Digital readiness in 3D bioprinting:
software, governance and hospitals' proto-clinical interfaces

Abstract

AIMS. To understand the process through which some hospitals have become ready to assimilate the digital technologies required for 3D bioprinting. By enhancing their digital readiness, hospitals will be able to develop the current proto-clinical potentialities of bioprinting. METHODS. We conducted interviews with bioprinting researchers, entrepreneurs, and regulators in three countries (the UK, Italy, and Brazil). We analysed bioprinting papers in which hospital-based researchers participated. We also analysed the international bioprinting market. FINDINGS. Digital readiness is more advanced in some hospitals and countries, which have noticed the strategic relevance of bioprinting. Furthermore, it is strengthened by the reformulation of the relations between hospitals and other institutions, a phenomenon that is here interpreted with the concept of interfaces.

Keywords: digital readiness; bioprinting; software; proto-clinical features; institutional interfaces

Summary points

- Bioprinting is a cutting-edge tissue-engineering technique that holds promising clinical potentialities
- The technology is highly dependent on the use of software, which helps perform different tasks in the bioprinting process
- The technology is expected to reach hospitals in the years to come, helping to treat various diseases
- In order to incorporate bioprinting, hospitals need to prepare to use relevant software packages requiring enhanced skill sets (digital readiness)
- For so doing, hospitals need to streamline their connections (or interfaces) with players such as companies and research institutions
- In the course of such process, the clinical dimensions of software will become more salient, deserving more attention from regulators

1 Introduction

After a therapy has been developed, tested, and incorporated into medicine's clinical routines, all the institutional, technical, and governance work required for its production tends to be normalized and taken for granted. However, when therapies are still being developed, it is important not to neglect the social and technical efforts that need to be made in order for the innovation landscape comprising clinical settings, companies, and regulators to become ready to deal with new therapies and help them evolve. This paper focuses on these adaptation tasks, highlighting the activities and relations necessary for hospitals to engage in digitally-based technologies and thus get ready to absorb the products of human tissue engineering and regenerative medicine. More specifically, we explore the current involvement of some hospitals in research on 3D bioprinting and the use of the software that such research requires.

We shall adopt here a very focused definition of bioprinting, according to which the field is characterized by the use of devices (bioprinters) that realize a layer-to-layer deposition of media containing living cells (bioinks) in order to produce tissues, biological structures or organoids [1-3]. Bioprinting promises a step-change in the production of implantable regenerative therapies, as well as in the advancement of personalised medicine [4, 5]. Its applications are varied, including drug development, disease modelling, and food production [6]. One of the applications that provoke the biggest enthusiasm among scientists is the printing of bioactive structures. This application enhances the potentialities of regenerative medicine, leading some researchers to frame bioprinting as "one of the most promising technologies for addressing diverse health problems" [7]. Prospects are particularly ambitious when the bioprinting of very complex structures, and even whole organs, is envisioned. "The holy grail of tissue engineering is to achieve a fully functional organ which can be transplanted into a patient" [6]. However, the technology has been confronted with technical limitations such as scientists' incapacity to integrate vascular networks into large bioprinting constructs [8, 9]. Thus it is nowadays possible to bioprint only relatively small and simply structures, not yet whole organs.

The prospects of bioprinting cannot be fostered without the parallel development of computer software. It can even be claimed that the promises of bioprinting go hand in hand with the promises of software. Hence the occurrence of

some predictions such as the one voiced by Mironov and colleagues: "Modern software will allow one to design the whole organ biomanufacturing process and the corresponding robotic biofabrication equipment […]" [2].

Software is present in all stages of the bioprinting process. It is used to design the model of the structure to be printed (an application that can be called biomedical computer-assisted design, or simply bioCAD). It calculates the parameters of the printing process and the properties of the bioactive materials used. It guides the movements of the bioprinter. It helps analyse the viability of the structure once it has been printed. These and other applications turn bioprinting into a digital-intensive technique, a truly "computer-assisted technology" [10].

So far academic groups and some specialized companies have been the main promoters of bioprinting development. The technology is generally regarded as being at an early stage in terms of therapeutic potential, as no bioprinted therapeutic products have reached the market or authorisation stage. Nevertheless, some hospitals, via their research groups, individuals and practising clinicians, have begun to collaborate with some bioprinting companies. We are arguably in the early stages of a process through which bioprinting will make its way into clinical settings.

Elsewhere , we argued that technological development depends on the features of the experimental space, defined as a confluence of regulatory, social, and geographical processes [11]. The current state of bioprinting suggests a pre-translational experimentational space where different technical approaches are developed and tested. If bioprinting has not yet resulted in clinical applications, its current shape, including the initial interest garnered from some researchers based in hospitals, points to the existence of what we call *proto-clinical* features of the technology. Translational achievements that might emerge in the future are fully dependent on such pre-translational efforts whose features will be analysed here.

These tentative technical developments may invoke the idea of "technology readiness," which was " initially developed over forty years ago in the USA" and "is primarily about how to prepare a new technology such that it is made ready for its deployment in a very specific (organisational) setting" [12]. The idea has more recently been complemented by sociologists seeking to account for the adaptations that institutions need to undergo in order to receive new technologies into their premises, a process captured by the idea of "institutional readiness" [13]. This idea points to an institution's (e.g. hospital's) preparation of innovation-enabling, receptive

structures for the identification of needs, evaluation of technologies, and redesign of organisational processes.

Drawing on the example of bioprinting, we highlight here a different aspect of this institutional dimension, proposing the idea of *digital readiness.* It will be claimed that hospitals, in their initial contacts with bioprinting, are confronted with a challenge that is manifested in several social domains: they are urged to assimilate digital technologies (in this case, software) whose presence can position them at the forefront of technological trends (such as regenerative medicine) and of the competitive global politics of biomedical advance.

In putting forward the concept of digital readiness, our goal is not to offer a methodology for health sector workers to assess the readiness of their institutions. Instead, we aim at capturing broad trends in terms of social relations, institutionalization, and regulation. This is not to say, however, that health professionals and hospital administrators will not find interesting insights in the following interpretation.

The challenges associated with digital readiness cannot be faced if hospitals are unable to build up the required *interfaces*, a concept that we take from computer scientist David Parnas [14]. It will be seen that such interfaces can only be established once relations and expectations have been normalized, by means of either interinstitutional agreements or formal regulations.

Indeed, regulation has enormous implications for various players and is frequently surrounded by technical uncertainties and controversial claims. It is such uncertainty that led to the creation of the EU Advanced Therapy Medicinal Products (ATMP) Regulation [15], which is applicable to many regenerative products. Such regulation contributes to defining the rules of the game for given technologies, hence setting conditions for both technological and institutional readiness. While bioprinting and its products will most often fall within the ATMP Regulation, the situation is further complicated by the deep digitalisation of bioprinting.

Software as a Medical Device (SaMD) has recently become an official term in the American Food and Drugs Administration, as well as in the International Medical Device Regulators Forum (IMDRF). Moreover, the SaMD concept is just beginning to gain territory in the EU as a result of the new Medical Device Regulation [16]. Software with the intended medical purposes of diagnostic, therapeutic or surgical applications would then be deemed as SaMD. However, in the case of bioprinting,

most software packages will not under current regulation be considered as standalone SaMD or having integral medical functions. In this way, there are considerable regulatory variations, making Bauer and colleagues [17] conclude: "From a global perspective, harmonizing standards is of pivotal importance for the current and future development of 3D bioprinting."

For analysing the proto-clinical space of digital bioprinting outlined above, we divide this paper into three sections. Initially, the research methods mobilised in our research are outlined. Subsequently, we analyse the interfaces built up by some hospitals which have been engaged in research collaborations, focusing on their connections with universities and bioprinting companies, as well as on their internal connections. The final section brings some considerations about the current shape of institutional and digital readiness as it is manifested in hospitals involved in bioprinting activities and institutional partnerships.

2 Methods

This paper derives from the research project called Governing Biomodification in the Life Sciences - BioGov (https://www.law.ox.ac.uk/biogov), conducted at the University of Sussex between 2018 and 2021, in collaboration with researchers based in the Universities of Oxford and York. In this project, four main research methods have been mobilised, with approval from the Central University Research Ethics Committee of the University of Oxford (under reference number R47474/RE001).

First, we have conducted qualitative interviews with professionals involved in bioprinting, including academics, entrepreneurs, and policymakers regulating or overseeing biomedical technologies. These interviews have been conducted in three countries, as summarized in Table 1.

Table 1. Current position of the interviewees

	Country where the interview was conducted		
Position	**UK**	**Italy**	**Brazil**
Biomedical engineer	6	2	1
Company manager	3	1	3
Mechanical engineer	1	0	1
Biologist	1	1	0
Physicist	1	0	0
Surgeon	0	3	0
Chemical engineer	0	0	1
TOTAL	12	7	6

We have also undertaken fieldwork observations at relevant workshops and conferences.

Second, we have conducted an analysis of the international commercial landscape of bioprinting. This has involved the identification of companies fully or partially dedicated to bioprinting, as well as the collection of data about them. For so doing, a variety of sources have been used such as academic papers, websites, and the interviews. Eventually, 83 companies were identified.

Third, we conducted an online survey with participation of companies exploring bioprinting either directly or indirectly. All the companies identified in the process described above were invited to participate via email. The invitation included a link to an online questionnaire. Eventually, of the 83 companies invited, 23 agreed to participate (a 27.7% acceptance rate).

Fourth, we conducted a quantitative analysis of academic bioprinting papers, by using two platforms: Web of Knowledge and Scopus. The search was conducted in June 2020 and was based on keywords. The search strategy used on Web of Science was as follows:

(TS=((bioprint OR bioink OR "bio-ink" OR biofabrication OR biomanufacturing OR bioassembly OR bioadditive OR bioprinter OR bioplotting) NOT (animal OR cow OR bovine OR insect OR rabbit OR mammal OR monkey OR baboon OR chimpanzee OR

primate OR cat OR feline OR dog OR canine OR ferret OR shrew OR gerbil OR "guinea pig" OR "guinea pigs" OR pig OR rat OR mouse OR mice OR opossum OR bird OR reptile OR frog OR amphibian OR fish OR shark OR plant OR vegetal OR yeast)))

An equivalent search was carried out on Scopus.

In total, we found 1,567 papers somehow related to bioprinting. Subsequently, by means of text mining techniques, we separated only papers with at least one author based in a hospital, identifying 116 papers. In this phase, we considered the list of authors' institutional addresses so that it was possible to also identify authors based in research institutes located within hospitals. We then downloaded the full text of these 116 papers and, by using keywords (*bioprinter, system, device, bioplotter*), separated only papers reporting a study where some kind of bioprinter or conventional 3D printer was used, identifying 45 papers. Bibliometric data were then collected from these 45 papers. To be sure, all the 116 papers initially found could be considered as bioprinting-related papers. However, we decided to adopt a narrower approach (that is, to consider only papers reporting studies where at least one kind of printer was used) in order to include only studies where some actual printing activity occurred and, consequently, some software was used. In this way, we excluded, for example, conceptual papers that might lead us to downplay the relevance of software for bioprinting.

All the quantitative analyses presented in this paper (data on bioprinting companies, processing of data from the online survey, bibliometric analysis, and the design of social networks), were performed with the R programming language. More specifically, the following R libraries were used: bibliometrix, stringr, dplyr, ggplot2, readr, igraph, and ggraph.

To a considerable extent, the activities covered by our interviews and literature analysis have not been completely addressed by existing regulatory frameworks, which have focused on local research-related quality management but have been silent in relation to issues such as safety assurance and production processes. This situation creates some uncertainties, which are focused on in the next section.

3 Technical, institutional, and social interfaces in bioprinting

The early adoption of bioprinting tasks by hospitals involves not only technical issues but social and institutional ones too, for two reasons. First, in order to get involved in bioprinting projects in which software is used, hospitals need to be furnished with rules and schemes enabling them to formally collaborate with universities and companies. Second, such institutional relations can be fraught with the hierarchies that have marked the evolution of global biomedical research.

This gradual preparation can be interpreted in the light of the concept of *interface*, which, in the computer sciences jargon, is used to describe the links between different parts of software. The modern way of designing software follows the principles of *modularization*, according to which a software package needs to be formed of mini-packages (modules), each of them responsible for a specific task [18, 19]. For example, a certain software package that analyses the images taken from a bioprinted tissue to gauge cell viability would have one module responsible for receiving the numeric input from the microscope, another module to process such data quantitatively, and another module to generate an image deriving from such calculation, and so on. We are dealing with "[…] the division of a complex task into a series of simple tasks that can be carried out by essentially autonomous modules […]" [19]. Interfaces are computer programming tools that software developers mobilise to make the dialogue between modules possible. According to computer scientist David Parnas, interfaces (which he sometimes called "connections") are, so to say, the awareness that each software module has of the workings of other modules. "The *connections* between modules *are the assumptions which the modules make about each other*" [20].

In bioprinting, hospitals play, at this moment, less prominent roles than companies and universities. In this sense, institutions can be interpreted to be operating as software modules with evolving connections and a certain hierarchical integration. As Parnas points out, the existence of interfaces implies a tension between collaboration and hierarchy, transparency and obscurity. "Every module […] is characterized by its knowledge of a design decision which it hides from all others. Its interface or definition was chosen to reveal as little as possible about its inner workings" [14].

This section takes this approach, focusing on the emergence of interfaces in the current involvement of hospitals with bioprinting research.

3.1 Hospital-academic interfaces

One of our interviewees, a biomedical engineer based in Italy, is engaged in an international collaboration whose goal is to produce a bioprinter that could be used in hospitals. The device would bioprint new living structures directly into the patient's body. According to this interviewee:

> I want to repair the tissue using the same cells of the patient, so I need something that is directly in the surgical room because I can take the cells directly from the patient, feed the syringe [of the bioprinter] and use the cells in order to reconstruct this tissue, in order to be sure that there is no rejection […].

This kind of approach has been described as *point-of-care manufacture*, a model of decentralised production of therapies. Thus we are dealing with a type of redistributed manufacturing that can accord new functions and responsibilities to hospitals [21]. Nevertheless, not everybody based in a hospital, and especially people with exclusive clinical responsibilities, is always aware of these trends, as well as of technological developments. One of our British interviewees, an academic researcher with 3D printing collaborations with clinicians, declared:

> […] it's been a very slow process for hospitals to realise the potential and the possibilities behind these 3D technologies. We've seen, not many clinicians know about the technology or they don't know how to use it or they simply don't know if there are people next to them that have all this technology available.

Hospital-based researchers and clinicians, in order to be capable of applying these 3D technologies, will need to become accustomed to a new kind of digital infrastructure, including software. Our data show that hospital-based researchers are getting involved in some studies where software is required. Generally, bioprinting researchers, based in hospitals or elsewhere, use a range of non-specific software packages, designed for various purposes, as illustrated in Table 2.

Table 2. Software packages cited in the 45 papers selected in our literature 10analysis: 2006-2019

Technique	Description	Software*
CAD	Design of 3D models	Autodesk, BioCAD, Mimics, Pro Engineer, SolidWorks, **Tinkercad**
CAM	Control of the process that generates a bioactive structure	**Cura**, **Repetier**, Simplify3D, **Slic3r**
Simulation	Modelling of the printing process	Fluent
Cell analysis	Assessment of cell viability after the printing process	cellSens, **ImageJ**, NIS Elements
Statistics	Performance of statistical operations	GeneSpring, GraphPad, MatLab, SPSS
Calculations	Conduct of other measurements, such as measuring the dimensions of a bioprinted structure	Avizo, BlueHill, **FEBio**, ImagePro, iNMR, **R**
Data visualization	Preparation of tables, charts, and images	Photoshop

* Open source packages are indicated in bold letters

Table 2 shows that most software packages currently used in bioprinting are not dedicated bioprinting software but packages that happen to be useful in bioprinting work. Of the 25 packages cited in the papers identified in our bioprinting literature search (papers with at least one author based in a hospital), only one is exclusively dedicated to bioprinting: BioCaD, released in 2007 by regenHU (a bioprinting company) and used for the modelling of the structures to be printed.

Moreover, bioprinting processes tend to combine different software packages. In our literature search, 26 papers mentioned at least one software package being used by the authors. Considering only those papers, we identified an

average of 1.8 software package cited per paper. Even if each package has no clinical potential, their combination brings about a cumulative effect, insofar as they are used in the framework of biomedical research that can eventually produce a clinical therapeutic product, most likely an ATMP tissue-engineered product. In this sense, software reinforces the proto-clinical nature of bioprinting. Moreover, we can envisage that future regulatory frameworks can target not only particular software packages but also the combination of different non-medical packages, associated as "software steps" with at least some degree of improvisation from the user.

To be sure, some researchers have considerable mastery of digital resources. For example, a 2016 paper published by Xiang and colleagues has authors based in two institutions only, two Chinese military hospitals: Southwest Hospital (city of Chongqing) and the 452nd People's Liberation Army Hospital (Chengdu). In this study, a bioprinter constructed by the researchers was used. According to the authors: "The bioprinter is controlled by software written by our laboratory" [22]. We are then dealing with an advanced exploration of bioprinting by hospital-based researchers capable to customize the bioprinting technologies they use.

However, this was the only example of such sophistication found in our literature analysis. Other hospital-based researchers are still relying, for the most part, on the technical expertise held by universities, as illustrated in Social network 1.

Social network 1 appears here

For producing this network, we considered every author from each selected paper, including authors based in universities, research institutions, and companies. The hospital-affiliated authors (that is, authors whose institutional address is connected with a hospital) are identified as 1st, 2nd or 3rd hospital in the authors list, regardless of the actual number or line-up of all authors. No paper involved four hospitals or more. Thus Social network 1 portrays research collaborations, not research leadership, as we have not at this point tried to identify, for example, the pattern of affiliations of first authors or principal investigators. Furthermore, the network focuses only on the collaborations built up by hospitals, ignoring the connections between universities, between research institutions and companies, and so on. The way in which we identified hospitals in the literature (that is, by considering the hospitals mentioned in

authors' institutional addresses) might have made us miss some papers where the name of a research institute is provided but not the name of the hospital. However, as most journals provide full addresses, it's very unlikely that we missed many papers for this reason.

Social network 1 shows how many times hospitals appear as collaborators of other institutions (including other hospitals) in research publications. For example, in a publication involving two hospitals and three universities, we considered one connection between "1st HOSPITAL" and "2nd HOSPITAL", three connections between "1st HOSPITAL" and "university," and three connections between "2nd HOSPITAL" and "university." This calculation considered institutions, not people. Thus if a certain paper had ten authors based in the same hospital collaborating with ten other authors based in a company, this would be considered as only one connection between a hospital and a company. By performing these calculations on all the 45 papers included in our analysis, we came to the ranges displayed on Social network 1. Eventually, over 100 connections (or joint publications) were found involving a university and the first hospital of the authors list, and only 1 to 4 connections between a bioprinting company and the first hospital. In social networks of this type, nodes with a small number of connections tend to be placed far away from the core. This is why the node corresponding to bioprinting companies occupy a marginal position on the figure.

It can be seen from Social network 1 that universities have been the main collaborators of bioprinting researchers based in hospitals. Furthermore, as one might expect, most of these researchers are based in teaching hospitals of universities, as seen in Table 3.

Table 3. Five first hospitals in terms of number of bioprinting papers: 2006-2019

Hospital	City	Country	Nature	Papers
Brigham and Women's Hospital	Cambridge	United States	Private university hospital	13
Zhongshan Hospital	Shanghai	China	Public university hospital	5
People's Liberation Army General Hospital	Beijing	China	Military hospital	4
Massachusetts General Hospital	Boston	United States	Private university hospital	3
Shanghai Jiao Tong Hospital	Shanghai	China	Public university hospital	3

Obviously, the relations between a university hospital and a university department are made easier by their previously established institutional arrangements. University hospitals rely on quick support from mechanical, bioengineering, and design departments [21]. Furthermore, some researchers are based, at the same time, in an academic laboratory and a teaching hospital. In this way, institutional interfaces are likely to be activated quite smoothly, in principle making the arrival of bioprinting at hospitals simpler.

Table 3 enables us to see two decisive trends. On the one hand, the relevance of the United States and China is evident; these countries are the only ones holding hospitals appearing in more than two papers. On the other hand, the United States, for lack of a comprehensive public health system, has depended on strategic decisions taken at private universities. As a consequence of such feature, bioprinting has found difficulties to be disseminated in the American territory as yet, as seen in Table 4.

Table 4. Countries with hospitals involved in bioprinting papers

Country	Hospitals	Author signatures*
China	16	79
Finland	4	6
Germany	4	38
United States	3	124
South Korea	2	2
Australia	1	2
Norway	1	1
Switzerland	1	1
Taiwan	1	5
United Kingdom	1	1

* Number of authors signing papers. If the same author signed 10 different papers, this is considered here as 10 signatures

The United States has the most productive hospitals, in terms of both bioprinting papers (Table 3) and number of author signatures (Table 4), but not the biggest number of hospitals engaged in bioprinting publications (Table 4). Furthermore, of its 124 signatures, 111 were associated with just one setting, the Brigham and Women's Hospital (Cambridge). This may have to do with the financial incentives present in the country, which might prevent doctors from favouring academic publications. China is the country with the highest number of hospitals participating in bioprinting papers, most of them linked to public universities. The leadership of China (from this point of view) reflects the strength gained by this country, which is coupling substantial growths in R&D expenditure with a sustained "ambition to challenge the Western hegemony in biomedical innovation" [23]. All the Finnish and German hospitals of Table 3 are also public university hospitals. Frequently, those hospitals collaborate with one another in the production of papers. This is seen, for example, in a paper by Schmidt and colleagues [24] showing a collaboration between the University Hospital Erlangen and the Comprehensive Cancer Centre (both in Germany). In this study two proprietary software packages were used: cellSens, with which images of bioprinted tissues were

"taken, merged and quantified"; and GraphPad, with which "graphs were designed" and "statistical analysis was performed" [24].

Therefore, the interfaces between hospitals seem to be fostered by the presence of institutional networks spread across the national territory. As university hospitals share clinical and teaching goals that are also present in academic groups, in addition to being more or less attuned to national health directives, it becomes easier for them to engage in pre-translational bioprinting collaborations, fostering the current proto-clinical nature of bioprinting activities.

This is not to say that hospital bioprinting researchers have failed to establish interfaces with private companies, as seen below.

3.2 Hospital-commercial interfaces

According to one of the tenets of the modular organization of software: "At implementation time each module and its inputs and outputs are well-defined, there is no confusion in the intended interface with other system modules" [14]. Even though social life is much messier than the structures of algorithms, social players are frequently in need of a similar clarity, enabling them to know what to expect from other players. However, the current lack of specific regulations for bioprinting, and especially its clinical dimension, can hamper such clarity.

For example, one of the Brazilian companies interviewed in our fieldwork is producing bioprinters which are sold, for the most part, to academic researchers. This kind of interface is reliable because, when sold to academics, bioprinters are not framed as medical devices but as laboratory equipment. According to the company's manager, this preferred contact with academic groups has to do with the country's regulatory framework. Even though there are regulations for medical devices and advanced therapies, Brazilian regulations have not yet addressed the clinical side of bioprinting, making it difficult for companies to approach potential users based in hospitals. If specific regulations were in place, the company's strategy could be different.

> I would think about the area of regenerative medicine, which is a richer field. I could develop cardiac segments (let's imagine), cartilaginous segments, bone

segments […] So, yes, I would have a bias towards the medical field if the regulations had been created […].

As a consequence, hospitals have been ancillary clients for bioprinting-related companies, as illustrated by Table 5, with data from our online survey.

Table 5. Relations of the 23 companies involved in the online survey

Company's relation with…	As R&D collaborators	As clients
academics	21	19
research institutions	16	16
other companies	16	9
government agencies	8	3
hospitals	8	1
others	0	3

The online survey confirmed the relevance of software for bioprinting. Of the 23 participating companies, 14 develop software or plug-ins, most of them realizing such task within the company instead of hiring external services. However, the survey also demonstrated a still modest engagement with hospitals. As seen in Table 5, the companies participating in the survey have key relations with academics. A total of 21 companies declared to have R&D collaborations with academics whereas 19 declared to sell products or services to academics. The relevance of hospitals is clearly smaller. Even though a considerable number of companies (8) have research collaborators based in hospitals, only one have sold products to hospitals. The latter are then playing a minor commercial role, which can be explained, among other things, by the regulatory uncertainties mentioned above.

As we claimed elsewhere [25], medical product regulation is both enabling and controlling of innovation, typically balancing the interests of public health safety and those of scientific and commercial entrepreneurship. Bioprinting and its products have not yet been framed by regulatory frameworks globally, and different evolving approaches are under debate [17, 26]. In the European Union, the ATMP Regulation sets a framework for regenerative products but it does not deal with software, which is covered by medical device regulation if it is deemed to have a medical function.

This status has been evolving, is most recently enshrined in the EU's new Medical Device Regulation, and has already informed the first judicial decisions [27]. Guidance on qualification and classification of software used as a medical device has been published. Furthermore, the biological parts of a bioprinted product can be considered as an ATMP product whereas its non-living parts can be considered as a medical device [28], adding complexities to the regulatability of bioprinting and its products.

The regulation of bioprinting is challenged by the technology's hybrid nature, with materials coming from various sources, integrated software, and the uncertain classification of bioprinted products [29]. Thus decisive regulatory decisions remain to be taken, such as the choice between a regulatory emphasis on the printing process or on the printed product, as well as the choice between relying on existing regulations or creating a totally tailored framework for bioprinting [30].

Regulators are becoming aware of such issues. For example, one of the British regulators we interviewed spoke of the shifts that can occur in hospitals as a consequence of techniques such as bioprinting. A distributed point-of-care model, in which clinical production would happen in different sites, would be difficult to oversee:

> What I think is becoming an issue […] is, if that manufacture occurs in a distributed way within the hospitals […] In terms of actually supervising what goes on in the site, there's nothing completely new in terms of GMP [good manufacturing practices]. What is […] tricky is how you license lots and lots of sites and make sure they're manufacturing to a consistent quality.

In addition, one might imagine that different manufacturing sites could be bioprinting similar products while using different software packages.

In this evolving situation, the relations between bioprinting companies and hospitals have developed in terms of research goals, instead of pursuing more applied or even clinical targets. For example, one company we interviewed, based in a European country, is collaborating with a hospital, aiming at bioprinting abdominal masses that could be used therapeutically.

> […] since the regulation is not written, we cannot go into clinical now, but they are making the research in the hospital to take the knowledge from the doctors to try to offer the best solution.

Such developments, even at this limited phase, show the growing institutional partnerships that testify to the proto-clinical emergence of this technology.

In our analysis of the commercial bioprinting landscape, we have identified 83 companies operating in 38 countries. They range from companies partially dedicated to bioprinting, offering products such as bioinks, to fully dedicated companies producing bioprinters or helping academics bioprint tissues for specific studies. There has been considerable research interaction between those companies and researchers based in hospitals. For example, American bioprinting company Organovo is collaborating with researchers based in the Royal Children's Hospital (Australia) to develop a bioprinted tissue formed of stem cells for treating kidney disease [31]. Chinese bioprinting company Revotek, in collaboration with researchers at the West China Hospital (linked to Sichuan University) is developing bioprinted blood vessels that could eventually be transplanted into patients' bodies [32]. And Brazilian company 3DBS is collaborating with the private hospital AC Camargo in the development of in vitro tumour models for the study of cancer [33].

Bioprinting companies, because of their specialized activities and focused interests, are key for the long-term clinical translation of bioprinting technologies. They have been very proactive in the establishment of research collaborations, as seen in Social network 2.

Social network 2 appears here

Social network 2 shows the collaborations of bioprinting companies, including collaborations with universities (their main partners), other bioprinting companies (identified as "other bioprinting"), pharma companies, and so on. For the construction of this network, we visited the website of each of the 83 bioprinting-related companies identified in our study. For 38 of them, information on research collaborations was available. For example, a certain company may collaborate with ten universities, five research institutions and two hospitals. Thee numbers were added to those of the next

company which may be collaborating with three universities and one pharma company. The final numbers were used to define the levels of collaboration shown on Social network 2. The biggest number of connections (over 100) was found between bioprinting companies and universities.

Hospitals were divided into two groups, depending on whether the hospital is located in the country where the bioprinting company has its headquarters (DOMESTIC HOSPITAL) or in a different country (FOREIGN HOSPITAL). It can be seen that foreign hospitals have not been major collaborators, being at the level of chemical and IT companies (11 to 25 connections) but domestic hospitals have been relevant partners, being at the level of pharma and electronic companies (25 to 50). Therefore, the lack of specialised regulations, in spite of possibly slowing down the translation of studies into clinical products, has not prevented the construction of interfaces between hospital-based researchers and companies exploring bioprinting. Moreover, some might claim that regulations, when set up too early, before the maturity of a technological field, might stifle the industry instead of fostering it. Either way, if current partnerships cannot yet take a clinical form, they can nevertheless build and reinforce the proto-clinical nature of bioprinting, enabling a deeper and increasingly shared knowledge of materials, bodily structures, cells, and other concepts that lay the groundwork for the future emergence of therapies.

In addition to research collaborations (which are accounted for in Social network 2), some hospitals have had commercial relations with bioprinting companies, acquiring bioprinters (and related software) for some studies. As explained by one interviewee, based in a bioprinting company which is located in Europe and sells bioprinters:

> [….] we are very competitive in the market and it is easy for them [researchers] to get one of our systems, since, normally, all the academics and hospitals are involved in European or international projects. They have enough funding to fund this kind of tools. What we do to […] offer better solutions is to give always 30 hours of training so we can support them the whole time and we are always in contact with them.

One of the main topics covered in these training sessions is the use of the software needed for the operation of the bioprinter. In this way, by means of research

projects, collaborations, and commercial relations, hospital-based researchers are gradually providing hospitals with interfaces that announce a period when digital resources will be used in more intense ways in clinical settings. Nevertheless, a key challenge is, once again, the uncertainties with which such software use has to occur today. As we showed elsewhere [34], the lack of specialised regulations for bioprinting creates a context where extant applicable laws tend to be less effective than the agreements between software developer and user, which are formalized in software licenses. At the moment, these licenses of software, whether they are open source or proprietary, are used by software developers to keep clinical responsibilities at bay, because, as those developers hasten to point out, their packages have not been certified for clinical use. As the clinical phase of bioprinting approaches, the licenses of individual packages, which are now quite vague, are likely to become more specific, addressing topics such as data sources, data sharing, software-hardware interfaces, and interaction with other packages.

On the one hand, hospital-based researchers are beginning to become aware of the digital readiness that bioprinting requires. On the other hand, however, the initial steps taken today will be crucial for a more robust use of software in the future, whether this is done in bioprinting activities or other digitalised biomedical fields.

3.3 Hospitals' internal interfaces

It was claimed above that hospitals are building up interfaces that will make them capable of using bioprinting in more comprehensive ways in the future. It will also be necessary for them to set up internal interfaces, because the adoption of a new activity such as bioprinting will ultimately require an effort of institutional reorganization. If it is not yet possible to precisely indicate what features this reorganization will take for the case of bioprinting, we can at least point to some trends by considering what is happening in hospitals that are exploring a similar domain: 3D medical printing (the use of printers to produce three-dimensional objects without living cells).

One of our Italian interviewees is a surgeon based in a hospital where a 3D printing research lab has been established. The main goal is to produce surgical guides and models that mimic diseased organs and help doctors plan surgeries. According to this interviewee:

> […] the real advantage of the […] lab is that it is inside the hospital. So the engineers can come to our surgical room, can see the procedure and then they can understand what the problem is, how to solve it using a way that can be used during the surgery. Because sometimes the problem is that the engineer is thinking a solution that could not be applied in the surgery, because this is the solution but will it work with a real patient?

Therefore, the use of 3D printing in this hospital has required not only the presence of a new actor in the clinical setting (the engineer) but also a new kind of interdisciplinary or multidisciplinary dialogue between the clinical staff and the engineering team. Thus new kinds of internal institutional interfaces must be in place. Drawing on this initial experience with 3D printing, this hospital is beginning to explore 3D bioprinting by means of a collaboration with an external academic laboratory. However, such collaboration has evolved less quickly because it "[…] requires more time, it's more difficult to bring the engineer and come to the surgery but we try to make something work."

Another example comes from the Washington University Medical Campus, where a large 3D printing centre has been established at the Barnes-Jewish Hospital. The resulting 3D-printed models have been used in the planning of surgeries but also in teaching activities of the university. According to information we collected in a webinar on the 04th of April 2019, the creation of such 3D printing facility has led to the design of an actual workflow involving suppliers and different departments of the hospital. The procedures begin with the collection of medical images by means of magnetic resonance or computed tomography scans. In the next phase, images are segmented and processed with computer software, generating a CAD model. After being reviewed by surgeons and engineers, the model is printed, used, and stored in a specially reserved area. For the generation of computer models, the hospital uses Materialise, proprietary software which has recently received clearance from the FDA [35]. Every year, around 8,000 dollars (around 6,000 British pounds) are spent with the software license.

Therefore, this example shows that the adoption of a new technology creates a need for the construction of external interfaces (with suppliers), internal interfaces (connections between different hospital sections), and the emergence of new costs

associated with machines and software packages. Such institutional reorganization will have to be further streamlined when the hospital finally incorporates 3D bioprinting, as it is planning to do in the years to come. For example, in terms of cost efficiency, there have been some initiatives aimed at producing open source, low-cost bioprinters [36, 37] but, at least at the beginning, hospitals are more likely to opt for proprietary printers and software, as they tend to be more intuitive and more conducive to a quick learning process.

The example of software license costs given above also makes it salient that digital readiness has a financial dimension. Our analysis of the bioprinting literature showed that proprietary software has been the main digital resource used by bioprinting researchers, as noticed in Table 2. Indeed, of the 26 software packages cited in this literature, only 7 (or 26.9%) are open source. This situation limits the bioprinting studies participated in by hospitals in two ways. First, the expenses made with software licenses may be too budget-consuming, especially when it is necessary to combine different software packages. Second, as we showed elsewhere [38], the use of proprietary software may bring about methodological limitations; open source software can enhance the scope and innovativeness of research, as source code can be modified to allow novel research approaches.

The increasing use of software places institutional demands on ethical issues of data privacy, security and processing. In Italy, we interviewed a bioprinting research group based in a hospital. The group has access to some tissues collected in clinical departments of the institution. As explained by one of the team members:

> Since […] we are in an [medical] institute around many, many surgical procedures […], people who undergo these surgical procedures give informed consent to give us tissue […].
>
> Along with tissues, the group may be provided with some data.
>
> Sometimes if we need to do some statistics for our work, we need to add also the characteristic of the patient, if the patient takes some drugs, the age, the gender, many clinical information. But every work, every research in our institute undergo analysis by an ethics committee from our institute.

Here, the reference to an ethics committee is understandable, because there are questions to be considered such as safety, confidentiality, and other issues. The digital dimension places institutional demands on ethical issues of data privacy and security. Thus bioprinting activities sharpen old dilemmas of clinical research, whereby clinicians-researchers need to decide if their procedures lie "within the limits of their rights as investigators" or if they are somehow overlooking "[…] those rights by subjecting the patients involved to more inconvenience and danger than the possible significance of those experiments for the 'advancement of health, science, and human welfare' […]" [39].

We showed elsewhere [30] that in the European Union, there is a current debate on the possible revision of the Product Liability Directive (PLD), designed to incorporate matters of digital integration into products [40]. Focusing again on liability, it is clear that this will impact the interaction of technological and institutional readiness of and for bioprinting. Particularly significant for bioprinting, in the PLD review, is the stakeholder discussion about the implications of digitalisation for the definition of the 'product' and the 'producer' [41]. Notably, for a product, 'there is a growing interaction between physical products and digital services,' while for the producer clarification is required to take account of 'who should be the producer in the case of an update, upgrade or modification' to software or digital services [42]. Such assignments of legal liability are key to the future readiness of bioprinting and its digitalised production.

The arrival of bioprinting at hospitals will surely entail shifts of considerable scale. In addition to the engineering dimensions of the field, it will be necessary to deal with its biological dimension, which may involve techniques such as the bioprinting of stem cells or gene-edited cells. In theory, 3D bioprinting clinical facilities are likely to be staffed with not only engineers but also professionals such as biologists, bioengineers, data analysts, software specialists, and others. There are then certain implications for the skills and training of existing and future hospital-based staff, as also noted by Munguia and colleagues [21]. In the UK, for example, training in clinical bioinformatics, including software engineering skills as part of clinical science, is moving in this direction [43].

Thus new knowledge and skills need to be mobilised. One our British interviewees spoke of recent changes undergone by some NHS hospitals:

> […] the NHS trusts of different regions, they realised they need another type of professional. They not only need […] medical physics clinicians or engineers, they started having a new position called 3D printing analyst and 3D printing technician. And some hospitals have 3D printing engineers […] I can think of Sheffield, I can think of Wales […] And I know, in some cases, for example, they hire industrial designers and they reconvert them into medical device experts. That's the case with at least two people that I know.

It can be expected that in the future, the range of expertise necessary to master 3D printing and bioprinting at hospitals can include all the knowledge necessary to make printers operate not only precisely but also safely. Hence the relevance of some studies like the one conducted by Petretta and colleagues [44] where a "[…] risk assessment model for the use of 3D printer machines producing engineered […] tissues" is delivered.

To sum up, the arrival of bioprinting at hospitals will require a series of preparedness measures in the form of institutional arrangements and strategic decisions. In this process, the internal and external interfaces of hospitals will need to be reshaped so as to guarantee a workable level of coordinated interactions. Or, coming back to Parnas' [14] computer science terminology: "We may make only those changes which do not violate the assumptions made by other modules about the module being changed. In other words, a single module may be changed only as long as the 'connections' still 'fit.'" When the right balance is finally struck, hospitals will be able to leave the proto-clinical phase of bioprinting, ceasing to be just analogic hospitals and moving "towards the digital hospital" [21].

4 Discussion

Hospital environments are increasingly permeated by digital technologies in a multitude of forms, not only in IT infrastructures and data communications but also through the incorporation of digitalised biomedical technologies. It is difficult to find precise data about the current relevance of hospitals for the digital market at large. Such assessment is beyond the scope of this paper, which focuses rather on the particular example of bioprinting. We have presented various research findings concerning the digital readiness of hospitals from the viewpoint of their early proto-

clinical exploration of the features of bioprinting. In the course of this exposition, we have reviewed the emerging interfaces that can enable hospitals to adopt the knowledge and the technologies required by the bioprinting field, a condition that we have termed digital readiness.

Initially, we showed how some hospital-based researchers have engaged in collaborations with academic researchers. Even though the United States holds the biggest number of papers and authors, China is the country with most hospitals involved in bioprinting research. This phenomenon is important, insofar as digital readiness in bioprinting at this point seems to be associated with the capacity to spread research activities through public research networks, and mainly those where university hospitals are key stakeholders.

The partnerships between hospitals and bioprinting companies are also crucial, since those companies have played outstanding roles in accelerating the translational side of bioprinting. Even though those partnerships have been limited by the current state of regulations, which do not address the clinical aspects of additive manufacturing in detail, we have given some examples of collaborations between hospitals and companies which are promising in terms of therapies. Moreover, bioprinting companies have provided hospital-based researchers with specialized training, including the contact with different software packages, thus speeding up digital readiness.

We also claimed that some hospitals are beginning to remodel their internal interfaces. This has been promoted by their exploration of 3D medical printing, while some hospitals are taking the first steps in their work with bioprinting, though not necessarily at institutional, structural levels. Such process encompasses the arrival of new players at clinical settings (such as bioengineers and software specialists) but also the compliance with new standards (such as those pertaining to the safety of bioprinters).

In order to make sense of these ongoing, potential, and future shifts, we have mobilised the concept of interfaces, as proposed by computer scientist David Parnas. We claim that digital readiness will require that hospitals adjust their connections with other players in focused ways, framing each group of partners in a way akin to modules within a software package. By mobilising a notion from computer sciences, we do not intend to claim that hospitals would be able to undergo social and institutional shifts in precise and tidy ways. To be sure, many would associate the

image of software development with a highly technical task endowed with an almost mysterious aura [45, 46]. However, computer scientists, including Parnas himself, are the first ones to recognize that software design is a messy and intuitive process. "[…] the picture of the software designer deriving this design in a rational, error-free way from a statement of requirements is quite unrealistic. No system has ever been developed in that way, and probably none ever will" [47]. By the same token, the interfaces built up by hospitals will surely evolve in hesitant and tentative ways, until viable balances are finally struck. Such institutional rearrangements bring about challenges pertaining to hospitals' internal and external relations. Thus we are dealing with a typical example of institutional readiness having to do with "[…] both the intra- and extra-organisational dynamics that shape the ways in which innovative technologies are given meaning, adopted and implemented" [12].

As different hospitals find themselves in different stages of such process, the changes that they may undergo are not likely to follow standardized pathways. Thus even though this paper raises some questions that will be worth considering in the future, it is not possible, at this point, to delineate a definite roadmap or pathway to be followed by hospitals in the years to come. Different solutions will possibly be successful for different institutions and researchers.

But beyond institutional readiness, we have claimed here that in the case of digital-intensive technologies such as bioprinting, attention must also be paid to the issue of digital readiness. Irrespective of the forms that the clinical evolution of bioprinting may take, it is sure that software will be a crucial tool. As pointed out by Kengla and colleagues [48], the clinical promises of bioprinting will not be kept without further developments on the software side. The field open to improvements is wide, and emergent approaches include internet-of-things elements and artificial intelligence techniques [6, 49].

To be sure, all the burdens will not, and should not, fall on the shoulders of clinicians, hospital-based researchers, and hospital administrators alone. Regulators will have to deal with thorny questions having to do with the ways in which software should be framed by laws and directives, especially in its clinic-related applications and in its as yet uncertain position in product liability. Academics have been key players in the development of new algorithms and whole software packages for bioprinting, and we can expect that they will continue to be so. Likewise, companies, and particularly specialized bioprinting companies, will continue to constitute bridges

between basic research and applications of ever-growing clinical features. However, much of digital readiness in bioprinting will be constructed inside hospitals as proto-clinical interfaces are consolidated and eventually gain an institutional translation into clinical applications. With a wise adaptation of workflows, relations, and infrastructure, software can eventually become an additional clinical tool in the hands of future surgeons, clinicians, and medical additive manufacturers.

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