# Future of Bioprinted Tissues and Organs: A Two-Wave Global Survey

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## Abstract

Technologies of 3D- and 4D-bioprinting make it possible to restore or replace tissues and organs, solving the problem of the lack of donor resources and reducing the risks of implant rejection. This article presents the results of a two-stage global survey of specialists in tissue engineering on the prospects of bioprinting in preclinical studies and clinical practice. A picture of possible tracks and horizons upon which the implementation of the considered solutions is possible is presented. According to the results of the survey, in the next two decades it will be possible to recreate tissues and organs suitable for implantation and drug testing. There will be a market for bioprinted products, the problem of organ shortages and adverse reactions to drugs will be solved. These changes may significantly affect not only the practice of biomedical research, drug testing, and medicine, but also the healthcare sector in general, which implies the need for a preventive review of current policies. A practical and accessible tool for identifying and interviewing a large number of experts around the world is proposed, which may be useful for new Foresight studies.

**Keywords:** future medicine; innovation ecosystem; 3D/4D-bioprinting; bioprinted organs; toxicity testing; organ implantation; tissue engineering; survey; expert opinion.

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## Introduction

Tissue and organs engineering is highly relevant to medicine due to huge impact on quality and longevity of life. There are new technologies currently being developed in research labs, which hold the potential to restore or replace tissues and organs in the future. These technologies include bioprinting of tissues and organs, recellularization[1] strategies, cellular repair or regeneration, and xenotransplantation (Hunsberger et al., 2016). Overall, three-dimensional (3D) printing technologies are usually seen as forming a very complex innovation ecosystem (Beltagui et al., 2020).

In this study, we focus on 3D and four-dimensional (4D) bioprinting technologies, and more specifically the bioprinting of tissues and organs. Bioprinting is a process for printing biological and functional systems (Thayer et al., 2020) that makes use of cells, biomaterials, biomaterial scaffolds, growth and biological factors (Ahn et al., 2016; Mao et al., 2020). The term three-dimensional refers to the printing of three-dimensional objects from digital models, and four-dimensional to the use of stimuli-responsive materials (Ashammakhi et al., 2018; Yang et al., 2019; Yu et al., 2020). The 4D bioprinting method uses the same bioprinter as 3D bioprinting. The difference is the use of stimulus-responsive materials, as inks, also called smart materials (Yang et al., 2020). When receiving a given external stimulus after they are bioprinted, 4D bioprinted constructs can transform, grow or shrink (Yang et al., 2019; Yang et al., 2020). Thus, in 4D bioprinting stimuli-responsive materials allow the bioprinted tissues and organs to change over time according to given environmental stimuli (Mao et al., 2020).

The global 3D bioprinting market size was valued at USD 1.4 billion in 2020 and is expected to reach USD 4.4 billion by 2028. Possible drivers of this increase are the lack of organ donors associated with an increasingly aging population with chronic diseases worldwide (Grand View Research, 2021). With such a large market expected for the coming years, in addition to the emergence of 3D bioprinting startups, 3D printing companies are expanding their business to offer bioprinters and hardware to take advantage of the growth opportunities offered by this expanding market (Combellack et al., 2018). In this emerging field, most of the companies were founded in the 21st century and the majority have 10 or fewer employees (Bicudo et al., 2021). Some relevant companies in this market include the Americans Aspect, Aether, SE3D, Organovo, Tevido, BIOLIFE 4D, Seraph Robotics, BioRobots, ASLS, and nScrypt; the Europeans Ourobotics, Poietis, 3Dynamic, EnvisionTEC, regenHU, REGEMAT 3D, GeSiM, CELLINK, and 3D Bio; and the Asians Sichuan Revotek, Regenovo Biotech, ROKIT, Cyfuse, Pensees and Bio3D Tech (Choudhury et al., 2018). Recent patent mapping has shown that China's Sichuan Revotek and US company Organovo are two of the leading companies with the most patents related to bioprinting (Mota et al., 2020).

Today, this is an unsolved problem that largely relies on health policies aimed at increasing the number of registered donors (Shanmugarajah et al., 2014). Bioprinting technologies offer great promise to provide fully-functional tissue and organs for implantation in humans (Wang et al., 2020b; Yu et al., 2020), which could lead to the elimination of organ shortage in the future (Unagolla, Jayasuriya, 2020; Bea, 2020). Also, bioprinting technologies are expected to provide human-based methods for research and drug toxicity testing (Rosania, 2013; Gardin et al., 2020; Mota et al., 2020), which might lead to the elimination of adverse drug reactions (ADRs) in humans (Haris et al., 2020). As known, serious ADRs can lead to deaths and morbidity, and drug withdrawals. In the United States alone, serious ADRs affect about 2 million patients every year, resulting in 100,000 deaths (Giacomini et al., 2007; Niu et al., 2015). The occurrence of ADRs would be related to the use of animals in preclinical research, considered not to be good predictors of toxicity in humans (Giacomini et al., 2007; Niu et al., 2015). In the coming decades, it is conceivable that human-based methods can replace the use of animals in research and preclinical research (Bandyopadhyay et al., 2018).

So far, a variety of tissues (skin, bone, cartilage, neuronal tissue, etc.) have been generated using 3D/4D bioprinting (Duan, 2017; Heinrich et al., 2019; Lukin et al., 2019). Some examples of successful bioprinted tissues implanted in animals are bones, cartilage, skin, and vascular grafts (Singh et al., 2020; Wang et al., 2020b). An example of a human application was the bioprinting of a tracheal splint, which was implanted in a child with tracheobronchomalacia (Yang et al., 2019). However, the use of bioprinted tissues and organs either in preclinical studies or in human implants is still very limited (Vijayavenkataraman et al., 2018; Murphy et al., 2020). Before this can happen, important challenges such as the building of vascularized tissues and organs must be addressed (Gao, Cui, 2016; Murphy et al., 2020; Zhu et al., 2021). Vascularization is required to maintain bioprinted constructs alive for a long time (Vries et al., 2015). Bioprinting vascularization networks require the improvement of bioprinters and bioinks (Dias et al., 2020; Heinrich et al., 2019). While bioprinters still lack optimal resolution and speed, high-performance bioinks still need to be enhanced with the ability to support cell proliferation, cell differentiation, and tissue/organ production (Albritton and Miller, 2017; Heinrich et al., 2019; Huang et al., 2017; Mori et al., 2018; Park et al., 2016).

One can say, then, that the future of 3D/4D bioprinting as a way to provide human tissues and organs for

[1] Removal of cells from tissue while preserving the extracellular matrix and three-dimensional structure of the organ.

research, toxicity testing, and implantation in humans is still uncertain. As far as we know, a few studies have tried to foresee the future of 3D/4D bioprinting (Mir, Nakamura, 2017; Vijayavenkataraman et al., 2018; Silva, 2019; Mota et al., 2020; Unagolla, Jayasuriya, 2020). Yet, none of them offer a long-term perspective, based on researchers' opinions, on future 3D/4D bioprinting developments and their expected impacts on biomedical research, drug testing, medicine. Our study addresses this gap by assessing the opinions of over 1,400 researchers from around the world in the field of tissue engineering[2] who are authors of recent scientific publications related to tissue engineering indexed in the Web of Science Core Collection (WoS). The respondents' opinions were assessed through a two-wave global web-based survey with a two-year interval (2018 and 2020). The second wave sought to assess if there were changes in expectations regarding the future of tissue engineering technologies that involve the fabrication of functional tissues for regenerative medicine and drug testing (Richards et al., 2013), and aim to enable the replacement, restoration of lost or diseased tissues and organs (Leberfinger et al., 2019; Yu et al., 2020; Zhu et al., 2021). Being both developers and users, it can be said that the researchers invited to take part in this study are among the most qualified to point out future developments of these technologies and their implications on biomedical research, drug testing, and medicine.

This study is based on Technology Foresight (TF) (Martin, 1995; Martin, Johnston, 1999; Georghiou et al., 2008; Martin, 2010; Miles, 2010), which refers to "the process involved in systematically attempting to look into the longer-term future of science, technology, the economy and society with the aim of identifying the areas of strategic research and the emerging generic technologies likely to yield the greatest economic and social benefits" (Martin, 1995). Overall, TF studies aim to provide strategic information for long-term decision-making and planning in science and technology (Martin, 1995; Martin, Johnston, 1999; Georghiou et al., 2008; Martin, 2010; Miles, 2010; Popper, 2008). Yet, as time goes by, advancements in scientific knowledge and technology developments may lead to changes in expectations of the future. This makes the monitoring of changes in expectations about emerging technologies of great importance for decision making and long-term planning in science and technology, and periodic surveys like the one conducted in this study are a way to address this task.

## Technology Foresight and intertemporal comparison of researchers' expectation

Approaches to forecasting technology emergence arose more systematically after the Second World War, mainly because technological progress started to be seen as a result of collective knowledge cumulativeness rather than the result of individual efforts (Miles et al., 2017). This perception led to the creation of new tools to support forecasting technologies, ranging from quantitative analysis developed by the US Department of Defence to qualitative approaches developed at think tanks like the RAND Corporation (Linstone, 2011). At first, these efforts undertaken in the 1940s and 1950s in the United States were put under the broader terms 'forecast' and 'forecasting', and then becoming known as Technological Forecasting. It aimed to provide probabilistic results with a high degree of confidence about the future, giving somewhat of a deterministic view of economic and innovative dynamics. Later, in the late 1980s and early 1990s, another approach would recognize that choices made today shape the future in a non-deterministic way, and are socially and politically affected by the agents involved in the decision-making processes (Martin, Irvine, 1989; Martin, 2010). That approach is what is known today as TF. The TF approach was initially outlined by John Irvine and Ben Martin in an attempt to delineate a field of research for future-oriented studies in science and technology (Irvine, Martin, 1983; Martin, Irvine, 1989). Their works were especially important to distinguish TF from Technological Forecasting and to establish the first as the standard for technology emergency analysis in innovation studies (Martin, 2010; Miles, 2010). Later, other authors continued to explore this differentiation and added that TF also had the potential to influence the direction technology takes and help the desired future to materialize (Miles, 2010) and that its participatory structure ensured the inclusion of agents who can expand potential strategies beyond individual interests (Lall, 2004).

Foreseeing technologies that may be economically or socially relevant in the future is key for governments that aim to enable long-term economic growth and productivity, improve the delivery of public services, enrich the lives of its citizens and inform policy development (Government Office for Science, 2017). This is true for many areas but healthcare is certainly among the ones that benefit the most from innovations. From new devices such as labs-on-a-chip (LOCs), that may lower costs and increase access to diagnostics (Mendes et al., 2019), to 3D/4D bioprinted tissues and organs, that can replace diseased, damaged, or lost human tissues and organs (Jang et al., 2016; Kačarević et al., 2018; Lerman et al., 2018). TF projects often have a form of broad government-funded studies that may require large amounts of money, resources, and personnel. Our method, in turn, is low-cost, requires fewer researchers, produces faster results, and can collect opinions of experts from all over the world. It consists of conducting periodic web-based surveys to re-evaluate previous TF studies and thus identify whether there have been changes in experts' expectations regarding the

[2] Tissue engineering is an interdisciplinary field that combines chemistry, biology, and engineering (Richards et al., 2013).

**Box 1. Search Queries**

(ti=("4D bioprint*" OR "4D bio-print*" OR "four-dimensional bioprint*" OR "four-dimensional bio-print*" OR "4-dimensional bioprint*" OR "4-dimensional bio-print*" OR "four-D bioprint*" OR "four-D bio-print*" OR "4D print*" OR "four-dimensional print*" OR "4-dimensional print*" OR "four-D print*" OR "3D bioprint*" OR "3D bio-print*" OR "three-dimensional bioprint*" OR "three-dimensional bio-print*" OR "3-dimensional bioprint*" OR "3-dimensional bio-print*" OR "three-D bioprint*" OR "three-D bio-print*" OR "3D print*" OR "three-dimensional print*" OR "3-dimensional print*" OR "three-D print*") and ti=(«Tissue Engineer*» OR «tissue culture*» OR «Cell Engineer*» OR «cell culture*» OR «Bioengineer*» OR «Bio-engineer*» OR «organ* culture*» OR «in vitro»)) AND LANGUAGE: (English)

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Horizon = 2013-2018

(ti=("animal* testing alternative*" OR "alternative* to animal* testing" OR "animal* use alternative*" OR "alternative* to animal* use" OR "animal* experiment* alternative*" OR "alternative* to animal* experiment*" OR "animal* research alternative*" OR "alternative* to animal* research" OR "animal* model* alternative*" OR "alternative* to animal* model*" OR "lab* animal* alternative*" OR "alternative* to lab* animal*" OR "reduction refinement and replacement*" OR "3Rs" OR "three-Rs")) AND LANGUAGE: (English)

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Horizon= 2013-2018

*Source*: authors.

future results of a given technology. TF benefits greatly from a reassessment of experts' estimates after some time, whether to better understand experts' projection mechanisms or to assess if their expectations are confirmed (Brandes, 2009; Kaivo-oja, 2017; Apreda et al., 2019). Thus, considering the high degree of novelty of much of the technologies that are subject to TF exercises, the decision-making in science and technology may greatly benefit from intertemporal comparisons of expert opinions. Periodic surveys not only update the results of previous TF exercises but also assess if there were changes in researchers' expectations.

## Materials and Methods

### *Literature review and questionnaire*

The questionnaire was based on a literature review of 3D and 4D bioprinting, tissue engineering, and alternatives to animals in research. The publications were gathered in WoS using the following queries (Box 1).

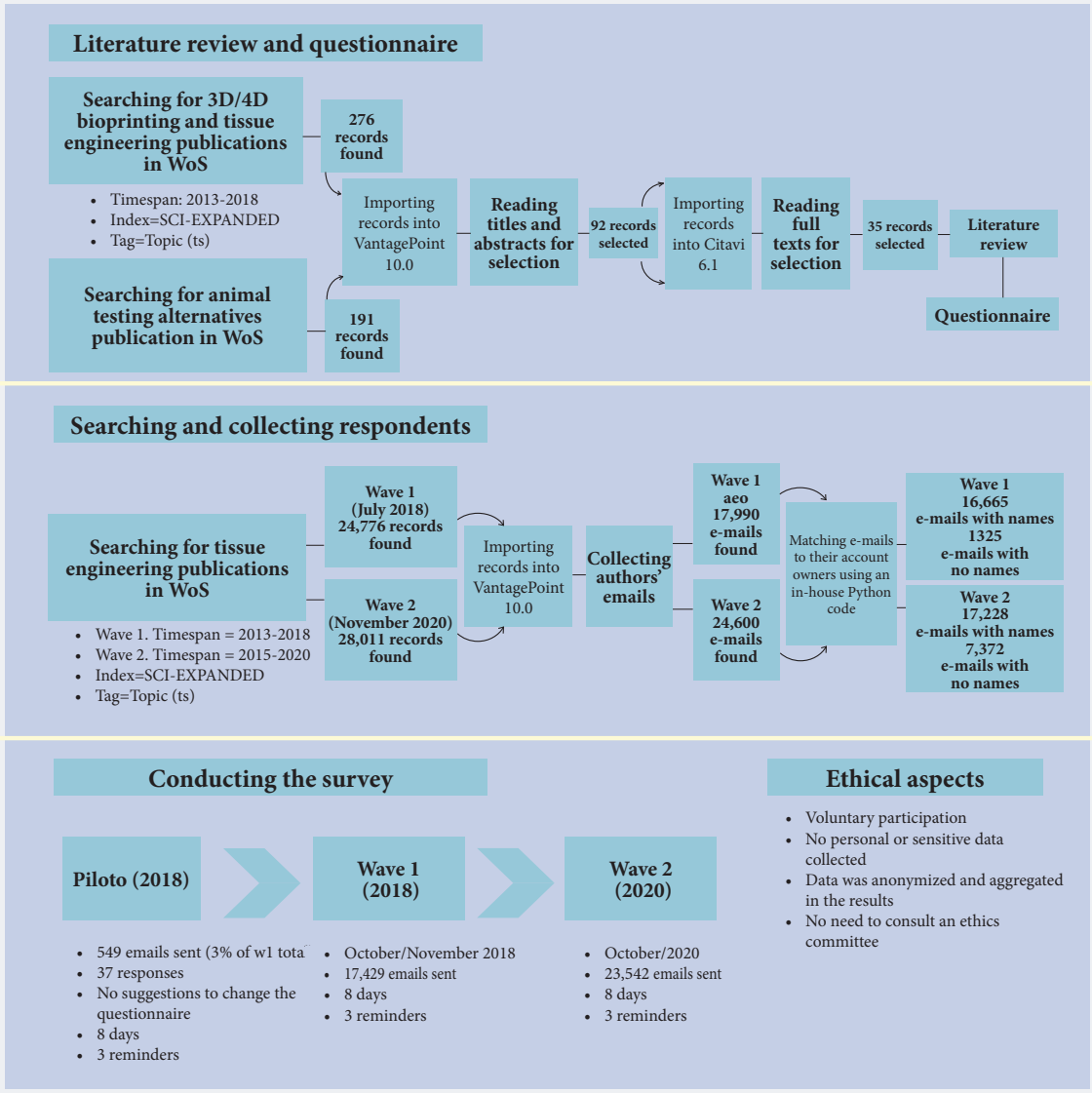
We used the tag Title (ti) to search for the queries' terms only in the publications' titles. Both queries used terms of the Medical Subject Headings[3] and free text words. We used only the Science Citation Index Expanded (SCI-EXPANDED) to collect records of publications (all document types) published in science journals between 2013 and 2018.

The search was done in July 2018 and yielded 276 records of publications (all document types) from the first query and 191 from the second. All the records were imported into the VantagePoint 10.0, where a preliminary selection of the publications was made by reading the titles and abstracts. This procedure reduced the number of documents of interest to 92. These documents were then imported into the reference management software Citavi 6.1, where the final selection was made by reading the full texts. Finally, 35 publications were selected, which formed the basis of the literature review and the questionnaire (Richards et al., 2013; Balls, 2014; Doke and Dhawale, 2015; Fleetwood et al., 2015; Goh et al., 2015; Graham, Prescott, 2015; Mosadegh et al., 2015; Obregon et al., 2015; Stokes, 2015; Zhang, Zhang, 2015; Ahn et al., 2016; Brunello et al., 2016; Colasante et al., 2016; Gao, Cui, 2016; Groeber et al., 2016; Mehrban et al., 2016; Mohanty et al., 2016; Ng et al., 2016; Park et al., 2016; Zhao et al., 2016; Zhu et al., 2016; Albritton, Miller, 2017; Burden et al., 2017b; Cheluvappa et al., 2017; Duan, 2017; Garreta et al., 2017; Huang et al., 2017; O'Connell et al., 2017; Vanderburgh et al., 2017; Almela et al., 2018; Faramarzi et al., 2018; Löwa et al., 2018; Mori et al., 2018; Stratton et al., 2018; Tarassoli et al., 2018).

The questionnaire asked the respondents to consider 2018-2038 (W1) and 2020-2038 (W2) as a future time frame. It was structured into three parts. The first part was designed to ascertain the respondents' level of knowledge of 3D and 4D bioprinting applications in the field of tissue engineering, ranging from no knowledge to good knowledge. Respondents with no knowledge of the survey's subject were disqualified from the survey and did not answer the questionnaire. The second part presented five statements about the future. The aim was to obtain the respondents' opinions on the likelihood of 3D and 4D bioprinting leading to: fully functional human tissues and organs for implantation; repair of lesions directly at the wound site; drug testing models for toxicity testing; human disease models for research; and replacement of animals in research and toxicity testing. They were asked to indicate both the likelihood of each statement and when they expect it would come about (before or after 2038). The final part asked respondents to indicate the likelihood of five selected scientific and technological challenges being overcome within the given time

[3] ncbi.nlm.nih.gov/mesh, accessed 02.06.2021.

Figure 1. **Summary of the Method**




*Source*: authors.

horizon. These challenges covered expected advancements in bioprinters, vascularisation of tissues, and scalability of bioprinted models. The questionnaire was set to be answered within 2-3 minutes to avoid respondent's fatigue, skipped questions, survey dropout. Demographic questions were not asked because the results of this type of survey are not expected to be influenced by the respondents' demographics (Pereira Cabral et al., 2019a, 2019b; Cabral et al., 2021; Mota et al., 2020; Rocha et al., 2020).

### *Searching and collecting respondents in scientific publications*

The respondents of this survey were found in scientific publications related to tissue engineering indexed in WoS between 2013 and 2018 (Wave 1) and 2015-2020 (Wave 2). To do so, we used the following query:

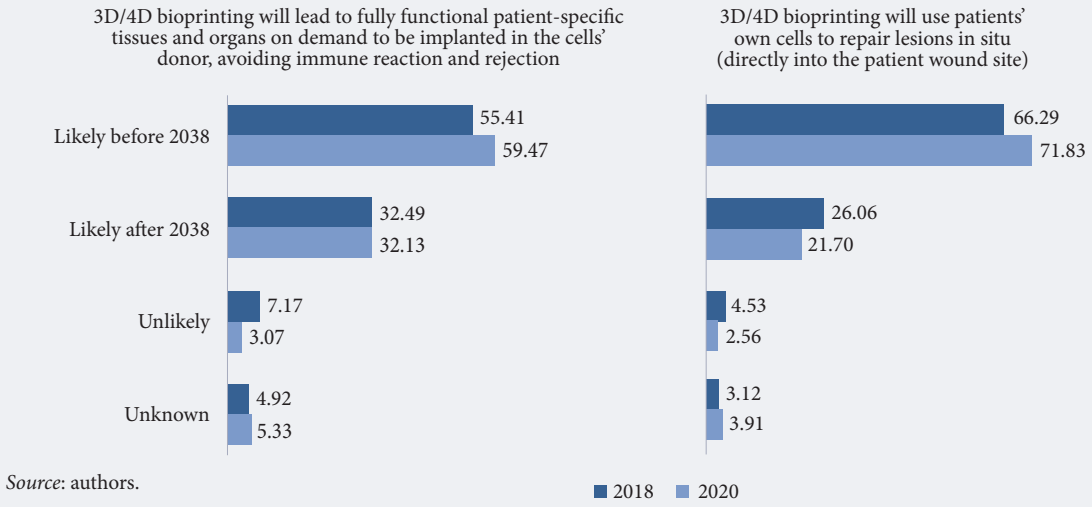
(ts=("tissue engineer*"))

Indexes=SCI-EXPANDED Timespan=2013-2018 (Wave 1) and 2015-2020 (Wave 2)

We used the tag Topic (ts), which searches for descriptors in the publications' titles, abstracts, and keywords, and the term tissue engineering. Since the objective was to find out the expectations of natural scientists, the query was set to retrieve documents indexed in the SCI-EXPANDED. In both waves, the period was set to identify authors who had published their research results recently.

The wave 1 (W1) search was done in July 2018 and retrieved 24,776 records of publications (all document types), and the wave 2 (W2) search in November 2020, retrieving 28,011 records of publications. All the records were imported into the data/text mining software VantagePoint 10.0, where 17,990 (W1) and

Figure 2. **Likelihood of 3D/4D Bioprinting Effects — part 1 (share of responses, %)**




*Source*: authors.

24,600 (W2) authors' emails were collected. Then, we generated a CSV file to link about 81% of these emails to their account owners using an in-house Python code. Thus, it was possible to forward personalized e-mails with the respondents' names to most of them.

### *Conducting the Survey and ethical aspects*

In W1, we validated the questionnaire through a pilot study with an aleatory sample of 549 respondents (about 3% of the total). As we did not receive any suggestions for changes of the 37 respondents who answered the pilot study, the questionnaire was not modified. The data collected was then included in the statistical analysis of the survey. Since the questionnaire is the same in both waves, there was no need for a pilot study in the 2020 survey. The pilot and the formal study of W1 were conducted between October and November 2018, and the formal study of W2 in October 2020. The questionnaire was available for completion for eight days after the invitation email was sent. All data collected were anonymized in the study results.[4] Figure 1 summarizes the method used.

### *Statistical Analysis*

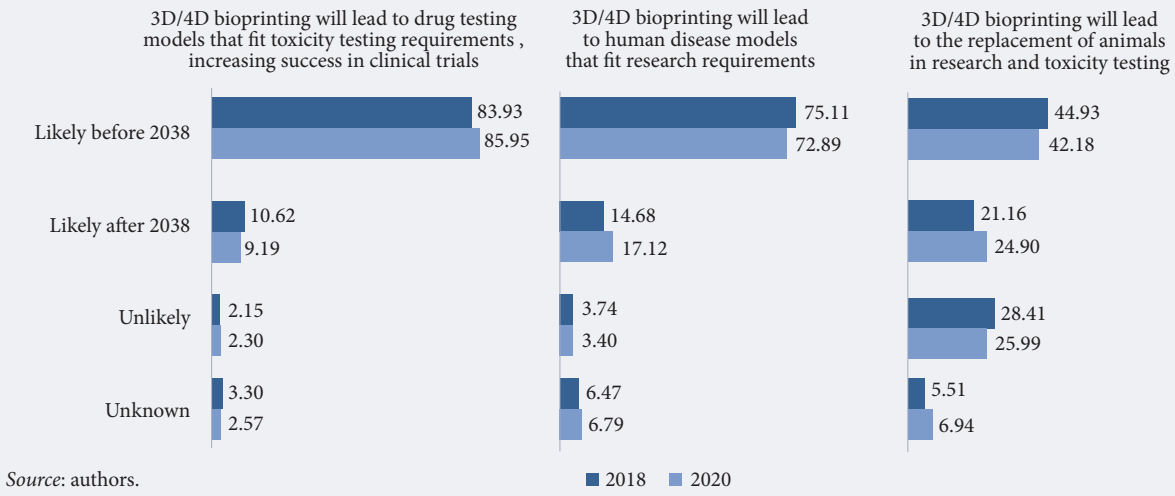
We used the Shapiro-Wilk and the Kolmogorov-Smirnov to test whether the sample follows a normal distribution. The Shapiro-Wilk normality test is usually used due to its good power properties. That is, it is not necessary to know the average and variance of the sample beforehand. In turn, the Kolmogorov-Smirnov is a test of a distribution's adherence to a parameter. It becomes a test of normality when the maximum absolute difference between an expected (normal) function and the empirical distribution of data is observed. Both tests are generally used in empirical studies. The Kolmogorov-Smirnov is more suitable for large samples, while the Shapiro-Wilk test is indicated for small samples (less than 50 observations). As the sample did not follow a normal distribution, we used non-parametric tests with a 95% confidence level.[5]

For the question related to the knowledge level of the respondents, we used the binomial non-parametric test to assess whether the two groups of valid respondents (good knowledge and some knowledge) are statistically homogeneous or whether one is predominant over the other. For all the other questions we used the non-parametric test of Mann-Whitney U to assess whether the level of respondents' knowledge interferes with the predominant median. Additionally, we used the non-parametric tests of Wilcoxon to assess the median of the responses collected. The tests of Mann-Whitney U and Wilcoxon assign value 1 for the lowest rank (position 1), value 2 for the next rank, and so on. This process generates high scores being represented by high posts and low scores being represented by low posts. Lastly, to compare the responses obtained in 2018 with the responses obtained in 2020, the non-

[4] The methods we used to identify respondents from scientific publications, retrieve and link the emails to their account owners, design and manage the web-based survey follow recent future-oriented studies on health-related technologies (Pereira Cabral et al., 2019a, 2019b; Cabral et al., 2021; Mota et al., 2020; Rocha et al., 2020).

[5] Non-parametric tests do not require normally distributed observations, but the distribution of observations in an ordinal scale. Although parametric tests are more robust than non-parametric tests, their use requires normally distributed observations (Hesse et al., 2017), which makes them inadequate for this study.

Figure 3. **Likelihood of 3D/4D Bioprinting Effects — part 2 (share of responses, %)**




*Source*: authors.

parametric test of marginal homogeneity was applied. The non-parametric test of marginal homogeneity follows a chi-square distribution. It generates a frequency table for each survey and compares them. The data analysis was carried out using the IBM-SPSS Statistics 26. The results of the statistical analysis are available as Supplementary Material.

## Results

The results reported here consider all valid responses. To simplify the graphical presentation and the description of the results, we combined the responses of good and some knowledge respondents. The binomial non-parametric test rejects the null hypothesis that there are two groups of respondents (good and some knowledge) each with 50% of the responses. The result shows that, in both waves, respondents who said they have some knowledge are preponderant. Thus, the results obtained in both waves may suffer bias depending on the level of knowledge of the respondents. Significant statistical differences between them will be described in the results when they occur.

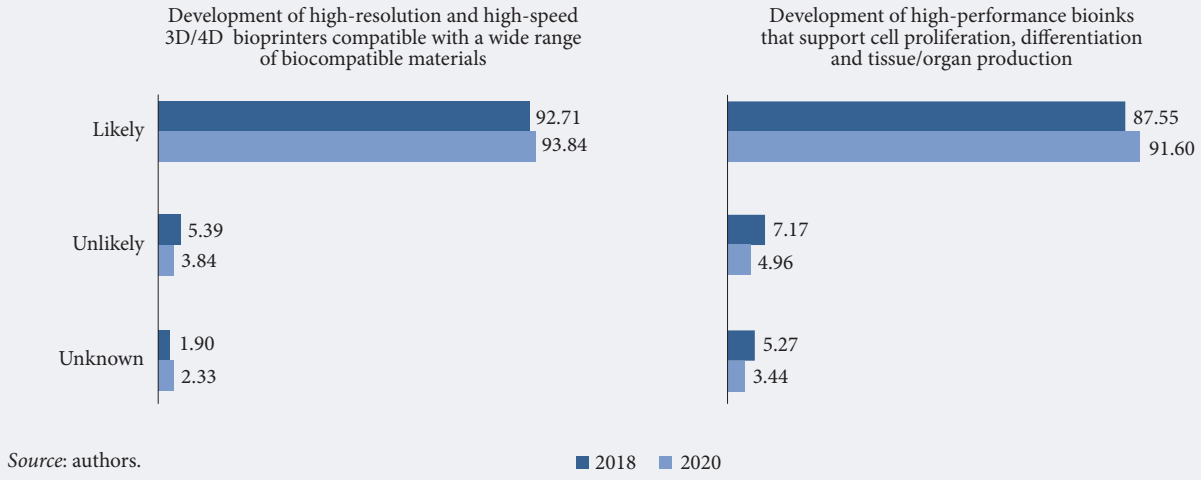
In 2018, 801 researchers accepted to participate in the study, which corresponds to a response rate of 4.3%. Of those, 61 were disqualified from the survey after reporting having no knowledge of 3D and 4D bioprinting applications in the field of tissue engineering. Of the 740 valid responses, 38.4% were from good knowledge and 61.6% from some knowledge respondents. Taking into account only the 673 fully completed questionnaires (90.9% of total valid responses), we obtained a representative sample with a 95% confidence level and a margin of error of 3.7%. As for the 2020 survey, 836 researchers accepted to participate in the study (3.3% response rate), 60 were disqualified for having no knowledge, 40.1% of the 776 valid responses were from good knowledge and 59.9% from some knowledge respondents. We received 708 fully completed questionnaires, which corresponds to 91.2% of the total. Considering these fully completed questionnaires and a 95% confidence interval, the margin of error in the results is 3.6%. Of the 1,516 respondents qualified for the surveys, 110 participated in the two waves. According to the respondents' internet email protocols, researchers from 67 and 66 countries participated in W1 and W2, respectively.[6]

In W1, about 87% of respondents expected that 3D/4D bioprinting will likely lead to fully functional patient-specific tissues and organs on demand to be implanted in the cells' donor, avoiding immune reaction and rejection. In W2 this percentage increased to over 90% (Figure 1). Besides the slight increase in likely responses and the reduction of unlikely responses between 2018 and 2020, the marginal homogeneity test shows that there is no statistical difference between the responses of the two waves. For its part, the Mann-Whitney U test indicated that, in both waves, the level of respondents' knowledge does not interfere with the predominant median. According to the Wilcoxon test, the statistically predominant response, in both waves, is that the 3D/4D bioprinting will likely lead to the mentioned fully functional patient-specific tissues and organs before 2038.

In both waves, according to over 90% of the researchers, 3D/4D bioprinting will use patients' own cells to repair lesions directly into the wound site. Most of them expect it before 2038 (Figure 2). Comparing the experts' opinions between 2018 and 2020, there is a modest increase in the percentage of likely before 2038 and a

[6] In both waves, the highest proportion of respondents were from Europe (38.70% W1; 41.15% W2), followed by Asia (23.82% W1; 25.12% W2), North America (21.52% W1; 15.67% W2), and South America (10.96% W1; 15.19% W2).

Figure 4. **Likelihood of Scientific and Technological Challenges Being Overcome until 2038 — part 1 (share of responses, %)**




*Source*: authors.

reduction of unlikely. However, the marginal homogeneity test does not show a statistical difference in the responses of the two waves. Besides that, the Mann-Whitney U test indicated that the level of respondents' knowledge also does not interfere with the results.

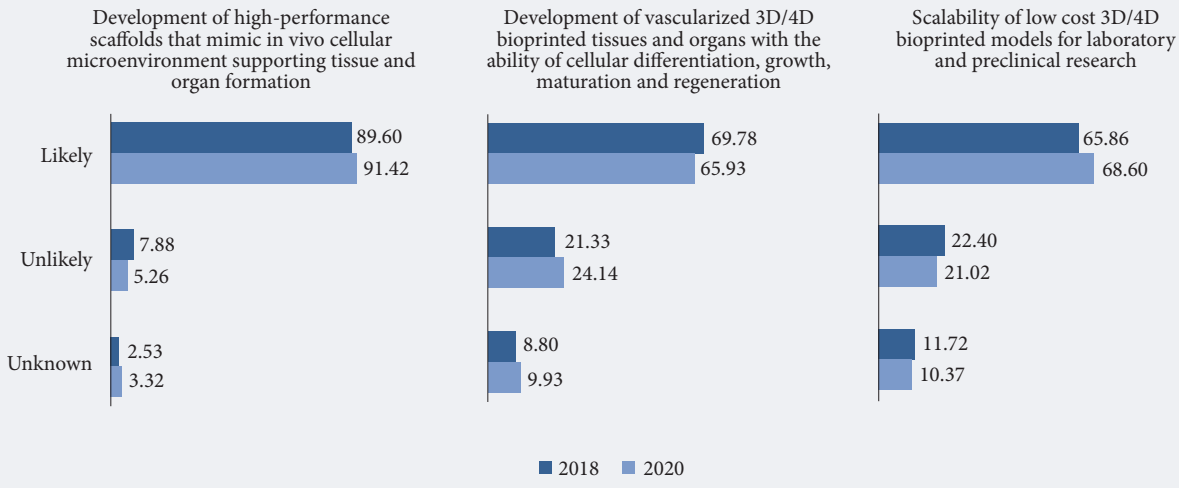
Most W1 researchers (83.9%) considered that, before 2038, 3D/4D bioprinting will likely lead to drug testing models that fit toxicity testing requirements, increasing success in clinical trials. The percentage of W2 researchers who expected this same outcome was a bit higher (85.95%) (Figure 3). The statistical test (marginal homogeneity) confirms that there was no statistical difference between the responses of W1 and W2. According to the Wilcoxon test, in both waves, the statistically predominant response is that 3D/4D bioprinting will lead to the above-mentioned drug testing models before 2038. However, according to the Mann-Whitney U test, in both waves, the level of the respondents' knowledge interferes with the result. Thus, it can be said that some knowledge respondents influenced the outcome related to the period in which these drug testing models are likely to occur. In both waves, about 57% of the respondents who believe this outcome is likely before 2038 have some knowledge of 3D and 4D bioprinting applications in the field of tissue engineering.

The respondents' expectations about 3D/4D bioprinting leading to human disease models that fit research requirements were also very similar in W1 and W2. In both waves, about 90% of respondents considered it likely, with over 70% expecting it to happen before 2038 (Figure 3). Yet, statistical non-parametric tests show that there is no significant difference between the 2018 and 2020 responses. According to the Wilcoxon test, in both waves, the statistically predominant response is that 3D/4D bioprinting will lead to those human disease models before 2038. In both waves, the Mann-Whitney U test indicated that some knowledge respondents' interfered with the results. Of those who believe these human disease models would be likely before 2038, over 55% have some knowledge of 3D and 4D bioprinting applications.

Respectively 66.09% and 67.08% of W1 and W2 respondents reported that 3D/4D bioprinting will likely lead to the replacement of animals in research and toxicity testing, with over 40% of them expecting this before 2038 (Figure 3). Although most respondents expect this to be likely at some point in the future, a good number of them do not believe in this outcome. Of all the statements about the future presented to the experts' analysis, this was the one who had the highest percentage of unlikely answers: 28.41% in 2018 and 25.99% in 2020. The statistical results pointed out that there were no changes in the researchers' perception between W1 and W2. According to the Mann-Whitney U test, in W1, the level of respondents' knowledge does not interfere with the survey results. In W2, for its turn, some knowledge respondents had a statistically significant influence on the result. Overall, according to the Wilcoxon test, the expectation is that 3D/4D bioprinting will lead to animal replacement in research and toxicity testing.

We presented the respondents to five scientific, technological challenges for which 3D/4D bioprinting offers great promise, asking them about the likelihood of these challenges being overcome before 2038 (Figure 4 and Figure 5). High-resolution and high-speed 3D/4D bioprinters compatible with a wide range of biocompatible materials are expected to be developed in up to 18 years according to over 90% of respondents of both waves (Figure 4). High-performance bioinks capable of supporting cell proliferation, differentiation, and

Figure 5. **Likelihood of Scientific and Technological Challenges Being Overcome until 2038 — part 2 (share of responses, %)**




tissue/organ production we also considered likely before 2038 to 87.55% of W1 respondents and 91.60% of W2 respondents (Figure 4). For both statements, there was no statistical difference in W1 and W2 responses and, for both waves, the level of the respondents' knowledge does not interfere with the survey results. The Wilcoxon non-parametric test shows that, in both waves, the statistically predominant response is that these bioprinters and bioinks will likely occur.

The last three challenges are depicted in Figure 5. In both waves, over 90% of respondents considered that the development of high-performance scaffolds that mimic in vivo cellular microenvironment supporting tissue and organ formation is likely to happen until 2038. As for the development of vascularized 3D/4D bioprinted tissues and organs with the ability of cellular differentiation, growth, maturation, and regeneration, there was, from 2018 to 2020, a decrease in the percentage of respondents who expect this result will occur (from 69.78% in W1 to 65.93% in W2). From W1 to W2, both unlikely and unknown answers increased. This was also the challenge with the highest percentage of unlikely answers (24.14%). Finally, the scalability of low cost 3D/4D bioprinted human models for laboratory and preclinical research was considered likely by more than 65% of respondents of both waves. The percentage of likely answers was slightly higher in W2 (68.60% against 65.88% of W1). From W1 to W2, there was a slight decrease in the percentage of unlikely and unknown answers. Nevertheless, they remain high (a little over 20% and 10%, respectively). This was also the only challenge with more than 10% of unknown answers.

The statement related to the development of vascularized 3D/4D bioprinted tissues and organs was the only one that showed a statistical difference between W1 and W2, according to the marginal homogeneity non-parametric test. The frequency distribution of responses suggests that respondents in W2 were more pessimistic about the development of these bioprinted tissues and organs. To both waves, for all the three statements presented in Figure 5, the Mann-Whitney U test shows that the level of respondents' knowledge does not interfere with the results, and the Wilcoxon test that the statistically predominant response is that they will occur.

## Discussion

In the future, fully-functional bioprinted tissues and organs are expected to be translated into clinical practice, being implanted in humans (Gilbert et al., 2018; Gershlak, Ott, 2020), which may lead to the creation of a new market for the commercialization of on-demand patient-specific bioprinted tissues, organs (Gilbert et al., 2018). In line with that, most W1 and W2 respondents expect patient-specific tissues, organs produced on demand before 2038. But for this to become a reality, some key issues need to be addressed. For example, it is uncertain whether bioprinted organs can be patient-specific (Colasante et al., 2016; Faramarzi et al., 2018), or even be produced on demand (Colasante et al., 2016). The production of bioprinted patient-specific tissues, organs still requires improvements in computer-aided design software to better reproduce 3D images, better bioprinting resolution to reproduce original shapes, and the development of tissue-specific biomaterials (Colasante et al., 2016; Ng et al., 2016). For its turn, on-demand production of bioprinted tissues, organs will depend not only on the ability of the technology to bioprint functional organs on a human scale but also on the availability of the bioproducts needed for their production (Mir et al., 2019) and the regulation for their commercialization (Gilbert et al., 2018). If on-demand production of patient-specific

tissues, organs will be viable in the future, we can expect a reduction of organs waiting lists (Gershlak, Ott, 2020) and immune rejection, leading to improvements in patients' lives (Loai et al., 2019; Mir et al., 2019).

It is also uncertain if 3D/4D bioprinting can lead to the treatment of patients directly at the wound site (Huang et al., 2017). In both waves, respondents expected this to be a reality before 2038. The concept of in situ (or in vivo) bioprinting refers to a system that could scan a patient's lesion and then print a repair using their cells directly at the wound site (Mehrban et al., 2016; Dias et al., 2020). Such a procedure could prevent the need for subsequent surgical interventions (Huang et al., 2017; Chen et al., 2020) and also reduce the patients' recovery time (Park et al., 2016). Yet, in situ bioprinting still has a long way to go before it can be used by surgeons in operating rooms. Among other things, it needs to be fast, automated, and user-friendly (Dias et al., 2020). So far, in situ bioprinting of skin, bones, and cartilages have been tested and achieved positive results on mice (Albanna et al., 2019), but is not yet available for use in humans (Unagolla, Jayasuriya, 2020).

Due in part to interspecies differences, high failure rates in clinical trials are often related to the use of animals as models of diseases and predictors of toxicity in humans (Rosania, 2013; Balls, 2014; Löwa et al., 2018). To improve success rates in clinical trials and so in drug development, more human-based methods would have to be adopted in basic and preclinical research (Burden et al., 2017a; Löwa et al., 2018). This could be achieved through 3D/4D bioprinting, which is expected to be able to provide drug delivery and human disease models for research and drug testing, reducing risks in clinical trials (Richards et al., 2013; Lukin et al., 2019; Gardin et al., 2020; Mota et al., 2020).

In line with that, most W1 and W2 respondents expect 3D/4D bioprinted drug testing models for toxicity testing and 3D/4D bioprinted human disease models for research to be available before 2038. If these expectations are met, and 3D/4D bioprinted models lead to increased success rates in clinical trials, they may be strong candidates for animal replacement (Weinhart et al., 2019). An example of validation with positive results was made in a 3D bioprinted liver model, which was able to predict the toxicity of Trovafloxacin, a drug that had been previously tested in animals in the preclinical phase and was only rejected in phase III of clinical trials. In this case, the 3D bioprinted model proved to be better than animal testing, and if it had been used instead of animals in the preclinical study, the drug would not have entered the following phases, saving time and money (Peng et al., 2017). Thus, if bioprinted models can predict efficacy and toxicity better than animals in preclinical research, we can expect higher success rates in clinical trials (Charbe et al., 2017; Peng et al., 2017) and thus an increase in demand for 3D/4D bioprinted models to replace animal, especially by pharmaceutical companies that are already leading investments in this field (Fonseca et al., 2020).

Although promising, 3D/4D bioprinting still has to overcome a variety of scientific and technological challenges before reaching its full potential (Mao et al., 2020). While the production of less sophisticated human tissues has already proved feasible (Garreta et al., 2017; Stratton et al., 2018; Chen et al., 2020; Matai et al., 2020), the production of more complex functional organs is not there yet (Mir, Nakamura, 2017; Stratton et al., 2018; Wang et al., 2020b). While some organs, like the skin, with a flat structure and a few different cells, are simpler to be built, organs as the kidney, with multiple regions, multiple shapes, and about thirty different cell types, are much more complex to build (Jorgensen et al., 2020). Unlike less sophisticated organs – skin, cartilage, and bones, for example –, complex functional organs – such as kidneys, heart, and liver – requires high-performance scaffolds (Brunello et al., 2016) and vascular networks (Mohanty et al., 2016), whose development is still considered a great challenge today (Unagolla, Jayasuriya, 2020; Wang et al., 2020b). Scaffolds are biocompatible structures that provide an environment where cells can attach and grow (Brunello et al., 2016). Yet, it is not clear which biomaterials and bioprinting methods are most suitable for scaffolds (Tarassoli et al., 2018). At present, scaffolds lack porosity and perfusion, compromising cell growth and differentiation (Brunello et al., 2016), affecting vascularization (Wang et al., 2020a). Such shortcomings in scaffold development hamper the capacity of artificial human tissues and organs to stay alive for longer periods (Vries et al., 2015). Most W1 and W2 respondents considered the development of high-performance scaffolds likely before 2038. Complementarily, bioprinting approaches that seek to produce tissues and organs without the use of scaffolds are also under development. By avoiding problems such as material biocompatibility, the mismatch between scaffold degradation and the growth of the cells that should replace it, and the barriers to the permeability of oxygen, nutrient, and metabolic waste (Khoshnood, Zamanian, 2020).

Scaffold-free bioprinting is also being considered a promise, including for better vascularization of bioprinted tissues and organs (Heinrich et al., 2019; Unagolla, Jayasuriya, 2020). So far, these methods have been used mainly for bioprinting smaller tissues. In part, this is because scaffold-free pre-print preparations are more complex, making them more time-consuming and expensive (Gardin et al., 2020; Khoshnood, Zamanian, 2020). The choice between scaffold-based or scaffold-free methods is based on the desired application (Khoshnood, Zamanian, 2020). Overall, scaffold-based methods are suitable for large, cell-homogenous, matrix-rich tissues, while scaffold-free methods are used for small, cell-heterogeneous, matrix-poor tissues (Alghuwainem et al., 2019). Vascular networks are microchannels of blood vessels and capillaries (Vanderburgh et al., 2017), which are required for cell growth and regeneration since they conduct nutrients and oxygen among the tissues

(Mohanty et al., 2016). Keeping cells alive demands the integration and maturation of vascular networks (Zhang et al., 2020). Today, 3D/4D bioprinting is not fully able to build complex vascular networks capable of performing natural cellular activities (Zhang et al., 2020) and support the production of more complex organs (Zhao et al., 2016). Vascularization and cells need to be bioprinted together, at the same speed, to prevent tissue death (Leberfinger et al., 2019). Also, current bioprinting methods face problems with the bioprinting of hierarchical vascular networks that contain capillaries, vessels and arteries together with other tissues (Murphy et al., 2020; Wang et al., 2020b), and most of them can only print vessels (Leberfinger et al., 2019). According to most respondents of both waves, we can expect the challenge of network vascularization to be overcome before 2038.

The 5D bioprinting has recently emerged as a new technology to create vascularized models (Foresti et al., 2020). It is an evolution of 3D/4D bioprinting, which allows the bioprinting of more complex systems with curved shapes (Kumar et al., 2019). The 5D bioprinting is performed at five different angles by rotating print heads – while 3D/4D bioprinting uses a print head at a fixed angle (Ahmad et al., 2019), allowing the bioprinting of more complex and personalized structures (Dey, Ozbolat, 2020). Yet, none of the mentioned possibilities related to the use of 3D/4D bioprinting can be achieved without improvements in bioprinter and bioink technologies. Bioprinters use fluids containing biomaterials and/or living cells. Known as bioinks, they range from hydrogels (using alginate, collagen, fibrin, gelatin methacrylate) to cell aggregates, microcarriers, and decellularized matrices (Whitford, Hoying, 2016; Hospodiuk et al., 2017; Gungor-Ozkerim et al., 2018). Today, the most common bioprinting techniques are inkjet bioprinting, extrusion bioprinting, laser-assisted bioprinting (Sears et al., 2016; Vijayavenkataraman et al., 2018; Dias et al., 2020; Zhang et al., 2020), which are still time-consuming and labor-intensive (Duan, 2017). In the future, high-resolution and high-speed 3D/4D bioprinters compatible with a wide range of biocompatible materials are expected to be developed (Park et al., 2016; Heinrich et al., 2019). In line with that, more than 90% of W1 and W2 respondents considered this development likely before 2038. High-performance bioinks capable of supporting cell proliferation, cell differentiation, and tissue/organ production are also expected (Mosadegh et al., 2015; Albritton, Miller, 2017; Huang et al., 2017; Mori et al., 2018). In both waves, more than 87% of respondents reported that bioink technology will likely have reached this level of development before 2038. Essentially, the biological functionality of bioprinted constructs is dependent on bioinks having such qualities (Murphy et al., 2020). The absence of high-performance bioinks limits progress in the field of tissue engineering and thereafter the translation of research results to clinical practice (Mori et al., 2018). In an ideal set-up, the bioprinters of the future will be able to combine different bioinks at a speed that enables vascularization, cell growth, and differentiation, allowing tissues and organs to be bioprinted on a larger scale (Dias et al., 2020).

The adoption and diffusion of 3D/4D bioprinted human models in research laboratories not only requires improvements in methods, bioprinters, and bioinks, but also the scalability of low-cost tissues (Tarassoli et al., 2018; Weinhart et al., 2019). Although this was the challenge with the highest percentage of unknown answers, most of the respondents of the two waves expect it to be overcome by 2038. The scalability of low-cost tissues is not a problem when bioprinting a single organ for a patient, but it may be for applications that require multiple constructs for testing, such as preclinical research (Daly et al., 2017). Current bioprinting processes are time-consuming and costly (Wang et al., 2020b), but are the most promising to produce tissues and organs on a larger scale (Correia Carreira et al., 2020), and at low cost (Heinrich et al., 2019).

## Final remarks

This study presented the results of a two-wave global survey of tissue engineering-related researchers about the future of 3D/4D bioprinting on biomedical research, drug testing, and medicine. Also, it assessed changes in respondents' expectations between the waves performed in 2018 and 2020. For most of the statements presented to respondents, we can see a growth in optimism from W1 to W2 as it increased the rate of those who reported that it was expected to occur 'before 2038'. The increase in optimism may, perhaps, be related to scientific and technological advancements in the field of tissue engineering over the past two years, allowing respondents to have a clearer view of what the future might look like. In summary, the results suggest that we can expect 3D/4D bioprinted tissues, organs either for implantation in humans or for research and toxicity testing in less than two decades. If the future confirms these expectations, we will probably see the emergence of a new market for the commercialization of bioprinted products, and perhaps a solution to both the problem of organ shortage and adverse drug reaction. As such, these technology-driven changes can have a strong impact not only on the practice of biomedical research, drug testing, and medicine but also on healthcare and public health as a whole. Assuming that the influence of technology on the health sector tends to increase over time, preparing for the future is a necessity for those involved not only in research, clinical practice, or technology management, but also for those responsible for healthcare delivery and for developing and implementing public health policies.

The type of study we performed can be considered a narrow TF (Mota et al., 2021) as opposed to the broader TF studies, best known as fully fledged

foresight studies (Miles, 2010). Despite a lack of participatory orientation and policy-relatedness (Miles, 2010), their narrower scope makes them better suited for the study of a given technology (Mota et al., 2021). From this perspective, we offer to the foresight community a feasible and low-cost method of finding, collecting, and consulting a large number of experts from all over the world, which can benefit new future-oriented studies. Therefore, we hope our method to contribute to new studies aimed not only at foreseeing the future from expert opinions but to comparing their expectations over time. Thus, generating information that can keep track of scientific and technological developments.

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