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A Bibliometric Study to Assess Bioprinting Evolution

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Abstract: Bioprinting as a tissue engineering tool is one of the most promising technologies for overcoming organ shortage. However, the spread of populist articles among on this technology could potentially lead public opinion to idealize its readiness. This bibliometric study aimed to trace the evolution of bioprinting literature over the past decade (i.e., 2000 to 2015) using the SCI-expanded database of Web of Science® (WoS, Thomson Reuters). The articles were analyzed by combining various bibliometric tools, such as science mapping and topic analysis, and a Technology Readiness Scale was adapted to assess the evolution of this emerging field. The number of analyzed publications was low (231), but the literature grew exceptionally fast. The "Engineering, Biomedical" was still the most represented WoS category. Some of the recent fronts were "hydrogels" and "stem cells", while "in vitro" remained one of the most used keywords. The number of countries and journals involved in bioprinting literature grew substantially in one decade, also supporting the idea of an increasing community. Neither the United States' leadership in bioprinting productivity nor the role of universities in publications were challenged. "Biofabrication" and "Biomaterials" journals were still the leaders of the bioprinting field. Bioprinting is a young but promising technology.

Keywords: bioprinting; biomedical technology; bibliometrics

1. Introduction

"Bioprinting" was defined in 2010 as "the use of computer-aided transfer processes for patterning and assembling living and non-living materials with a prescribed 2D or 3D organization in order to produce bio-engineered structures serving in regenerative medicine, pharmacokinetic and basic cell biology studies" [1]. Groll et al., recently confirmed this definition and suggested distinguishing this methodology from "bioassembly" by specifying the length scale of the bioprinting minimum fabrication unit as "down to molecular level" [2]. Bioprinting as a tissue engineering tool is one of the most promising technologies for overcoming organ shortage [3–8]; and the level of publication on Bioprinting has been continuously increasing over the past decade. However, the spread of populist articles among on this technology could potentially lead public opinion to idealize its readiness [9]. This enthusiasm is perhaps encouraged with reports of nearing clinical applications, however, the final necessary step of testing via in vivo implantation is rarely mentioned in bioprinting publications [8,10,11]. Indeed, most bioprinting products are not actually intended for clinical implantation, but in vivo experiments are still often required to prove a tissue engineering concept [9]. The canonic process for implementing a novel clinical therapy includes animal implantation prior to studies involving humans. In the bioprinting field, few authors implant their constructs into animals to control for engraftment (including vascularization) and functionality (including cell differentiation).

Furthermore, there is not yet a publication covering human bioprinting trials (clinicaltrials.gouv); perhaps due to regulations and approvals. Regardless, the deployment of bioprinting has been surprising slow and it is worth examining the process of its evolution to distinguish actual development from over-ambitious promises [11].

Bioprinting promises a vast array of potential clinical applications, but there is a high uncertainty as to when and where they will enter the healthcare market. When communicating on bioprinting either with general public or granting organizations, researchers are often asked: when will bioprinting tissues/organs be available for human transplantation? Reducing bioprinting research to this question may seem out-of-scope for a researcher, but characterizing this new technology evolution could be a decent answer. Future-oriented Technology Analysis (FTA) tools are designed to capture the complexity of a science or technology and provide intelligence that will support assessment of its technological evolution and provide direction for decision-making and strategic development [12]. However, emerging technologies are characterized by heterogeneous and dispersed data, and require specific FTA methods to investigate issues in their management [13]. Indeed, like many emerging technologies, Bioprinting is a domain with substantial coherence, as defined above, but also an umbrella-term covering multiple domains that have differing dynamics. It is a young field with a limited history that complicates trend extrapolation and co-evolvement with governance processes. Pertinently, socioethical issues that beckon for public discussion if not for national policy and regulation have already been identified [14–16]. Having been specifically designed to analyze these complex emerging technologies, the Forecasting Innovative Pathways (FIP) framework suggests beginning with an understanding of the technology's level of maturation [13]. This can be achieved using the Technology Readiness Level (TRL), an adaptable scale commonly used by companies and government agencies [17,18]. In this context, academic publications can be a source of data to decipher the readiness of a technology. When compared with qualitative or quantitative method-based literature review, bibliometrics can provide a description of previous dynamics and current innovations, but also to forecast trends of the near future [19,20].

Our hypothesis was that the maturation level of the bioprinting technology has been high enough to generate an increasing number of publications from the academic medical community, but is still too low to garner the investment required for proper development and movement to clinical trials. Our objective here was to assess the evolution of bioprinting technology through the scientific literature over a period of 10 years. Thus, this bibliometric study seeks to analyze several statistics characterizing the evolution of bioprinting literature (e.g., production, countries, journals, impact factors, domains). We then sorted the publications on a biotechnology development scale ranging from "in vitro experiments" to "industrial commercialization", mimicking the TRL. To trace the bioprinting evolution based on the technological content, science mapping was performed via related bibliometric techniques. Science category mapping and keyword co-occurrence analysis were used to detect research fronts, co-citation network analysis for examining journals, and citation analysis for studying research organizations.

2. Material and Methods

Data was obtained in April 2017 from the Science Citation Index (SCI)-expanded database of Thomson Scientific Web of ScienceTM (WoS). To retrieve a comprehensive set of the bioprinting literature, all original articles or reviews published in English with the keyword "bioprinting" (or "3D printing") in the titles or abstracts were included. The corresponding Wos data (title, authors, institutions, year of publication, journal name, abstracts, keywords, subjects, disciplines, references, etc.) were downloaded for further bibliometric analyses.

Data sets were selected, analyzed, and ranked in decreasing order of productivity by country and journal, using Microsoft Excel. When mentioned, two time-slices of 5 years were compared: 2006–2010 and 2011–2015. After excluding review papers, original articles were considered and analyzed to assess the maturity of the bioprinting technology. For this purpose, we used the technology readiness level

(TRL) for medical devices, which was the same scale designed by the US Army Medical Research and Materiel Command (MRMC) to assess the maturity of developing medical technologies [18]. Its 9 levels ranked from "basic principles observed and reported" to "actual system proven through successful operation". The scale needed adjustments and was called the bioprinting technology readiness level (BTRL). Data sets of original publications were divided into 4 groups for analysis: in vitro levels (BTRL levels 1–4), animal in vivo levels (BTRL level 5), human in vivo levels (BTRL levels 6–8) and the clinical follow-up level (BTRL level 9). Two investigators went independently through the retrieved abstracts to determine the level of each study. When uncertain, investigators went through the full paper. At the end, the sorting of both investigators was compared and discussed until agreement was reached.

Combining various bibliometric tools, such as science mapping and topic analysis, allowed a better overview of the evolution of the technology. Science maps are spatial representations of relationships that help in deciphering a network. These graphic references point out emerging research fronts and profile insights to elaborate strategies. They analyze measure similarities through many bibliometric indicators, such as citation analysis, co-citation analysis and co-word analysis. These tools uncover innovative and dynamic concepts by exploring the relationships between either the publications that were co-cited frequently or the terms from textual records.

- Science mapping of WoS categories:

  In order to explore research fronts, a science mapping was applied to locate bioprinting research and development among the WoS categories (threshold value at 1) [21,22]. The 225 WoS categories classify journals included in the SCI. The aggregated journal-journal citation matrix contained in the Journal Citation Reports were aggregated on the basis of these categories. In this study, the 53 retrieved-WoS categories were grouped into "macro-disciplines": Matter Sciences (such as chemistry and physics), Engineering (technology), Biology (bio-related sciences) and Medicine.

- Keyword co-occurrence:

  Keyword co-occurrence networking was also used to examine subject domains in various fields (threshold value at 5). This tool is used to measure, via a term-document matrix, the document similarities between clusters of topics such as scientific domains. This tool is less precise than the citation-based analysis but is remarkable for big data analysis.

- Citation and co-citation network analysis:

  Citation analysis and co-citation analysis were introduced for topic identification, such as emerging topics, that can be useful for Research & Development strategies. Co-citation analysis was developed to analyze interdisciplinary relationships, multidimensional indicators or geographical maps using large scale publication datasets. It was used here for identifying journals of the bioprinting literature by agglomerations of papers based on common references (threshold value at 20). Citation organization analysis was used for analyzing the structural backbone of bioprinting through the publishing journals (threshold value at 1 for 2006–2010 and at 3 for 2011–2015).

VOSviewer (free software, version 1.6.6, Centre for Science and Technology Studies, Leiden University, The Netherlands, 2017) was employed to generate the network analyses. The VOSviewer software defines association links with co-word, co-citation, and bibliographic couplings and visualizes grouped nodes as networks [23,24].

3. Results

3.1. Publication Productivity (Figure 1)

Bioprinting and 3D printing literature grew at a faster rate than all literature published (Figure 1). The first bioprinting papers appeared in 2006. Bioprinting literature increased 24-fold faster than the

overall scientific literature between 2006 and 2015. Over the 2000–2015 period, only 2.8% of the 3D printing literature mentioned the term "bioprinting". The number of retrieved/analyzed bioprinting publications was 231 (32 for 2006–2010 and 199 for 2011–2015).

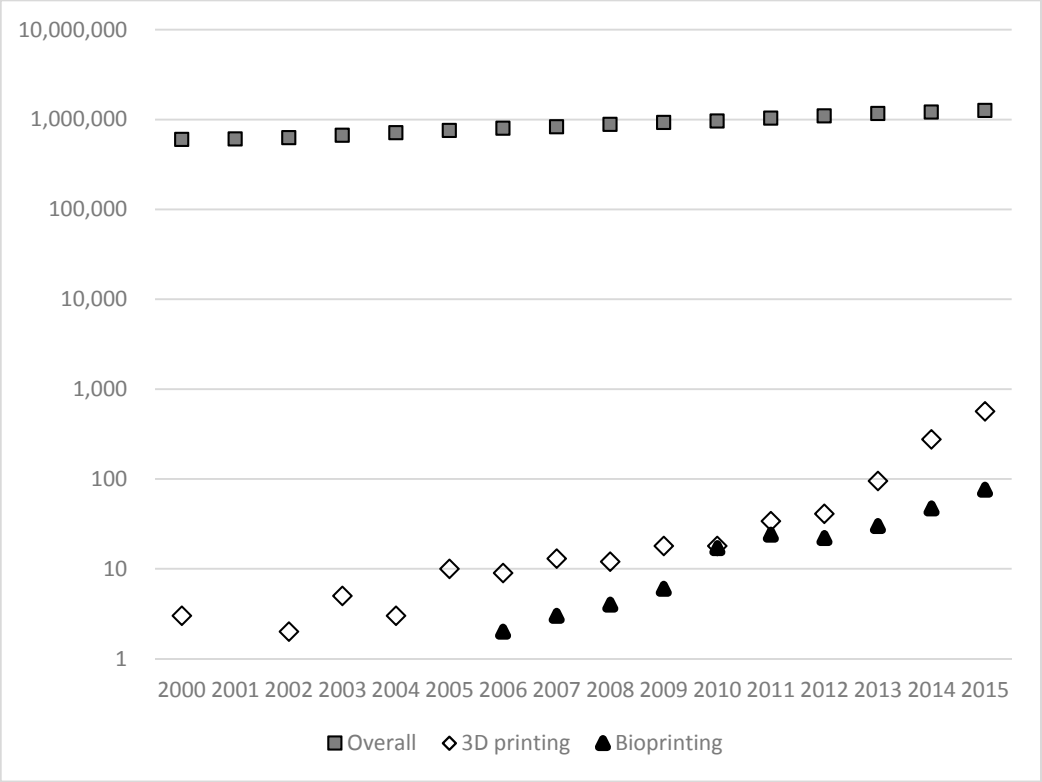
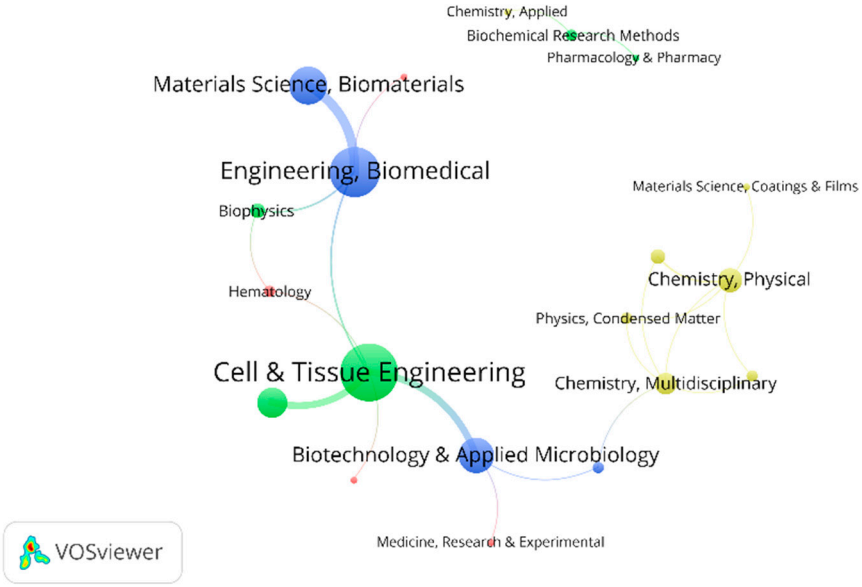


Figure 1. Trends of publication productivity in the scientific literature involving "3D printing" and "bioprinting" from 2000 to 2015 (articles and reviews published in English). Overall: scientific literature.

3.2. Science Mapping with WoS Categories (Figure 2)

For studying the science mapping of WoS categories, we set two time slices to trace the evolution of bioprinting topics (Figure 2) [21,22,24]. The first slice was the beginning of bioprinting, and showed some early-stage topics, such as "Cell & Tissue Engineering" and "Engineering, Biomedical". These categories combined the biological and the technological aspect of bioprinting, but the emphasized keywords differed. Only few clinical applications were mentioned, and studies focused on the technological development. The second slice showed that the precursors developed, and some newly generated topics indicating recent ideas and innovations [24]. This slice showed rather a development of matter sciences ("Chemistry" and "Materials sciences, Biomaterials"), than of medical applications [9]. Similarly, the raise of "engineering" sciences vouched for research on improving the technological aspect of 3D printing (such as scale and automation). The biological applications were not yet obvious, probably limited by issues in having physiologically relevant and clinical grade products. There still was a need for a better bioprinter, a better bio-ink, a better bio-paper or vascularization [25,26]. Ethical and economical considerations may had also been in the way. From the first to the second slice, 3 WoS categories disappeared: "Chemistry, Applied", "Neurosciences" and "Oncology". These 3 categories were replaced by 31 new or more specialized categories during 2011–2015. The approach of bioprinting publications seemed rather driven by technology (techno-push) than by healthcare market (market-pull).



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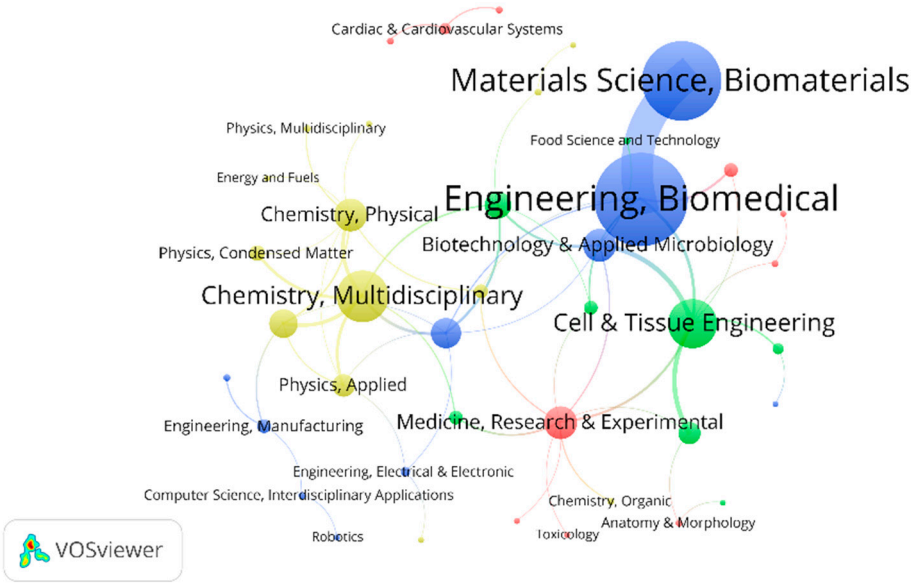

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Figure 2. The science mapping of Web of ScienceTM (WoS) categories for assessing bioprinting evolution in time slices, (**a**): 2006–2010; (**b**): 2011–2015. The WoS categories were grouped into "macro-disciplines": Matter Sciences (yellow), Engineering (blue), Biology (green), and Medicine (red). The size of each node is proportionate to its degree and the thickness of the links represents the tie strength.

3.3. Keywords Co-Occurrence (Figure 3)

The keyword co-occurrence showed that the network was loose during the first slice (Figure 3). There were only few keywords, but these were still present in the second slice. This showed a relatively straight forward dynamic since the beginning of bioprinting. The innovative concept was set with, among others keywords, "cells" and "deposition". At this time, probably none of the research teams could handle all the scientific aspects of bioprinting. The number of keywords grew then dramatically between 2011 and 2015 and the network became denser than the previous

period. Interestingly, the term "bioprinting" became one of the most used keywords and defined the identity of a field. A new bioprinting topic emerged with the rise of "hydrogel" issues and the need for a perfect bio-ink. Indeed, the hydrogel is required to fulfill a lot of expectations, from the matter sciences, engineering, biological and medical point of views. In this context, the extracellular matrix components of connective tissue, such as "collagen" and "gelatin", were often used despite their limitations [27]. As expected, the "in vitro" keyword remained one of the most relevant, as a necessary step to prove a tissue engineering concept. The frequent iteration of "cells" rather than "tissue" or "organs" may be seen as marker of immaturity when considering the organ transplantation. Interestingly, "stem cells" and "differentiation" seemed to indicate the emergence of a new pathway towards regenerative medicine, such as bony transplants [9]. However, engineering in vitro complex systems with enough "vascularization" and "angiogenesis" for cell survival and proliferation is still a challenge. "Cartilage" was the most cited tissue, probably thank to its structural simplicity and its limited needs in cells, proteins and vascularization.

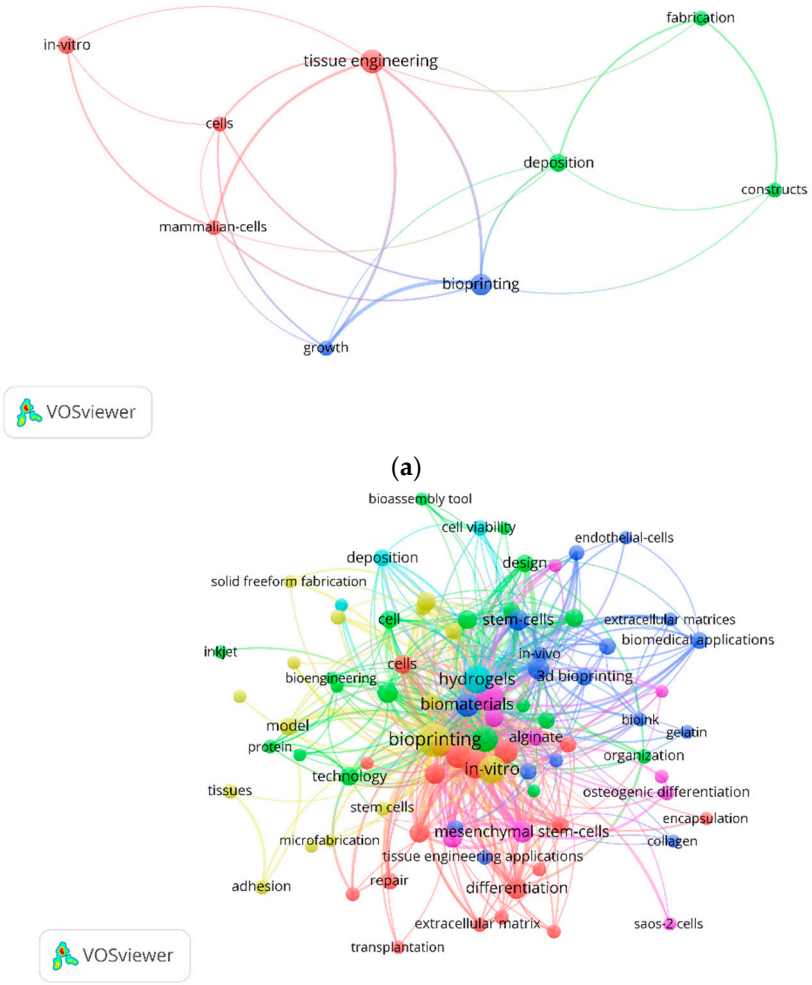


Figure 3. Temporal evolution of keyword co-occurrence networks between 2006 and 2016 with a time interval of 5 years, (**a**): 2006–2010; (**b**): 2011–2015. The size of each node is proportionate to its degree and the thickness of the links represents the tie strength.

3.4. Bioprinting Publications and Biotechnology Readiness Level (Figure 4)

TRLs adaptations have been developed for all types of medical products, including pharmaceuticals (drugs, biologics, vaccines), medical devices, etc. The concept is that when a critical technology is

incorporated into the fabrication of a product, the probability for a successful outcome is great when the level of readiness of the technologies is high. We analyzed the distribution of bioprinting original articles according to the bioprinting technology readiness level (BTRL), as described in the M&M section (Table 1 and Figure 4). The publication scale ranged from "in vitro experiments" to "industrial commercialization", mimicking the TRL. Over the decade, the groups were highly disproportioned. Group 1 (in vitro papers) accounted for 92% of the bioprinting original articles, when groups 2 and 3 (in vivo papers) represented respectively 7.3% and 0.6% (one article). There was not a single paper from group 4. Interestingly, the group 1 proportion increased with time, but not the in vivo groups. These results confirmed the actual lack of readiness of the bioprinting for medical applications and called for further analyses about the number of research actors.

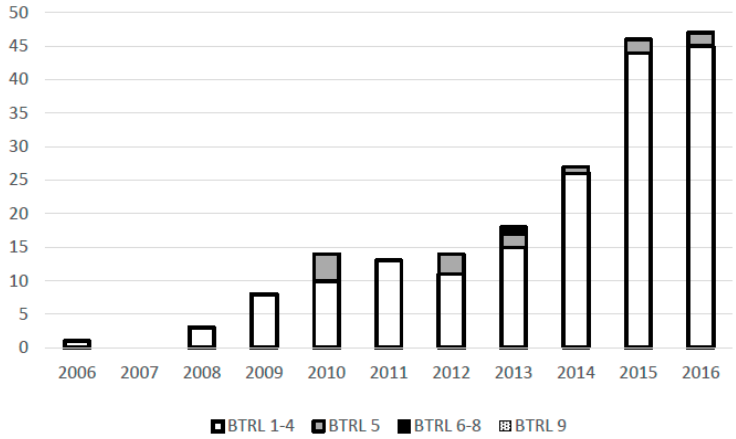


Figure 4. Distribution of bioprinting original articles according to the bioprinting technology readiness level (BTRL). The 2006–2015 bioprinting articles were analyzed and distributed into 4 groups: 1 (in vitro, BTRL 1–4), 2 (animal-in vivo, BTRL 5), 3 (human-clinical grade, BTRL 6–8) and 4 (industrial, BTRL 9). There has never been any paper in group 4.

Table 1. Bioprinting technology readiness level (BTRL) scale, adapted from the Medical Devices scale of the Medical Research and Materiel Command (MRMC) [18].

Technology Readiness Level	Level	Bioprinting Readiness Level
Basic principles observed and reported	1	Literature reviews and initial market surveys
Technology concept and/or application formulated	2	Research plans and protocols are developed, peer reviewed, and approved.
Analytical and experimental critical function and/or characteristic proof of concept	3	In vitro: Initial proof-of-concept is demonstrated in a limited number of laboratory models.
Component and/or breadboard validation in laboratory environment	4	In vitro: Proof-of-concept and safety of candidate systems demonstrated in defined laboratory models.
Component and/or breadboard validation in relevant environment	5	In vivo animal: devices tested through simulation, in tissue or organ models, or animal models if required. Initial testing is complete.
System/subsystem model or prototype demonstration in a relevant environment	6	In vivo human: Clinical trials conducted to demonstrate safety of candidate medical device in a small number of humans.
System prototype demonstration in an operational environment.	7	In vivo human: Clinical safety and effectiveness trials conducted with a fully integrated medical device prototype in an operational environment.
Actual system completed and qualified through test and demonstration.	8	In vivo human: Implementation of clinical trials to gather information relative to the safety and effectiveness of the device.
Actual system proven through successful mission operations.	9	The medical device may be distributed/marketed. Follow-up after commercialization

3.5. Publishing Countries (Table 2)

The number of retrieved/analyzed bioprinting publications was 231 (32 for 2006–2010 and 199 for 2011–2015; Table 2). The percentage of bioprinting review articles tripled between the two time periods (from 6.3 to 19.6%; data not shown). The number of countries publishing bioprinting literature increased over the decade from 9 to 31. The USA published the most at both time points, but its share declined by 18.1% between 2006–2010 and 2011–2015. South Korea remained in the top 5 with the USA. A country could belong to the top 5 with only two publications in 2006–2010, whereas 11 publications were needed in 2011–2015. Three countries reached the top 5 for the first time in 2011–2015, and each produced at least 13 publications within the 5 years: China, Germany and the Netherland. France and England were replaced but remained in the new top 10 with eight papers each.

Table 2. Top 10 publishing countries during the periods 2006–2010 and 2011–2015 (IF: impact factor). The countries publishing bioprinting research are displayed in decreasing order according to the number of publications for each time period.

2006–2010					2011–2015				
Countries/Territories	**Papers**	**% of 32**	**Rank**	**Average IF (2010)**	**Countries/Territories**	**Papers**	**% of 199**	**Rank**	**Average IF (2015)**
USA	23	71.875	1	4.478	USA	107	53.769	1	5.393
France	5	15.625	2	4.525	Peoples R China	32	16.080	2	4.187
Spain	2	6.250	3	4.839	Germany	27	13.568	3	4.057
South Korea	2	6.250	3	1.771	The Netherlands	13	6.533	4	8.202
England	2	6.250	3	4.869	South Korea	11	5.528	5	4.582
Finland	1	3.125	6	4.636	Australia	11	5.528	5	8.323
Japan	1	3.125	6	1.857	Switzerland	8	4.020	7	5.433
Portugal	1	3.125	6	4.636	France	8	4.020	7	5.465
Romania	1	3.125	6	2.013	England	8	4.020	7	7.648
					Japan	6	3.015	10	2.452

In terms of impact factor (IF), the top 5 average (calculated as the average of each country's average) increased by almost 30% (4.096 $\pm$ 1.312 and 5.79 $\pm$ 1.971 respectively). Among the 2011–2015 top 10, Australia had the highest average IF (8.323) and Japan the lowest one (2.452). This worldwide research could be either conducted by government or by private companies.

3.6. Citation Analysis of the Involved Organizations (Figure 5)

The citation analysis of the organizations involved in bioprinting research showed that universities were pioneering all around the world (Figure 5). Five years later, universities were still the major actors. However, analyzing publications evaluates rather the academic activity than the economic activity. In the first slice, USA (Missouri, Drexel, Carnegie Mellon, Utah, Clemson, Columbia, Yale ...) and European universities (Bordeaux, Barcelona, Helsinki, Beira Interior ...) were numerous. Organovo, Novalase and Sciperio were private companies. In the second slice, many other USA (Carolina, Iowa ...) and European (Utrecht, Hannover, Twente ...) universities strengthened the field, with new players such as China (Tsinghua, Wuhan, Nankai ...).

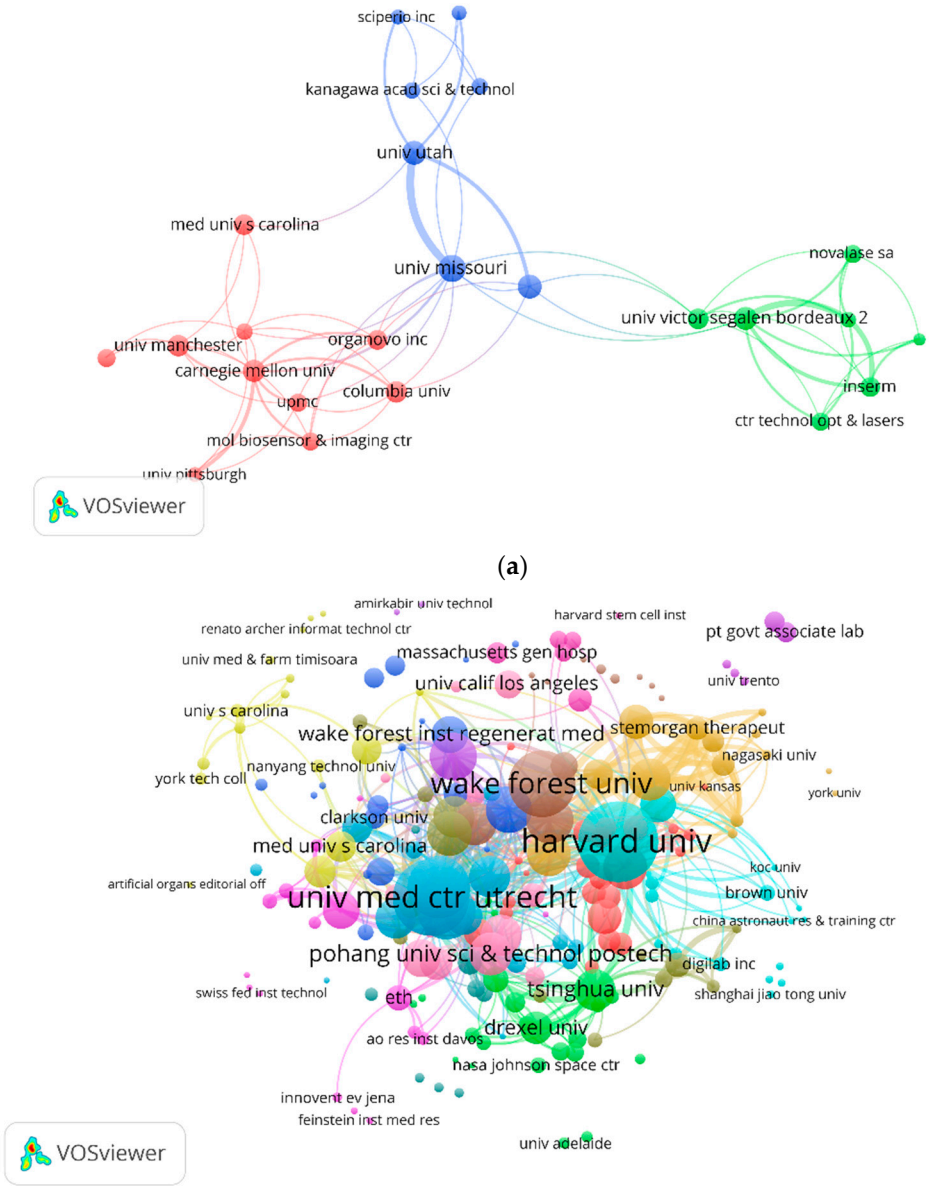


Figure 5. Temporal evolution of the involved organizations. Citation analysis of the organizations between 2006 and 2016 with a time interval of 5 years, (**a**): 2006–2010; (**b**): 2011–2015. The size of each node is proportionate to its degree and the thickness of the links represents the tie strength.

3.7. Publishing Journals (Table 3)

The mean IF remained increased by 10% between 2006–2010 and 2011–2015 for the 6 top journals publishing bioprinting papers (4.608 and 5.056; Table 3). The Top 6 journals IFs ranged between 1.857 and 7.883 in 2006–2010, and between 1.113 and 12.065 in 2011–2015.

Table 3. Top-6 journals most abundant in bioprinting research papers and their impact factors for 2006–2010 and 2011–2015 periods (IF: impact factor). The minimum record count was publishing 2 papers in 2006–2010 (13 journals were hidden), and 3 in 2011–2016 (81 journals were hidden).

2006–2010						2011–2015					
Journals	**# Papers**	**% of 32**	**Rank**	**IF (2010)**	**Web of Science Category**	**Journals**	**# Papers**	**% of 199**	**Rank**	**IF (2015)**	**Web of Science Category**
Biofabrication	6	18.750	1	1.857	Engineering, Biomedical; Materials Science, Biomaterials	Biofabrication	36	18.090	1	4.72	Engineering, Biomedical; Materials Science, Biomaterials
Biomaterials	4	12.500	2	7.883	Engineering, Biomedical; Materials Science, Biomaterials	Biomaterials	8	4.020	2	8.387	Engineering, Biomedical; Materials Science, Biomaterials
Tissue Engineering Part C Methods	3	9.375	3	4.636	Cell & Tissue Engineering; Biotechnology & Applied Microbiology; Cell Biology	Jove Journal of Visualized Experiments	6	3.015	3	1.113	Multidisciplinary Sciences
Tissue Engineering Part A	2	6.250	4	4.636	Cell & Tissue Engineering; Biotechnology & Applied Microbiology; Cell Biology	Biotechnology and Bioengineering	6	3.015	3	4.243	Biotechnology & Applied Microbiology
Journal of Tissue Engineering and Regenerative Medicine	2	6.250	4	3.534	Cell & Tissue Engineering; Biotechnology & Applied Microbiology; Cell Biology; Engineering, Biomedical	Acta Biomaterialia	6	3.015	3	6.008	Engineering, Biomedical; Materials Science, Biomaterials
Journal of Materials Chemistry	2	6.250	4	5.101	Materials Science, Biomaterials	Trends in Biotechnology	4	2.010	6	12.065	Biotechnology & Applied Microbiology
						Tissue Engineering Part C Methods	4	2.010	6	3.892	Cell & Tissue Engineering; Biotechnology & Applied Microbiology; Cell Biology
						Journal of Materials Chemistry B	4	2.010	6	4.872	Materials Science, Biomaterials
						Journal of Biomedical Materials Research Part A	4	2.010	6	3.263	Engineering, Biomedical; Materials Science, Biomaterials
						Artificial Organs	4	2.010	6	1.993	Engineering, Biomedical; Transplantation

The 6 most publishing journals represented around 59% of the 2006–2010 production, and 41% of the 2011–2015 production. The number of papers from the 6 most publishing journals increased by 4.3 fold during the decade. The most cited paper is a review written by Murphy and Atala in 2014 (136 citations in 2015 and 299 in 2016) [28].

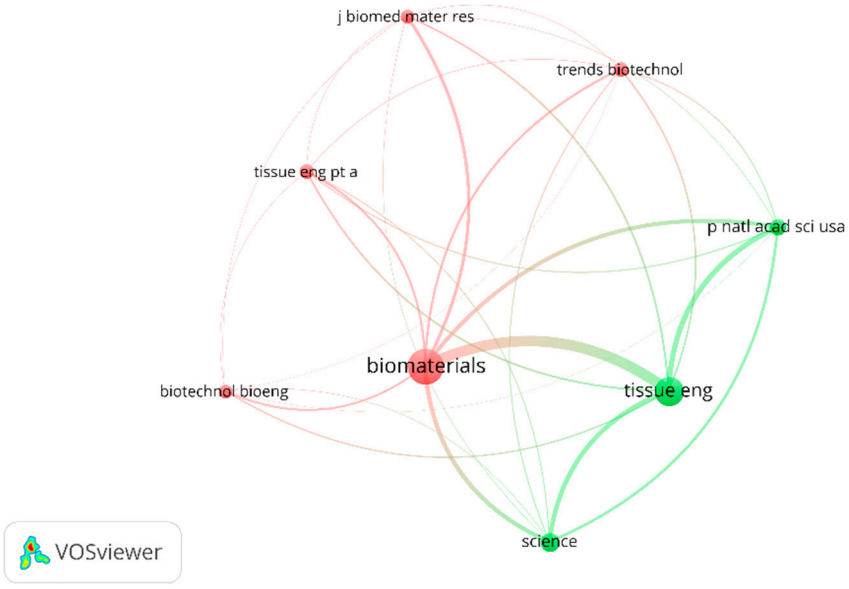
The three first journals in 2006–2010 remained in the Top 6 five years later. Top 6 journals were published in England and USA (50–50%) at both time periods. The number of journals involved in the bioprinting literature increased 4.8 fold during the decade (from 19 journals in 2006–2010 to 91 in 2011–2015).

The Biofabrication journal was launched in 2009 and immediately took the leadership during the decade in terms of bioprinting productivity. This journal was born and raised with the bioprinting developing field, being the official journal of the International Society for Biofabrication (ISBF). Biofabrication's IF increased by 2.5 fold between 2010 and 2015.

Four Web of Science categories were equally represented in the 2006–2010's Top 6. In 2011–2015, two additional categories appeared ("Multidisciplinary Sciences" and "Transplantation"), but the most represented articles belonged to "Engineering, Biomedical" and "Materials Science, Biomaterials" categories.

3.8. Co-Citation Analysis of the Sources (Figure 6)

As impact factors might not give a clear overview of the bioprinting publishers, we performed a co-citation analysis of the sources (Figure 6). Co-citation network analysis was used to identify journals of the bioprinting literature by agglomerations of papers based on common references. This figure illustrated the tendencies highlighted with Table 3. The journals "Biomaterials" and "Biofabrication" remained major actors in bioprinting through the decade, as suggested by their ranking and IF (Table 3). Many journals appeared in the 2nd slice, including some that were not tissue engineering specialists. This trend showed a growing interest from the scientific community and the extension of the bioprinting field. As a need for strengthening the biological and technological bases appeared (Figure 2), new teams were involved and joined the bioprinting community.



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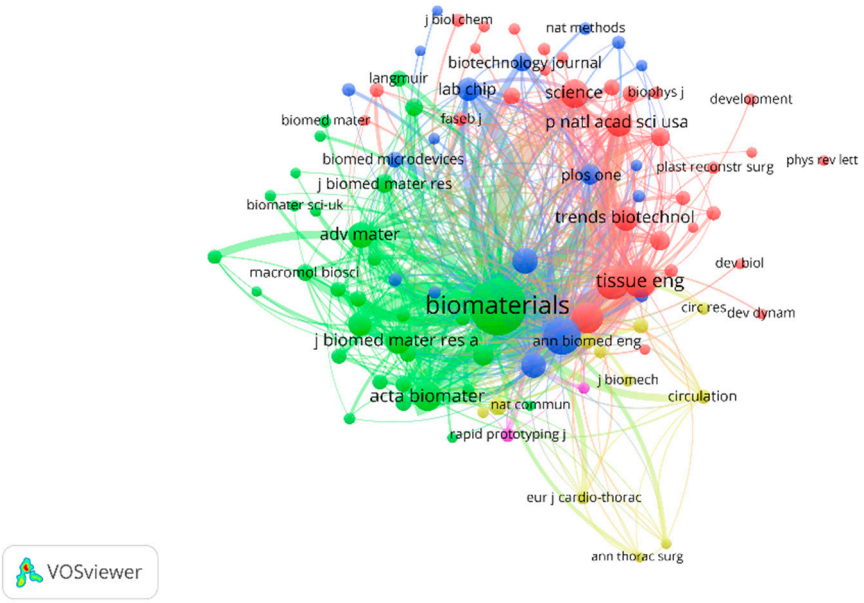

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Figure 6. Temporal evolution of the publishing journals. Co-citation analysis of the citations sources between 2006 and 2016 with a time interval of 5 years, (**a**): 2006–2010; (**b**): 2011–2015. The size of each node is proportionate to its degree and the thickness of the links represents the tie strength.

4. Discussion

The focus of our study was to trace the evolution of bioprinting technologies and to provide empirical insights for related researchers or stakeholders. The results of this bibliometric study showed that bioprinting literature generates increasing interest from medical authors and publishers around the world. Our first finding was that bioprinting literature had grown exceptionally fast. This was supported by the comparison with the literature from related scientific domains. The second finding was that the "Engineering, Biomedical" was still the most represented WoS category. Some of the recent fronts were "hydrogels" and "stem cells", while "in vitro" remained one of the most used keywords. The third finding showed that the number of countries and journals involved in bioprinting literature growing substantially in one decade, also supporting the idea of an increasing community. Neither the United States leadership in bioprinting productivity, nor the role of universities in publications, are challenged yet. "Biofabrication" and "Biomaterials" journals are still the leaders of the bioprinting field.

4.1. Risks and Gaps of Bioprinting Technologies in Applications Development

One of our major findings was that the BTRL group 1 (in vitro) proportion increased with time. These studies focused on cell viability, interactions, differentiation, structural resistance, function preservation, and synthesis after bioprinting. During 2006–2010, papers focused on the new bioprinting technics, while few others studied pharmaceutical models for drug testing [29]. Nowadays, engineering in vitro complex systems with enough vascularization for cell survival and proliferation is still a challenge (Figure 3). Also after the initial proof of concept, the consequences of molecular interactions are more in-depth studied and improved before pretending to a clinical transplantation. As a consequence, there were very few in vivo animal studies (BTRL group 2). These essentially focused on skin, bone, cartilage, dental or vascular tissues, and used bioprinting to engineer mechanical/passive modules whose objective was to support biological tissues, eventually as a barrier or a carrier [10]. Surprisingly, complex systems (other than plane or tubular structures) with a complex function (such as endocrinal function, filtration, exchange, contraction, reception, information transmission . . .) were not tested yet in vivo on animals. The only paper in BTRL group 3 was Zopf et al., (2013) reporting

the 3D printing of a resorbable airway splint in polycaprolactone implanted in a child with a severe tracheobronchomalacia [30]. Although this 3D printing study was one of the more advanced in the field, no biological element was printed on the implant, and it should not be considered as a bioprinting study. The major issue with developing a BTRL group 3 study could be the difficulty to vascularize the 2–3 mm^3 constructs. This issue is not overcome yet, although many leads exist, such as bioprinting angiogenic growth factors, networks in scaffolds and pre-vascularization in vitro or in vivo.

4.2. Risks and Gaps in Bioprinting Manufacturing Development

Numerous review papers recently gave an update on the industrial feasibility of manufacturing organs and human-scale tissue constructs [4–7]. Once a human in vivo experiment occurred, the process remains long before being able to offer an actual tissue/organ transplantation therapy [25,26]. Wu et al., recently published a very complete critical review about bioprinting and Manufacturing Readiness Level (MRL) [31]. This study aimed to assess manufacturing maturity and to identify risks and gaps in translating bioprinting from lab-bench experiments to ultimate full-scale manufacturing of tissues and organs. The rational was to optimize bioprinting applications and to defeat the pessimistic market expectations [32]. The authors concluded that "we are still a long way from full-scale tissue/organ fabrication".

One of the expected gap is the "Valley of Death" zone, which corresponds to the "production in laboratory" and the "capacity to produce a prototype" steps. Indeed, the United States Government Accountability Office (GAO) pointed out the investment/funding gap in the nanomanufacturing development between the proof of concept in laboratories (government and universities) and the capacity in production environment (private sector) [33]. Some newly emerged companies aim to meet this healthcare need in tissue and organs by developing a viable business model around bioprinting technologies. These start-ups are designed to effectively develop and validate a scalable business model. They usually begin with raising funding from investors and selling a prototype, such as tissue-equivalents, to develop the concept and to become self-sufficient.

4.3. Bioprinting TRL

The 9 levels of the TRL were created for the National Aeronautics and Space Administration (NASA) to assess the maturity of developing technologies [17]. When transitioning from development to commercialization, the TRL level informed on the probability for a successful outcome. The US Army Medical Research and Materiel Command (MRMC) developed a medical device TRL based on consideration of the applicable Federal Drug Administration (FDA) regulatory process [18]. This scale allowed to communicate the medical device development to the federal regulators (among others). According to the MRMC experience, the application of the guidelines to biomedical TRL showed considerable variation in timing, activities and programmatic events [18]. The risks of failure for a medical technology remain high until the clinical application, and their reduction is not linear across TRLs. The maturation and risk characteristics of bioprinting being unique, the scale was specifically adapted to match TRL decision criteria with the steps biomaterials are required to go through before reaching the healthcare market. By sorting the publication on the BTRL scale (ranging from "in vitro experiments" to "industrial commercialization"), we showed that bioprinting technology, in a context of medical application, was still at the beginning of its development. The decision criteria allowing a study to enter the "in vivo" levels were rarely fulfilled as the risks encountered by the technology at the "in vitro" level still need to be addressed. Moreover, still according to the MRMC's experience, FDA-regulated products do not achieve significant risk reduction (i.e., >50%) until completion of clinical trials [18]. This statement may give some hope for bioprinting studies that will overcome the "in vitro" level. However, we should keep in mind that other issues may appear upon completion of a pilot clinical study, leading to some additional requirements and other TRL steps.

4.4. Limits of This Bibliometric Study

The limits of this bibliometric study were numerous. First, the volume of the retrieved publications (231) was very low for deciphering clear trends. Deeper analyzes could have been performed with FTA tools, but the size of the samples limit their relevance. Our study focused on the publications mentioning the term "bioprinting", because we assumed that since its definition, most of the studies would have use the keyword in their abstract. Although this approximation may have led to the exclusion of few historically important papers, we thought the bibliometric volume of the remaining papers were still representative enough for analyzing the last decade bioprinting production. A second flaw was the choice of 5-year analyses, rather than comparing some years. The rationale for this choice was to cover most of bioprinting publications, to have similar periods and big enough samples for analysis. As the technology is recent, the number of publications was too low for analyzing into detail the publications year by year. Furthermore, the pivotal point corresponded to the TED conference of Atala in 2011, which brought bioprinting a bit more under the spotlight (with 2.7×10^6 views on Youtube®). The third weakness was the exclusion of patents, which could have brought interest to the analysis. The delay between patent applications and their publication may reduce the number of scientific publication linked to the patent. Though, patents would not have change the TRL data in this approach.

5. Conclusions

In this bibliometric study, the evolution of bioprinting technologies was traced to provide empirical insights for related researchers or stakeholders. Bioprinting literature has grown exceptionally fast and developed concomitantly on several topics, including biomedical engineering. Recent fronts had emerged through the last decade, such as "hydrogels" and "stem cells". This increasing community was located worldwide and communicated through selected journals such as Biomaterials and Biofabrication. Sorting the bioprinting literature on a TRL scale underlined that this technology was at the beginning of its maturation, and that bioprinted products had to go through a long journey before entering the healthcare market. Bioprinting authors could benefit from appending TRL key-words to abstracts. A glance would allow the reader to evaluate the maturity of the presented concept, from in vitro pilot studies to in vivo follow-up after commercialization.

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