZ method and allows to introduce innovative concepts as the resolution of a contradiction between design parameters.

In this context, the current study proposed an innovative design and fabrication of hybrid scaffolds for multi-tissue regeneration in the field of Tissue Engineering. In particular, the design of osteochondral tissue regeneration was taken into account. Typical natural processes, such as the adaptation to different environments, were considered and implemented during a typical tissue regeneration pathway. The solutions suggested by nature and BioTRIZ involved the design of a two-compartment, hybrid, and functionally graded scaffold.

The hybrid scaffold for multi-tissue regeneration was designed and additively manufactured (i.e., 3D Fiber Deposition). Taking inspiration from nature, a nanocomposite material (i.e., PCL reinforced with HA nanoparticles) and plain PCL were considered for bone and cartilage regeneration, respectively. The scaffold concept was characterized by a gradient in porosity/pore size, material composition and mechanical properties, thus adapting to the different tissue environments. Analogies were stressed between nature and typical engineering design methodologies, such as topology optimization, in terms of prevention of structural and functional failure by directly acting in the design phase.

The designed hybrid scaffolds were also experimentally tested, showing appropriate mechanical properties for osteochondral tissue regeneration.

REFERENCES

[1] R. De Santis, I. Papallo, I. Onofrio, V. Peluso, V. Gallicchio, A. Rega, V. D'Antò, G. Improta, M. Catauro, A. Gloria, T. Russo, Analyzing the Role of Magnetic Features in Additive Manufactured Scaffolds for Enhanced Bone Tissue Regeneration, Macromolecular Symposia, (2021), 396(1). DOI: 10.1002/masy.202000314

[2] D. Ronca, F. Langella, M. Chierchia, U. D'Amora, T. Russo, M. Domingos, A. Gloria, P. Bartolo, L. Ambrosio, Bone tissue engineering: 3D PCL-based nanocomposite scaffolds with tailored properties, Procedia Cirp, (2016), 49, pp. 51-54. DOI: 10.1016/j.procir.2015.07.028

[3] V. Guarino, A. Gloria, M. G. Raucci, L. Ambrosio, Hydrogel-based platforms for the regeneration of osteochondral tissue and intervertebral disc. Polymers, (2012), 4(3), pp. 1590-1612. DOI: 10.3390/polym4031590

[4] S. Maietta, T. Russo, R. De Santis, D. Ronca, F. Riccardi, M. Catauro, M. Martorelli, A. Gloria, Further theoretical insight into the mechanical properties of polycaprolactone loaded with organic–inorganic hybrid fillers, Materials, (2018), 11(2), p. 312. DOI: 10.3390/ma11020312

[5] S. Reitmaier, A. Shirazi-Adl, M. Bashkuev, H.-J. Wilke, A. Gloria, H. Schmidt, In vitro and in silico investigations of disc nucleus replacement, Journal of the Royal Society Interface, (2012), 9(73), pp. 1869-1879. DOI: 10.1098/rsif.2012.0016

[6] A. Borzacchiello, A. Gloria, L. Mayol, S. Dickinson, S. Miot, I. Martin, L. Ambrosio, Natural/synthetic porous scaffold designs and properties for fibro-cartilaginous tissue engineering, Journal of Bioactive and Compatible Polymers, (2011), 26(5), pp. 437-451. DOI: 10.1177/0883911511420149

[7] J. F. Vincent, O. A. Bogatyreva, N. R. Bogatyrev, A. Bowyer, A.-K. Pahl, Biomimetics: its practice and theory, Journal of the Royal Society Interface, (2006), 3(9), pp. 471-482. DOI: 10.1098/rsif.2006.0127

[8] M. W. Glier, J. Tsenn, J. S. Linsey, D. A. McAdams, Methods for supporting bioinspired design, in ASME International Mechanical Engineering Congress and Exposition, 2011. DOI: 10.1115/IMECE2011-63247

[9] N. Bogatyrev, O. Bogatyreva, BioTRIZ: a win-win methodology for eco-innovation, in Eco-innovation and the Development of Business Models, 2014, Springer, pp. 297-314.

[10] G. S. Al'tshuller, The innovation algorithm: TRIZ, systematic innovation and technical creativity, 1999: Technical innovation center, Inc. ISBN: 0964074044

[11] K. Melemez, G. Di Gironimo, G. Esposito, A. Lanzotti, Concept design in virtual reality of a forestry trailer using a QFD-TRIZ based approach, Turkish Journal of Agriculture and Forestry, (2013), 37(6), pp. 789-801. DOI: 10.3906/tar-1302-29

[12] H. Yuan, K. Xing, H.-Y. Hsu, Generate basic conceptual solutions for 3DPVS via utilizing TRIZ, Bio-Design and Manufacturing, (2019), 2(2), pp. 76-95. DOI: 10.1007/s42242-019-00039-6

[13] N. Bogatyrev, Ecological engineering of survival, Novosibirsk, Russia: Publishing house of SB RAS, (2000).

[14] J. F. Vincent, D. L. Mann, Systematic technology transfer from biology to engineering, Philosophical Transactions of the Royal Society of London, Series A: Mathematical, Physical and Engineering Sciences, (2002), 360(1791), pp. 159-173. DOI: 10.1098/rsta.2001.0923

[15] R. H. Da Silva, P. C. Kaminski, F. Armellini, Improving new product development innovation effectiveness by using problem solving tools during the conceptual development phase: Integrating Design Thinking and TRIZ, Creativity and Innovation Management, (2020), 29(4), pp. 685-700. DOI: 10.1111/caim.12399

[16] O. Bogatyreva, A. Shillerov, N. Bogatyrev, Patterns in TRIZ contradiction matrix: integrated and distributed systems, Development and implementation of TRIZ Theory, (2004).

[17] A. Gloria, T. Russo, U. d'Amora, S. Zeppetelli, T. d'Alessandro, M. Sandri, M. Bañobre-López, Y. Piñeiro-Redondo, M. Uhlarz, A. Tampieri, Magnetic poly (ε-caprolactone)/iron-doped hydroxyapatite nanocomposite substrates for advanced bone tissue engineering, Journal of the Royal society interface, (2013), 10(80), p. 20120833. DOI: 10.1098/rsif.2012.0833

[18] R. Langer, J. Vacanti, Tissue engineering, Science, (1993), 260(5110), pp. 920-926. DOI: 10.1126/science.8493529

[19] M. S. Chapekar, Tissue engineering: challenges and opportunities, Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials, (2000), 53(6), pp. 617-620. DOI: 10.1002/1097-4636(2000)53:6<617::AID-JBM1>3.0.CO;2-C

[20] A. Gloria, R. De Santis, L. Ambrosio, Polymer-based composite scaffolds for tissue engineering, Journal of Applied Biomaterials and Biomechanics, (2010), 8(2), pp. 57-67. DOI: 10.1177/228080001000800201

[21] D. W. Hutmacher, Scaffold design and fabrication technologies for engineering tissues—state of the art and future perspectives, Journal of Biomaterials Science, Polymer Edition, (2001), 12(1), pp. 107-124. DOI: 10.1163/156856201744489

[22] D. W. Hutmacher, T. Schantz, I. Zein, K. W. Ng, S. H. Teoh, K. C. Tan, Mechanical properties and cell cultural response of polycaprolactone scaffolds designed and fabricated via fused deposition modeling, Journal of Biomedical Materials Research, (2001), 55(2), pp. 203-216. DOI: 10.1002/1097-4636(200105)55:2<203::aid-jbm1007>3.0.co;2-7

[23] F. Causa, P. A. Netti, L. Ambrosio, A multi-functional scaffold for tissue regeneration: the need to engineer a tissue analogue, Biomaterials, (2007), 28(34), pp. 5093-5099. DOI: 10.1016/j.biomaterials.2007.07.030

[24] F. Causa, P. Netti, L. Ambrosio, G. Ciapetti, N. Baldini, S. Pagani, D. Martini, A. Giunti, Poly-ϵ-caprolactone/hydroxyapatite composites for bone regeneration: In vitro characterization and human osteoblast response, Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials, (2006), 76(1), pp. 151-162. DOI: 10.1002/jbm.a.30528

[25] A. Gloria, T. Russo, R. De Santis, L. Ambrosio, 3D fiber deposition technique to make multifunctional and tailor-made scaffolds for tissue engineering applications, Journal of Applied Biomaterials and Biomechanics, (2009), 7(3), pp. 141-152. DOI: 10.1177/228080000900700301

[26] E. Sachlos, J. Czernuszka, Making tissue engineering scaffolds work, Review: the application of solid freeform fabrication technology to the production of tissue engineering scaffolds, Eur Cell Mater, (2003), 5(29), pp. 39-40. DOI: 10.22203/ecm.v005a03

[27] M. Martorelli, S. Maietta, A. Gloria, R. De Santis, E. Pei, A. Lanzotti, Design and analysis of 3D customized models of a

human mandible, Procedia Cirp, (2016), 49, pp. 199-202. DOI: 10.1016/j.procir.2015.11.016

[28] P. Fucile, I. Onofrio, I. Papallo, V. Gallicchio, A. Rega, V. D'Antò, G. Improta, R. De Santis, A. Gloria, T. Russo, Strategies for the design of additively manufactured nanocomposite scaffolds for hard tissue regeneration, Acta IMEKO 9 (2020) 4, pp. 53-59. DOI: 10.21014/acta_imeko.v9i4.739

[29] D. P. Byrne, D. Lacroix, J. A. Planell, D. J. Kelly, P. J. Prendergast, Simulation of tissue differentiation in a scaffold as a function of porosity, Young's modulus and dissolution rate: application of mechanobiological models in tissue engineering, Biomaterials, (2007), 28(36), pp. 5544-5554. DOI: 10.1016/j.biomaterials.2007.09.003

[30] K. Gadd, TRIZ for engineers: enabling inventive problem solving, 2011: John wiley & sons, ISBN: 978-0-470-74188-7

[31] K. Schlichting, H. Schell, R. U. Kleemann, A. Schill, A. Weiler, G. N. Duda, D. R. Epari, Influence of scaffold stiffness on subchondral bone and subsequent cartilage regeneration in an ovine model of osteochondral defect healing, The American journal of sports medicine, (2008), 36(12), pp. 2379-2391. DOI: 10.1177/0363546508322899

[32] D. Shepherd, B. Seedhom, The 'instantaneous' compressive modulus of human articular cartilage in joints of the lower limb, Rheumatology (Oxford, England), (1999), 38(2), pp. 124-132. DOI: 10.1093/rheumatology/38.2.124