REVIEW ARTICLE

Revealing emerging science and technology research for dentistry applications of 3D bioprinting

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Abstract: Science and technology (S&T) on three-dimensional (3D) bioprinting is growing at an increasingly accelerated pace; one major challenge represents how to develop new solutions for frequent oral diseases such as periodontal problems and loss of alveolar bone. 3D bioprinting is expected to revolutionize the health industry in the upcoming years. In dentistry, this technology can become a significant contributor. This study applies a Competitive Technology Intelligence methodology to uncover the main S&T drivers in this domain. Looking at a 6-year period from 2012 to 2018 an analysis of scientific and technology production was made. Three principal S&T drivers were identified: Scaffolds development, analysis of natural and synthetic materials, and the study of scaffold characteristics. Innovative hybrid and multiphasic scaffolds are being developed to regenerate periodontal tissue and alveolar bone by combining them with stem cells from the pulp or periodontal ligament. To improve scaffolds performance, biodegradable synthetic polymers are often used in combination with bioceramics. The characteristics of scaffolds such as fiber orientation, porosity, and geometry, were also investigated. This research contributes to people interested in bringing innovative solutions to the health industry, particularly by applying state-of-the-art technologies such as 3D bioprinting, in this case for dental tissues and dental bone diseases.

Keywords: Competitive technology intelligence; three-dimensional bioprinting; dentistry; dental; Science and technology trends.

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1. Background

Over the past few years, three-dimensional (3D) printing has attracted the attention of the science and technology (S&T) community. Since Chuck Hull's invention of stereolithography, which was patented in 1984, new technologies and applications in a variety of industries have been emerging; and since the early 2000s, their applications have sky-rocketed. Although conventional use of 3D printing technology is becoming increasingly accessible to people, applications in the health industry are still in a nascent stage, particularly those that involve bioprocesses to prevent, maintain, or heal body tissue.

3D bioprinting technology opens a large innovative window, giving the potential to bring in new solutions that could have a major impact in many fields including complex organs study, ophthalmology, drug delivery, and so forth. In the realm of dentistry, one of the most frequent illness concerns is periodontal diseases and the loss of alveolar bone. In this context, the current research applies a Competitive Technology Intelligence methodology to uncover principal S&T trends.

1.1 Competitive Technology Intelligence

Competitive intelligence is based on the systematic and ethical process of gathering, analyzing and transforming information into actionable knowledge in the context of the competitive environment of an organization[1]; it contributes to making decisions in organizations of all sizes and across different disciplines. Specifically,

Competitive Technology Intelligence involves the analysis of S&T environment. Moreover, it has been applied for years in different industries; however, in the field of 3D printing and, moreover, for bio-applications, the studies are still scarce. In this sense, Rodríguez-Salvador *et al.* (2017)[1] combined competitive technology intelligence with scientometrics tools to analyze scientific and patent literature from 2000 to mid-2016, determining the knowledge landscape on 3D bioprinting. On the other hand, Trappey *et al.*[2] evaluated the development of 3D printing technology for biomedical applications through a US patent analysis where a search time frame was set from 1980 to August 2014. While both studies analyze 3D printing from a general perspective, this research pursues to fill the gap associated to the lack of competitive technology studies on specific applications of 3D bioprinting, in this case by analyzing its innovative presence on dentistry.

1.2 3D Bioprinting

3D printing is a revolutionary technology that is also known as additive manufacturing. The American Society for Testing and Materials (ASTM International) define additive manufacturing as a group of techniques which apply the additive shaping principle and thereby build physical 3D geometries by successive addition of material. Hence, it is important to clarify that according to the ASTM the terminology of 3D printing can also be used as synonymous of additive manufacturing in a non-technical context (Cerneels, 2015; ISO/ASTM 52900, 2015). The application of this technology is growing because it offers unique characteristics, such as customization, the production of complex geometries and waste reduction. The principal processes of 3D printing involve the following: Fused deposition modeling[3], selective laser sintering[4], electron beam melting[5], inkjet 3D printing[6], extrusion 3D printing[7], and laser-assisted printing[8]. As a diverse number of industries, ranging from automotive and aerospace to health, have a growing interest in the development and implementation of this technology; knowing scientific and technology trends will play a fundamental role to identify and manage opportunities to innovate.

In recent years, the use of these technologies for medical applications has increased[9], and as a result, the term 3D bioprinting has born as a specialized class of 3D printing. 3D bioprinting is a layer by layer precise positioning of biological materials and living cells[10]. Some applications of 3D bioprinting include stem cell research[11], cancer model[12], drug testing[13], and tissue engineering[14]. In tissue engineering, for manufacturing scaffolds, these technologies are able to control pore size, shape, distribution, and interconnectivity of pores. In addition to this, combined with the ability CAD and 3D medical imaging such as computed tomography, 3D printing permits the fabrication of personalized constructs (patient-specific)[15].

3D bioprinting was first introduced by Thomas Boland in 2003; he patented the use of inkjet 3D printing for cells[16]. According to a recent publication by the founder of one of the biggest 3D bioprinting centers, Antony Atala, 3D bioprinting is based on three central approaches: Biomimicry, autonomous-self-assembly, and mini-tissue building blocks[10]. Biomimicry consists of the creation of exact replicas of the cellular and extracellular parts of a tissue and organ[17]. Self-assembly is the scaffold-free method that mimics the behavior of embryonic stem cells. Finally, mini-tissues can be defined as the smallest structural and functional component of a tissue[18]. In the review of the field by Murphy and Atala, they suggest that the combination of these three mentioned approaches are needed in order to print complex 3D biological structures with multiple functionality, structure, and mechanical properties[10].

The main technologies used for 3D bioprinting living and biological materials are inkjet, laser-assisted printing, and micro-extrusion. Different specifications and features of them have to be contemplated based on the most important factors that affect bioprinting which are a resolution, cell viability, and the materials used for printing. Inkjet 3D printing is a non-contact (nozzle away from the substrate) printing technology where 2D and 3D structures are generated using picoliter ink droplets jetted onto a substrate following a digital pattern[19]. The usual amount of material dispensed is between 1 and 100 picoliters allowing very high resolution. All drops are spherical in flight and identical to their neighbors[20]. Several mechanisms can be used to generate the bioink droplets, the most frequently used for cells are thermal and piezoelectric. In the thermal method, a heat generator increases the temperature up to 300°C within the chamber. Then, the heating produces a bubble which expels the droplet[21]. With the piezo-electric method, a direct mechanical pulse is applied to the bioink which results in the ejection of the droplet[20].

A standard laser assisted bioprinting (LAB) set-up is usually composed of three elements: A pulsed laser source, a target coated with the material to be printed (the ribbon) and a receiving substrate. Depending on the bioink optical absorption and the laser wavelength, a laser absorbing interlayer may be necessary to induce transfer and is placed between the support and the bioink[8]. LAB functions using focused laser pulses on the absorbing layer of the ribbon to generate a high-pressure bubble that propels cell-containing materials toward the collector substrate. This technology allows for the precise deposition of materials and high densities of cells in relatively small 3D structures without affecting cell viability[22].

Extrusion 3D printing is a contact dispensing system (nozzle in contact with the substrate) where continuous strands of material are forced thought a micro-nozzle from a movable head onto a platform. The print head can move in three axes xyz[23]. This printing method can be used for creating scaffolds with defined architectures from biocompatible materials and cell-laden hydrogels. Different extrusion systems have been used for 3D printing such as pneumatic pressure, piston, and screw driven. For the pneumatic pressure and piston systems, the material is usually loaded into a syringe and dispensed with the respective methods[24]. The screw-driven method has a separate reservoir with or without temperature control. This method is usually used for highly viscous materials. The material is transported from the reservoir to the printhead by pressure then the screw assists the deposition process[25].

During the bioprinting process, biocompatible materials (bioinks) are used to facilitate the printing and act as matrices for printed cells[26]. The bioink should act as a cell carrier during the printing process and allow the cells to grow and secrete their own emulate the extracellular matrix (ECM) post-printing. The bioinks can be natural, synthetic materials or combinations of both. Polymeric hydrogels, highly hydrated 3D polymeric networks, are one of the most viable classes of bioinks due to their structural similarities to natural tissue and can offer a synthetic surrogate of ECM[27]. Hydrogels can facilitate matrix remodeling, cell migration, and cell-cell interactions necessary for the normal development of functional tissue[28]. The bioink properties that need to be considered for deciding if it is suitable for printing to include viscosity, shear-thinning, viscoelasticity, cytocompatibility, gelation kinetics, and biodegradation. These properties will determine the fidelity, stability, and functionality of the final cell-laden construct[29]. Important efforts of S&T are being devoted to the development of methods that enable printing and to the production of bioinks and biomaterial inks that can produce scaffolds that can mimic the functions of the human body[30].

1.2.1 Importance of Scaffolds in Dental Applications

Scaffolds play a key role in obtaining functional tissues. They are designed to ECM by providing structural support that stimulates attachment, proliferation, and differentiation[31]. Dentistry applications of scaffolds are recently being investigated with the aim of enhancing the regeneration of tissue and alveolar bone.

Recently, Sharma *et al.*[32] identified a variety of biomaterials that can be used to develop either natural or synthetic scaffolds. As they indicate, natural scaffolds offer good cellular compatibility but have some disadvantages, such as limited range of mechanical properties and a lack of control over pore size. In addition, they specify that synthetic biomaterials are cheaper and can be customized regarding their shape, mechanical and chemical properties (strength, pore characteristics, and degradation rate) for specific applications. Nevertheless, they require chemical modifications to improve cell adhesion. Given this, it is necessary to combine different types of materials to meet the tissue requirements in terms of porosity, surface area, and mechanical strength. Asa'ad *et al.*[33] established biodegradable synthetic polymers that hold potential in bone tissue engineering applications due to their low cost and ability to be produced in large quantities with a long shelf life, especially when compared with natural biomaterials.

2. Methodology

The methodology applied in the current study was adapted from the competitive technology intelligence approach of Rodríguez-Salvador *et al.*[1], and it consists of a hybrid model that combines a virtuous knowledge cycle with expert feedback, comprising of the following:

- Planning process: The main goals, activities, and participants are stated. In this research, the principal purpose was to identify S&T trends in 3D bioprinting for dental tissue and bone applications.
- Selection of primary and secondary information sources: Primary information mainly consists of expert participation. In this case, distinguished dentists, periodontists, and experts in 3D printing and 3D bioprinting were consulted. They kindly asked to remain anonymous. Secondary sources encompass explicit and documented knowledge through papers, patents, reports, and websites. In this case, Web of Science, Scopus, EBSCO Health and Science Direct were analyzed.
- Information collection: To gather information from databases, it is important to establish a proper search strategy, including the terminology that defines the field under analysis and the query for information retrieval. The terms that define 3D bioprinting and dental domains were identified from a literature review and the experts consulted. Different queries were designed and tested according to each database consulted. Boolean operators and inclusion and exclusion terms were used for this task. The time frame for gathering the information was a 6-year period from 2012 to 2018 (when this research concluded).
- Analysis: It consists of the transformation of information into intelligence. In this case, a statistical analysis combined with manual examination was developed. Given the novelty of this domain, and after a cleaning a deduplication process, only a few documents were identified, coming out to <100.

Experts participated throughout the entire process to validate collection up to the final analysis.

3. 3D Bioprinting Global Trends for Dental Applications

The main findings from the current research show three principal S&T drivers for knowledge management (Table 1).

Specific research efforts were identified for each of these trends. The following tables (Tables 2-4) correspond to the most recent and representative studies from the documents analysed for each global trend:

4. Discussion and Conclusions

To face current global changes, it is important to keep abreast of breakthrough technologies including detecting

Table 1. 3D bioprinting global trends for dental applications

S&T driver	Description
Scaffolds development	Creation of hybrid and biphasic scaffolds to regenerate periodontal tissue and alveolar bone
Analysis ofnatural and synthetic materials	Emphasis on biodegradable synthetic polymers such as PCL, PLA, PGA, and PLGA that are combined with bioceramics such as HA
Study of the scaffold functional characteristics	Assessment and improvement of properties such as fiber orientation, porosity, and geometry

S&T: Science and technology, PCL: Polycaprolactone, PLA: Polylactic acid, PGA: Polyglycolic acid, PLGA: Polylactide-co-glycolic acid, HA: Hydroxyapatite

Table 2. Global trend: Scaffolds development

Article	Institution/country	Description
Rasperini *et al*.[34] "3D-printed bioresorbable scaffold for periodontal repair"	University of Milan Italy University of Michigan USA Dankook University South Korea	The first reported human case of treating a large periodontal osseous defect with a 3D-printed bioresorbable patient-specific polymer scaffold and signaling growth factor
Costa *et al*.[35] "advanced tissue engineering scaffold design for regeneration of the complex hierarchical periodontal structure"	University of Minho headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine Portugal Queensland University of Technology Australia Sichuan University China Griffith University Australia	Construction of biphasic scaffolds by attaching a fused deposition-modeled bone compartment to a melt electrospun periodontal compartment. The main purpose is to simultaneously regenerate alveolar bone, periodontal ligament, and cementum
Lee *et al*.[36] "3D printed multiphase scaffolds for regeneration of periodontium complex"	Columbia University Medical Center US	Development of multiphase region-specific micro scaffolds with spatiotemporal delivery of bioactive cues for integrated periodontium regeneration. It is demonstrated that by seeding these scaffolds with DPSCs, PDLSCs, or ABSCs, distinctive tissue phenotypes can be formed with collagen I-rich fibers especially by PDLSCs and mineralized tissues.

3D: Three-dimensional, PDLSCs: Periodontal ligament stem cells, DPSCs: Dental pulp stem/progenitor cells, ABSCs: Alveolar bone stem/progenitor cells

Table 3. Global trend: Analysis of natural and synthetic materials

Article	Institution/Country	Description
Asa'ad *et al*.[33] "3D-printed scaffolds and biomaterials: Review of alveolar bone augmentation and periodontal regeneration applications"	University of Milan Italy University of Michigan USA	PCL is the most used biomaterial for periodontal applications due to its biocompatibility, suitability for various scaffold fabrication techniques, remarkably slow degradation rate and mechanical stability. It might enhance the maintenance of produced bone volume and the bone contour over time. Similar to PCL, PLA, and PLGA are hydrophobic while PGA is hydrophilic. They are usually combined with bioceramics such as calcium phosphates for alveolar bone regeneration. The predominant calcium phosphate ceramic in BTE is HA because it has the same chemical composition as native bone minerals
Ma *et al*.[37] "bioprinted microarray for screening the response of peridontal ligament stem cells response to GelMA/PEG hydrogels"	Xi'an Jiaotong University China	PDLSCs have been found to promote formation of new bone, cementum and functional periodontal ligament in diseased periodontium when properly stimulated. A high throughput method for testing the response of PLDSCs to the different gradient of biomaterials was developed. This method exhibits that bioprinting can be utilized as a tool to screen cell-biomaterial interactions in a more efficient way.
Sharma *et al*.[32] "biomaterials in tooth tissue Engineering: A review"	ESIC Dental College and Hospital India	The biomaterials for tooth regeneration are categorized as natural or synthetic. Natural biomaterials are proteins such as collagen, fibrin, and silk and polysaccharides such as chitosan, hyaluronic acid, alginate, and agarose. Synthetic biomaterials can be organic like organic polymers such as PLA, PGA, PLGA, and PCL. Moreover, they can also be inorganic, as with calcium phosphate materials such as HA or β TCP and compositions of silicate and phosphate glasses. PLA, PGA, PLGA, and PCL are the few polymers that are commonly used for forming porous scaffolds. Synthetic polymers are the most frequent materials employed for teeth regeneration

BTE: Bone tissue engineering, PCL: Polycaprolactone, PLA: Polylactic acid, PGA: Polyglycolic acid, PLGA: Polylactide-co-glycolic acid, HA: Hydroxyapatite, 3D: Three-dimensional, PDLSCs: Periodontal ligament stem cells, β TCP: Beta-tricalcium phosphate

Table 4. Global trend: The study of scaffolds' functional characteristics

Article	Institution/Country	Description
Kim *et al*. (2018)[38] "*In vivo* evaluation of 3D Printed PCL scaffold combined with β-TCP for alveolar bone augmentation."	Korea Institute of Machinery and Materials Korea Seoul National University Bundang Hospital Seoul	*In vivo* studies are primordial for studying the performance of scaffolds inside the body. In this study, 3D printed PCL scaffolds are implanted to evaluate the effect in bone augmentation of two different lattice designs and the addition of β-TCP
Do *et al*. (2015)[31] "3D Printing of Scaffolds for Tissue Regeneration Applications"	University of Iowa USA	3D printing can mimic the ECM by producing scaffolds with a high degree of complexity, where fine details can be included at a micro level. The criteria for printing viable and functional scaffolds, scaffolding materials and 3D printing technologies are assessed. Scaffolds should mimic ECM characteristics in terms of biological activity, mechanical strength, processability, and controllable degradation rates. Moreover, it is important to determine the inflammatory effect of the biomaterial(s) used and the scaffold structure designed to produce the desired tissue. Porosity, layer configuration, mechanical properties, and morphology are also characteristics to consider.
Bencherif *et al*.[39] "advances in the design of macroporous polymer scaffolds for potential applications in dentistry"	Harvard University USA École Polytechnique Fédérale de Lausanne Switzerland	Pore size and porosity are crucial when designing scaffolds in the tissue engineering domain as they influence tissue production and function. This includes cell distribution, interconnection throughout engineered tissues, and diffusion of nutrients and oxygen, specifically in the absence of a functional vascular system. 3D nano-fibrous gelatine/silica bioactive glass hybrid scaffolds that mimic the nanostructured architecture and chemical composition of a dental ECM are applied to improve odontogenic differentiation and biomineralization of human dental pulp stem cells

ECM: Extracellular matrix, PCL: Polycaprolactone, PLA: Polylactic acid, β TCP: Beta-tricalcium phosphate, 3D: Three-dimensional

new applications. 3D printing is an emerging field that has gained the attention of the academic community and industries such as automotive, aerospace, and more recently health. Although the initial efforts of 3D printing were focused on prototyping, new applications are being investigated, specifically those that deal with the human body, where there are challenges extremely complex. Oral diseases and tooth loss represent one of the most prevalent health problems. Overcoming the drawbacks that conventional procedures have, 3D bioprinting brings new solutions that could help restore and regenerate tissue and alveolar bone. In this research, a Competitive Technology Intelligence methodology was applied; insights revealed that recent S&T efforts in 3D bioprinting in dentistry are focused on developing scaffolds, the analysis of natural and synthetic biomaterials needed for their creation and the improvement of their characteristics. In addition, it was also found that a large part of the research in the field involves the assessment of the interaction and behavior of the cellular component with the materials and scaffolds microstructure.

Most of the studies agreed that controlling the biophysical properties and microstructure of the scaffolds is necessary to reproduce the periodontium complex which is formed by soft (periodontal ligament) and hard tissues (alveolar bone and cementum). As well it was determined that bioceramics such as β-TCP and thermoplastics such as polycaprolactone are the preferred type of biomaterial ink for bone, enamel, and cementum regeneration. In addition, it was found that the most used cell type for these applications is dental pulp stem cells and periodontal ligament stem cells due to their ability to differentiate into the different lineages of the periodontium complex. Finally, it was also determined that biphasic and multiphasic structures are able to mimic closely the microenvironment of cells of the periodontium complex and promote regeneration of the different tissues.

The current research adds value to the understanding of the emerging incursion of 3D bioprinting on dental applications. Moreover, the insights obtained can contribute to those who are involved in R&D and who are interested in finding opportunities to innovate through radical technologies such as 3D bioprinting.

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