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Master thesis - Innovation Sciences

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3D BIOPRINTING HUMAN ORGANS: AN UPCOMING SOLUTION FOR THE GLOBAL HUMAN ORGAN SHORTAGE

*EXPLORING THE INSTITUTIONAL READINESS OF HOSPITALS
WITHIN CALIFORNIA AND THE NETHERLANDS CONCERNING
THE BIOPRINTING ORGANS INNOVATION SYSTEMS*

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Abstract

With the increasing shortage of human organs globally, 3D bioprinted organs appear as a suitable solution. While its technological developments are often explored, little is known about the emerging 3D bioprinting organs innovation system (3D-BOIS) and its adoption at an organizational level. Hence, this research focused on two illustrative cases: University of California San Francisco Medical Centre and University Medical Center Utrecht. California is the frontrunner concerning 3D bioprinting organs, whereas the Dutch appear to be catching up. Hereby, developments from 2009 have been chosen as the Californian medical laboratory Organovo had a significant breakthrough in 3D bioprinted organs, resulting in the following research question: "*What are the barriers and potential solutions concerning hospitals' Institutional Readiness for the innovation system of 3D bioprinting organs in California and The Netherlands based on the emerging 3D bioprinting organ innovation system developments throughout 2009 – 2020?*". To answer this question, the Technological Innovation System (TIS) and Institutional Readiness (IR) approach were combined into an integrated conceptual framework. The former was applied to obtain insights into hampering aspects in the emerging 3D-BOIS. An event analysis was performed, using information from desk research, on five out of the seven system functions: 1 (*Entrepreneurial activities*), 3 (*Knowledge diffusion*), 4 (*Guidance of the search*), 5 (*Market formation*), and 7 (*Creation of legitimacy*). The IR was applied as specific barriers can arise for healthcare innovations on an organizational level. This was analyzed by conducting semi-structured interviews with experts, either experienced within organ transplantations or innovations surrounding organ shortage. The findings indicated two common barriers for both 3D-BOIS's: 1) the need for a regulatory framework for 3D bioprinted organs and 2) the necessity for financial support by the Dutch government and venture capitalists in California. Further, two specific barriers were observed for the Californian and Dutch 3D-BOIS. Regarding the former, key actors within the Californian hospital are not fully aware of how different actors perceive 3D bioprinting technology nor which novel technologies can solve organ shortage. Concerning the Dutch 3D-BOIS, a high dependency on Dutch governmental institutions for financial resources for 3D bioprinting research and the ability of Dutch hospital staff to anticipate organizational challenges during the adoption of 3D bioprinted organs were observed. Further, this study corroborates a connection between the system functions and IR categories as the interactions between innovation on systemic and organizational levels are shown. Lastly, as this thesis focuses on developing the 3D bioprinting organs' innovation system technique, it provides a good starting point for developing a refined, integrated framework for interactions between TIS and IR.

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*"It is not the strongest of the species, nor the most intelligent,
but the one most responsive to change."*

– Charles Darwin.

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List of abbreviations

3D	Three-dimensional
3D-BOIS	Bioprinting organs innovation system
AAAS	American Association for the Advancement of Science
EMA	European Medicines Agency
Erasmus MC	Erasmus Medical Center
EUR	EURO
EZK	Ministry of Economic Affairs
FDA	Food and Drug Administration
IP	intellectual property
IR	Institutional Readiness
IS	Innovation System
KPMG	Kleynveld Peat Marwick Goerdeler
MLP	Multi-Level Perspective
MOSI	Museum of Science and Industry
NIH	National Institutes of Health
NKCA	Netherlands Knowledge Centre on Alternatives to Animal Use
NOTA	National Organ Transplant Act
R&D	Research and development
SF analysis	Structural-functional analysis
THO	Transplantation of Human Organ Act
TIS	Technological Innovation System
UCLA	University of California Los Angeles
UCSF	University of California San Francisco
UK	United Kingdom
UMCG	University Medical Center Groningen
UMCU	University Medical Center Utrecht
USA	United States of America
USD	United States Dollar
UU	Utrecht University

1. Introduction

Global organ shortage is a well-known problem worldwide, with an increasing number of patients on the donor waiting list. The current organ transplantation procedure consists of organ donation from either a deceased human or a living one. However, the latter is only applicable for some organs, such as a kidney or part of the liver (HRSA, n.d.). Furthermore, the ongoing COVID 19 pandemic exacerbates the shortage problem as the number of organ donations decreases steeply (NTS, 2020a; Penn Medicine News, 2020). This is mainly due to the lack of personnel to perform a donation procedure and the longer time needed for careful examinations of all donor organs to ensure minimum risk of COVID-19 infection in the organs (McKinsey & Company, 2020; Nature, 2020).

Researchers began as early as the 18th-century with experiments to cope with organ shortage. However, it was not until the mid-20th-century that organ transplants could be carried out successfully (HRSA, 2020a). The discovery by the Belgian microbiologist and immunologist Dr. Jean-François Borel of cyclosporine, a drug that prevented the rejection of new organs in the patient's body, was a huge factor behind this success. Unfortunately, in the following years, the need for organ transplants started to exceed the supply (History, 2018). Therefore, researchers continued studying alternatives, namely tests with animal organs to use as human transplants, ultimately to find a way to mitigate the lack of organs. In the current era, which is characterized by rapid technological developments that increase convenience for individuals in every area, an innovative solution for the donor shortage could not be left behind (IGI Global, 2020). Not surprisingly, a promising technology emerged, in 1999, before the break of a new era, named three-dimensional (3D) bioprinting of human organs. A year later, in 2000, 3D bioprinting of organs gained visibility as scientists worldwide believed that within the following year a kidney could be 3D bioprinted (The Guardian, 2019). In fact, 3D bioprinting of organs holds great potential to tackle the issue of organ shortage globally and can be defined as the following: "*computer-aided transfer processes for patterning and assembling living and non-living materials with a prescribed layer-by-layer stacking organization in order to produce bio-engineered structures serving in regenerative medicine and other biological studies*" (Mitchell, 2017, p.11). As opposed to the conventional organ donation procedures, 3D bioprinting of organs is faster since the tissue can be printed on request, thereby reducing waiting time for patients. Also, 3D bioprinting of organs enable the creation of human organs with a high degree of anatomical precision, which is beneficial for the body's uptake of the organ (Ravnic et al., 2017).

Currently, the United States of America (USA) is the leading country in the technology of 3D bioprinted organs, with 39% out of the 119 (and counting) established bioprinting companies worldwide, followed by Europe with 35%. In fact, California is perceived as a '3D printing hub' due to the high number of biotech companies based there (Listek, 2019). In 2009, the laboratory Organovo in California succeeded in developing the first bioprinter for the commercial market and used it to create a biodegradable blood vessel, as shown in figure 1 (Invetech, 2009). Moreover, in



Figure 1: Printed blood vessel by Organovo (Kupper, 2010)

September 2020, a team of researchers from the Utrecht University (UU) and University Medical Center Utrecht (UMCU) in the Netherlands received a grant of 1.8 million euros from the European Research Council for developing a 3D technique that can supposedly reproduce parts of the human body, including living cells, within minutes (Utrecht Universiteit, 2020). These (promising) advancements are essential as both California and the Netherlands are coping with an increasing organ shortage. For instance, in the Netherlands, the number of patients waiting for a donor organ increased since 2015 by 30% to 1271 patients in 2019 (NTS, 2020b). In California, the donor waiting list grew since 2014 by 10% to approximately 23,000 in 2019 (Donate Life California, 2014; HRSA, 2020b).

Several studies focused on the opportunities and challenges of the techniques of 3D bioprinted organs. For instance, Murphy & Atala (2014) focused on the technical challenges of bioprinting since it involves complex aspects, such as cell types and material choice. Both Ozbolat & Hospodiuk (2016) and Udofia & Zhou (2019) concentrated on one of the four 3D bioprinting technologies¹, namely extrusion-based bioprinting, because of its substantial developments. The former researchers discussed the technological advancements and future pathways to develop human organs, while Udofia & Zhou (2019) put forward a framework with parameters regarding the resolution of the 3D bioprinting process that can impact the 3D bioprinted human organ. While the technical possibilities received ample attention, the (barriers for) implementation considerably remains unidentified. For example, Vermeulen et al. (2017) and Gilbert et al. (2018) pointed to a lack of consequences of implementing the technology of 3D bioprinted organs due to its complexity. Research upon the legal aspects of 3D bioprinted organs conducted by Kirillova et al. (2020) concluded the following: "[...] globally, there is neither suitable statutory framework nor special regulatory guidelines governing 3D bioprinting of tissues and organs and their further transplantation" (p. 7 - 8). The absence of a regulatory framework can hamper the adoption of 3D bioprinted organs in an organization. In this study, the organizations are the hospitals since those already have specific organ transplantation practices in place and hospital staff are in the front line to perform the donor procedures. Other barriers for the 3D bioprinted organs can arise from the lack of acceptance stemming from hospital stakeholders, such as specialists and patients, which was also pointed out by the Swedish American entrepreneur Erik Gatenholm, who created the world's first universal bio-ink (The Guardian, 2017). Consequently, questions are raised about implementing and adopting 3D bioprinted organs on an organizational level, namely within hospitals.

Henceforth, this research aims to obtain insights into the extent to which hospitals can adopt the technology of 3D bioprinted organs. For this, an analysis will be performed on the emerging 3D bioprinted organs' innovation system (3D-BOIS) in California and the Netherlands between 2009, which marked a significant breakthrough, and 2020, the starting year of this study. The Americans pose to be the front-runner regarding bioprinting organs, whereas Dutch researchers received a grant for a significant 3D bioprinted organs advancement in 2020, indicating that the Dutch are catching up. This could be because they are following a more advantageous path from which the Americans can learn and improve their 3D-BOIS, or the Dutch follow a similar path to the Americans and, thereby, can learn

¹ Jiang et al. (2019) discerned the following four bioprinting technologies:

Extrusion: Materials are loaded into the cartridges and extruded from a nozzle, which can be done via pneumatic or a mechanical system.

Stereolithography: A laser travels follows a preprogrammed path to develop either a one or multiplied layered structure.

Inkjet: Through small volumetric changes in a nozzle, a droplet discharge downstream is created to obtain the desired 3D structure.

Laser-Induced Forward Transfer: A pulsed laser beam is the driving force to project material from a donor thin film toward the receiving substrate.

from the front-runner case. In order to obtain more insight into the 3D-BOIS, an innovations systems (IS) approach will be applied, in which innovation is seen as a collective effort that involves many actors, technologies, networks, interactions and institutions (Edquist & Johnson, 1997). Edquist & Hommen (1999) mentioned that innovation is a systemic process, which potentially involves influences from interlinkages among elements of the innovation process. In order to study the emergence and embedding of 3D bioprinted organs over time, in this thesis, the Technological Innovation System (TIS) is applied. The TIS consists of seven elements, so-called system functions, which interact with each other. This interaction can be analyzed to observe the dynamic surrounding a specific technology, in this case 3D bioprinting of organs. Consequently, the dynamics can point out which system functions hamper or stimulate the diffusion of 3D bioprinting of organs (Hekkert et al., 2007; Bergek et al., 2008, 2015). Since the TIS can only assess the barriers on a systemic level, this study also incorporated the Institutional Readiness (IR) framework of Webster & Gardner (2019) to complement the TIS. The IR framework concentrates on the institutional framework, which refers to aspects such as values, norms that shape the interplay of social and economic factors regarding organ donations and social expectations (Scott, 2001). The IR framework complements the TIS by specifically assessing the barriers in the development of 3D-BOIS within hospitals. As mentioned before, the organizational and institutional aspects concerning 3D-BOIS are vastly unexplored. As Webster & Gardner (2019) explained, for the development and diffusion of technology, in this case 3D bioprinted organs, it is essential to understand the institutional framework to understand to what extent organizational and institutional aspects are hampering. Subsequently, this will also indicate if the organization, namely the hospital, is ready to adopt the technology of 3D bioprinted organs. This leads to the following research question:

What are the barriers and potential solutions concerning hospitals' Institutional Readiness for 3D bioprinting organs in California and The Netherlands based on the emerging 3D bioprinting organ innovation system throughout 2009 – 2020?

The theoretical contribution of this research is a further understanding of the innovation system surrounding innovations in the life sciences field, particularly regarding emerging bioprinting organ innovation systems. Kukk et al. (2016) also indicated the importance of institutional aspects in healthcare innovations as they can pose sector-specific barriers. Hence, an adaptation of the TIS, which was initially developed for sustainable technologies in the energy sector, is required for the field of life sciences. For instance, medicines cannot freely enter the market immediately as it requires approval from the European Medicines Agency (EMA) in Europe or the Food and Drug Administration (FDA) in America. Also, patients are bound to health insurance, which covers part of the cost and has certain restrictions. Furthermore, the ethical barrier is also higher in life sciences (Amalberti et al., 2005). For instance, researchers, such as Vermeulen et al. (2017) and Gilbert et al. (2018), already placed questions about how ethical it is to 3D bioprint human organs as the need for a living or deceased human donation will possibly be diminished. These aspects are not fully incorporated yet in the

Technological Innovation System (TIS) analysis. Hence, by coupling the TIS approach with an Institutional Readiness approach, insights can be obtained regarding which aspect (e.g., insurance, regulatory, ethical acceptance, etc.) is lacking at a systemic and organizational level. Subsequently, specific solutions can be implemented to solve these barriers and stimulate the performance of the 3D bioprinted organs innovation system.

Concerning societal relevance, it is crucial to understand a hospital's position regarding 3D bioprinted organs and what steps need to be taken to stimulate the transition to the 3D bioprinted organs innovation system to solve the organ shortage. Furthermore, by identifying the barriers in the 3D bioprinted organs innovation system, the proper measures can be taken for the corresponding actors, such as a biotech company or regulatory agencies. Consequently, the development and diffusion of bioprinting organs can be stimulated, which ultimately contributes to improving healthcare since 3D bioprinted organs increase the availability of human organs. Lastly, apart from these advantages for patients, an improved 3D bioprinted organs innovation system within California and the Netherlands can contribute to Californian and Dutch bioprinting companies' competitiveness. In turn, this can have a beneficial impact on the economic growth in California as well as the Netherlands.

The following sections in this research will firstly outline the theoretical framework, which includes a comprehensive description of the Technological Innovation System and Institutional Readiness approach, as well as the integrated conceptual framework that is applied to answer the research question ([section 2](#)). This is followed by a description of the methodological approach in [section 3](#), whereafter, the findings from desk research and interviews are discussed separately for California and The Netherlands ([section 4](#)). Subsequently, a case comparison is discussed in [section 5](#). Finally, a critical review of this study is provided in [section 6](#), before the answer to the research question is outlined in [section 7](#).

2. Theoretical framework

This thesis starts by explaining the theoretical concepts that were important to conduct this study. Firstly, in [section 2.1](#), the Technological Innovation System (TIS) is described, which is applied to obtain insights into the dynamics of the 3D bioprinted organs innovation system (3D-BOIS) in California and the Netherlands. As the TIS does not assess barriers beyond a systemic level, it is complemented by the Institutional Readiness (IR) framework. This framework provides insights into hampering features and the related institutional challenges on an organizational level ([section 2.2](#)). Finally, [section 2.3](#) presents the integrated conceptual framework combining these two concepts.

2.1 Technological Innovation System

This research focuses on the upcoming 3D-BOIS in California and the Netherlands, for which the Innovation Systems (IS) theory is used as a basis. The IS theory encompasses the interactions between actors, networks, institutions, and organizations, which conjointly affects technology development (Edquist, 2005). Both, Edquist & Hommen (1999) and Hekkert et al. (2007) explained that innovation has a systemic character, which can provide difficulties for an innovation to enter the market for two reasons, namely, 1) users are adapted to the existing technology, and 2) infrastructure, norms, and regulations are deeply integrated. There are several types of Innovation Systems (e.g., national, regional, sectoral, technological, and mission-oriented), each having a different focus area. Since this research centers on 3D bioprinting organs' technological application, a *Technological Innovation System* (TIS) is incorporated. The following TIS definition of Bergek et al. (2015) is made use of: "*Technological Innovation System is a set of elements, including technologies, actors, networks and institutions, which actively contribute to the development of a particular technology field*" (p.52). For this research, examples of elements are biotech companies, regulatory agencies (EMA and FDA), insurance companies, transplant organizations, hospitals, medical laboratories, the federal government of California, and the Dutch government. Recently, also researchers are applying the TIS approach in the life sciences field. For example, Kukk et al. (2016) and Moors et al. (2018) used the TIS framework to obtain insights into the development, implementation, and diffusion of innovative technologies within the field of personalized medicine.

Furthermore, Hekkert et al. (2007) described the interactions between the elements of a TIS in terms of seven functions that are essential for a well-performing innovation system, called system functions. Table 1 on the next page provides an overview of these system functions with regards to 3D bioprinting organs. The interactions between these system functions can be studied using a structural-functional (SF) analysis, an analytical tool to explore an innovation system's performance at a particular time and to identify obstacles. The SF analysis consists of two central components, being 1) four structural elements (i.e., actors, networks, institutions, and interactions) that make up the innovation system and 2) seven dynamic system functions, which are described in Table 1 on the next page (Wieczorek & Hekkert, 2012). The conducted SF analysis allows the portrayal of a feedback loop of the internal dynamics of the 3D-BOIS, which arises from the interactions between the system functions. A positive feedback loop generates momentum for an innovation. Whereas a negative feedback loop arising from

2.1 Technological Innovation System

a barrier in one (or several) system function(s) can hinder technology development (Hekkert et al., 2007). Identifying those systemic failures can point towards solutions and improve an innovation system (Wieczorek & Hekkert, 2012). This approach fits this research since the aim is to explore barriers in the 3D-BOIS of California, a frontrunner, and the Netherlands, which appears to be catching up regarding 3D bioprinting organs developments. The SF analysis provides insights into activities that either hampered or enhanced the 3D-BOIS in the two geographical locations of interest.

Table 1: Overview of the system functions for 3D-BOIS based on Suurs & Hekkert (2009)

System Function	Description
1: Entrepreneurial activities	At the center of an innovation system are the entrepreneurs, which involves risk takers that perform the innovative commercial experiments, seeing and exploiting business opportunities. For 3D-BOIS this can be experiments with 3D printers or 3D bioprinting techniques to develop human tissue.
2: Knowledge development	Research and development (R&D) activities aimed at improving the performance of 3D bioprinting organs, such as new or improved 3D bioprinting techniques.
3: Knowledge diffusion	Conferences and workshops regarding the potential of 3D bioprinting organs. Other methods through which this information is being exchanged are (policy) campaigns.
4: Guidance of the search	The extent to which actors have a positive/negative expectation about the possibilities of 3D bioprinting organs influence the choices being made, such as for investments. These expectations can be influenced by outcomes of studies, articles or policy targets.
5: Market formation	In order to stimulate 3D bioprinting organs it is necessary to facilitate the creation of a market, where this technology can grow. Hereby, a competitive advantage, such as tax exemptions or subsidies will enable 3D bioprinting organs to compete with the current organ transplantations regime.
6: Resource mobilization	Financial, material, and human factors are necessary for developments in the 3D-BOIS, e.g., investments by venture capitalists or subsidies.
7: Creation of legitimacy	The emergence of a new technology often leads to resistance from established actors. In order for 3D-BOIS to develop, actors need to raise a political lobby that counteracts this inertia and supports this new technology.

However, Suurs & Hekkert (2009) noted that not every function is equally important in every development stage of innovation, as different phases of technological development can be distinguished in an innovation process. A transition from the micro to the macro level of an innovation consists of four phases: 1) pre-development, 2) take-off, 3) acceleration, and 4) stabilization (Rotmans et al., 2011), whereby each stage has a different interaction of the system functions. Based on the key aspects that characterize technology as an emerging branch or stable path, presented by Robinson et al. (2019), 3D bioprinting organs is considered an emerging technological pathway in phase 2 *take-off* (Rotmans et al., 2011). This is primarily because new visions are still developed regarding utilizing 3D bioprinting to fulfill a societal issue, which in this case is the global shortage of donor organs. Simultaneously, several companies are pushing the early adoption of 3D printing machines (Choudhury et al., 2018; Carolo, 2020). Subsequently, according to Hekkert et al. (2011), the following system functions are essential for phase 2 *take-off*, in which 3D bioprinting organs currently is: *Entrepreneurial Activities (System function 1)*, *Guidance of the Search (System function 4)*, *Market formation (System function 5)*, and *Creation of legitimacy (System function 7)*.

2.2 Institutional Readiness

3D bioprinting organs is a relatively recent innovation, with the first breakthrough occurring merely a decade ago, and the 3D-BOIS currently in phase 2 (take-off) as mentioned above. In fact, 3D Bioprinting organs is a challenging and complex technology. Hence, actors that are involved should be ready and receptive to this 3D bioprinting technology, otherwise, the development and adoption of 3D bioprinting organs will be slowed down (Webster and Gardner, 2019). Furthermore, the TIS, as described above, might not cover all different actors and institutions involved in bioprinting organs, such as specialized bioprinting companies, hospitals, and complex supply value chains for bioprinting organs, etc. This is because the TIS focuses on barriers at a systemic level and is commonly used to obtain insight into sustainable technologies for the energy sector. Additionally, regulation and health insurance around bioprinting need to be organized in a specific way. These specific processes occur on an organizational level of the involved actors and are essential for gaining a comprehensive understanding of the hampering features in the 3D-BOIS and the related challenges on an organizational level (Webster & Gardner, 2019). Subsequently, by only using the TIS framework, institutional challenges on the micro-level (within an organization) can be overlooked. Hence, in this research, the TIS framework is complemented by the IR framework to obtain insights into hampering aspects and challenges on an organizational level within hospitals, which are experienced with organ procedures and applying bioprinting organ techniques in California and The Netherlands (see [section 3.2.2](#)). Webster & Gardner (2019) defined the IR framework as follows: “[The IR assessment involves] how new technologies are engaged with and made sense of through cultural processes and institutional structures within and outside of specific organizations” (p.1234).

Webster & Gardner (2019) set out an IR model that took recent developments in science, technology, and innovation studies into account. The IR framework assesses the organizational dynamics in adopting and implementing innovative technology in the socio-technical system, which is an aspect that is often lacking for revolutionary technology such as 3D bioprinting organs (Webster & Gardner, 2019). According to Webster & Gardner (2019), the IR of new technology can be determined based on eight categories, which do not inevitably presuppose another one (see Table 2 on the following page), being: 1) *Demand for new technology*, 2) *Strategic focus*, 3) *Relative need and benefit of new technology*, 4) *(E)valuation processes in place*, 5) *Enacted IR* 6) *Receptivity*, 7) *Adoptive capacity* and 8) *Sustainability*. The IR framework appears to be adequate to assess hospitals, for which receptivity to 3D bioprinting organs is essential. This is because hospital staff is responsible for performing the donor procedures, and hence, supposedly, within the hospital, specific organ transplantation practices are in place. Therefore, using the IR approach, an assessment can be performed that can indicate the barriers concerning the adoption of 3D bioprinting at an organizational level. In fact, the eight IR categories further refine the TIS approach as specific actors, and IR categories are included for 3D bioprinting organs, such as key actors that assess the technology. Ultimately, this sheds light upon whether a hospital is ready to adopt 3D bioprinting or has to solve challenges before such adoption can occur.

2.3 The integrated conceptual framework

Table 2: Overview of Institutional Readiness framework's categories for 3D-BOIS based on Webster & Gardner (2019)

Category	Description
C1. Demand for new technology	Describes a hospital's capacity to identify a new technology, such as 3D bioprinting human organs, to fulfill medical needs.
C2. Strategic focus	Determines if a hospital has identified other technologies that can cope with organ shortage and compared those to the 3D bioprinting of organs.
C3. Relative need and benefit of new technology	A hospital's capacity to have key actors assessing the adoption of 3D bioprinting technologies.
C4. (E)valuation processes in place	Measures if 1) a hospital assesses the value of 3D bioprinting organs and if this information is shared within the hospital and 2) whether there is an agreement upon the effectiveness and safety of the 3D bioprinting technology.
C5. IR enacted through specific enablers within and outside of the organization (Enacted IR)	Assesses if a hospital has employees that can support the adoption in terms of standards and regulatory requirements and how these actors incentivize this adoption.
C6. Receptivity	Determines if a hospital is capable of restructuring its institution to cope with (organizational) challenges known prior to adopting 3D bioprinting technology.
C7. Adoptive capacity	Measures a hospital's capacity to cope with unforeseen challenges that arise during the adoption of the 3D bioprinting technology.
C8. Sustainability	Describes if a hospital can use and assess the 3D bioprinting technology for an extended period. Subsequently, it also encompasses whether a hospital has enough resources and adequate knowledge.

2.3 The integrated conceptual framework

The incorporation of the TIS framework and Institutional Readiness frameworks provides insights into the readiness of hospitals within the 3D-BOIS in California and the Netherlands between 2009 - 2020 and also points to potential barriers among university hospitals (see figure 2). The SF-analysis is applied to analyze 1) the four structural elements that make up the innovation system (i.e., actors, networks, institutions, and interactions), and 2) the dynamic of the system functions over the period between 2009 – 2020. Finally, the IR framework is applied to obtain more insights on an organizational level, namely at the hospital level in California and the Netherlands, and the barriers that can delay the adoption of 3D bioprinting organs technology.

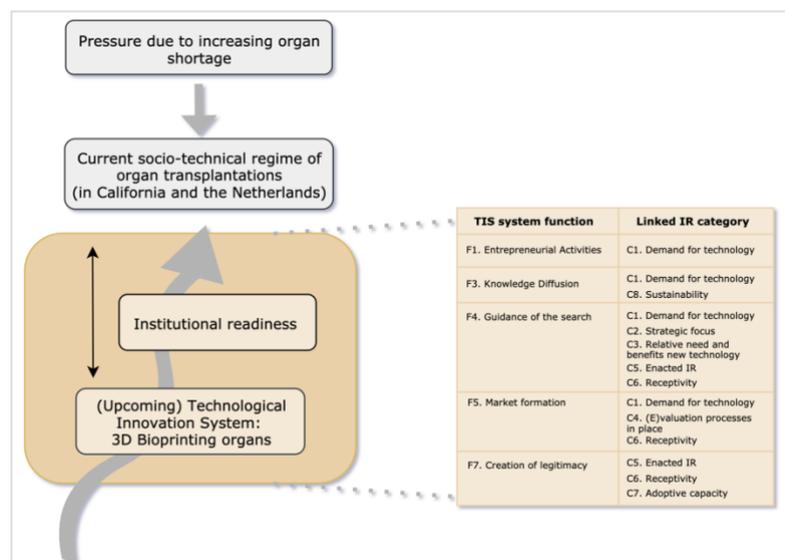


Figure 2: Overview of the integrated conceptual framework (Own figure)

2.3 The integrated conceptual framework

As mentioned in [section 2.1](#), 3D bioprinting is considered to be in phase 2 *take-off* for which *Entrepreneurial Activities (F1)*, *Guidance of the Search (F4)*, *Market formation (F5)*, and *Support from advocacy (F7)* are important (Hekkert et al., 2011; Rotmans et al., 2011). However, after desk research, it became apparent that also *Knowledge Diffusion (F3)* was an active system function within the 3D-BOIS of both California and the Netherlands. More specifically, a high number of collaborations between actors, such as medical biotech laboratories and biotech companies, can be seen. As Hekkert et al. (2007) stated, system function 3 (*Knowledge Diffusion*) is essential in a context whereby research is linked to several actors, such as the government, competitors, and the market. Consequently, system function 3 (*Knowledge Diffusion*) is also considered in this research. The following paragraphs and figure 3 below outline the connections between the categories of the IR framework and the system functions.

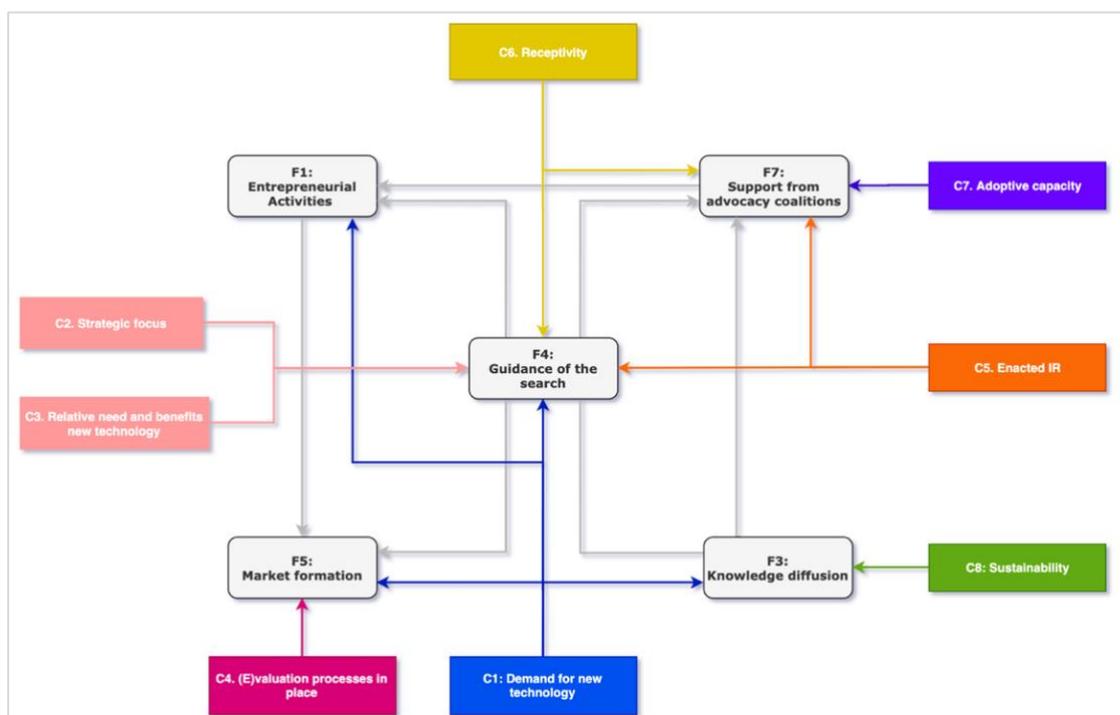


Figure 3: Assumed interactions between the system functions for the innovation system of 3D bioprinted organs and Institutional Readiness assessment in hospitals (Own figure)

Firstly, the interactions between the system functions, shown with a grey arrow in figure 3, are derived from research conducted by innovation scholars. For instance, Suurs & Hekkert (2009) assessed the biofuels innovation system in the Netherlands and subsequently discussed the dynamics that emerged among the system functions. Concerning the IR in the context of the upcoming 3D bioprinting organs innovation system (3D-BOIS), **IR category 1 (Demand for new technology)** is assumed to be related to system function 1 (*Entrepreneurial activities*), system function 3 (*Knowledge Diffusion*), system function 4 (*Guidance of the search*), and system function 5 (*Market formation*). The foremost reason is that innovation is driven by the unfulfilled medical need, which in this case is the shortage of organs for donor patients (Nathan, 2007; Vennemann et al., 2019). Hence, the hospital's ability to identify new technologies that can reduce organ shortage highly depends on entrepreneurs actively seeking and exploiting experiments. Namely, there will be nothing to identify without actors that develop

2.3 The integrated conceptual framework

technologies (*System function 1: Entrepreneurial activities*). Further, information exchange between diverse actors is crucial to ensure that everyone is informed about 3D bioprinting (*System function 3: Knowledge diffusion*), leading to the perception that 3D bioprinting can fulfill the organ shortage. Additionally, the expectation surrounding a technology (*System function 4: Guidance of the search*) allows the hospital to assess whether the medical need of organ shortage can be fulfilled. Also, the fulfillment of organ shortage (*System function 5: Market formation*) is expected to create a market where the 3D bioprinter can and will be commercialized. Moreover, both **IR category 2 (Strategic focus)** and **3 (Relative need and benefit of new technology)** are assumed to be connected with system function 4 (*Guidance of the search*). Regarding the former, the assumption is that comparing 3D bioprinting organs to other technologies to reduce organ shortage depends on the positive or negative perception that the hospitals have (Wieczorek & Hekkert, 2012). IR category 3 (C3) also involves evaluating the possibility of adopting 3D bioprinting technology by the hospital, depending on the policies and regulations that need to be met. As these guidelines affect the hospital's evaluation process, C3 is expected to be related to System function 4 (*Guidance of the search*).

Concerning **IR category 4 ((E)valuation processes in place)**, the assumption is that this category is related to system function 5 (*Market formation*) as the agreement upon the effectiveness and safety of the 3D bioprinting technology will create a demand and hence a market (Wieczorek & Hekkert, 2012). Moreover, **IR category 5 (Enacted IR)** is assumed to be linked with system function 4 (*Guidance of the search*) and system function 7 (*Support from advocacy coalitions*). Regarding the former, the actors within the hospital evaluate whether the adoption of 3D bioprinting can happen, which relates to their expectation of 3D bioprinting (*system function 4*). Additionally, as system function 7 (*Support from advocacy coalitions*) focuses on how actors within the hospital stimulate the adoption of 3D bioprinting and create legitimacy, it is expected to be linked with C5. Furthermore, **IR category 6 (Receptivity)** is assumed to relate to system function 4 (*Guidance of the search*), system function 5 (*Market formation*), and system function 7 (*Support from advocacy coalitions*). The extent to which a hospital can make changes before adopting 3D bioprinting influences how the technology is being perceived (*system function 4*). Similarly, the extent to which the hospital can change to adopt 3D bioprinting technology determines the implementation and hence the market (*system function 5*). Additionally, IR category 6 (*Receptivity*) involves determining possible change and implementation, for which legitimacy would need to be created (*system function 7*) (Webster & Gardner, 2019). Moreover, **IR category 7 (Adoptive capacity)** is expected to only relate to system function 7 (*Support from advocacy coalitions*) as the creation of legitimacy enhances the ability to cope with unforeseen challenges during the adoption. Lastly, **IR category 8 (Sustainability)** is assumed to be linked with system function 3 (*Knowledge Diffusion*), as information exchange enables the hospital to have enough resources and knowledge to assess the 3D bioprinting technology for an extended period.

To conclude, combining the system functions and IR categories appears to be a more holistic approach for obtaining insights into hampering and stimulating features in the 3D-BOIS and the associated challenges on an organizational level within hospitals in California and the Netherlands.

3. Methodology

This chapter discusses the methods to identify barriers UCSF Medical Centre and UMCU have to face regarding 3D bioprinted organs in, respectively California and the Netherlands. First, [section 3.1](#) represents the research design, whereby a general outline of the applied research methods is given. Hereafter, [section 3.2](#) describes data collection, followed by the operationalization for the structural-functional (SF) analysis and the Institutional Readiness (IR) in [section 3.3](#). Lastly, data analysis is outlined ([section 3.4](#)) before the validity and reliability of the applied methods is discussed ([section 3.5](#)).

3.1 Research design

To answer the research question "*What are the barriers and potential solutions concerning hospitals' Institutional Readiness for 3D bioprinted organs in California and the Netherlands based on the emerging 3D bioprinting organ innovation system throughout 2009 – 2020?*", this research used a qualitative research design. This approach was suitable as it provides comprehensive insights into the five system functions (1, 3, 4, 5, and 7) and their dynamics over time, as well as a detailed explanation of the barriers of emerging 3D-BOIS over time). Although the developments concerning 3D bioprinting organs started in 1999, specifically developments starting from 2009 have been chosen since a significant breakthrough of 3D bioprinting an organ, more precisely a heart occurred in this particular year by the medical laboratory Organovo in California. This signals that the Americans were frontrunners regarding bioprinting technologies and was considered a vital first step towards achieving functional human organs. In 2016, Organovo announced a collaboration with the University of California San Francisco (UCSF) Medical Center to accelerate 3D bioprinting innovations (Organovo, 2016). UCSF is currently ranked third in the top ten American hospitals of organ transplants performed between 1988 and 2019 (Michas, 2020). Hence, UCSF was chosen as an illustrative case. Within Europe, it was the Netherlands that reported success with 3D bioprinting of organs. According to the 3D Printing Sentiment Index, an index on the future potential of 3D printing worldwide, the Netherlands holds a position in the top ten countries with the highest expectations for implementing bioprinting organs exploiting its opportunities (Kohut, 2019). In fact, researchers of the University Medical Centre Utrecht (UMCU), in Utrecht (the Netherlands), received a grant of 1.8 million euros from the European Research Council after developing a 3D technique that can supposedly reproduce parts of the human body, including living cells, within minutes (Utrecht Universiteit, 2020). Additionally, as Utrecht ranks in third place nationally in terms of organ transplantations (NTS, 2020c), UMCU was chosen as the second illustrative case for this research. Moreover, Europe appeared to be lagging behind the USA in terms of innovative capacities for advanced manufacturing or digitalization manufacturing, to which bioprinting belongs, but is catching up since 2018. In fact, Europe exceeded the USA in 2018 and 2019 in terms of innovative performance regarding technological developments, partially due to the massive investments of more than 265 billion euros from the European Commission (Crescenzi et al., 2007; European Commission, 2020). Hence, it became interesting to explore hospitals' Institutional Readiness regarding bioprinting organs in California and the Netherlands in 2009 - 2020.

The focus is particularly on extrusion² technology, which is the most common technique applied within 3D printing (Chua, 2020).

Further, in order to conduct an in-depth analysis, the research was divided into two parts. First, a structural-functional (SF) analysis was conducted, in which the structural elements of the emerging 3D bioprinting organ innovation systems were mapped. Hereafter, a dynamic analysis was conducted, for which both qualitative and quantitative information was used. This provided input to perform an event analysis. The event analysis involves describing and analyzing the development, distribution, and application of bioprinting organs in California and the Netherlands between 2009 and 2020 (Hekkert & Negro, 2009). Since the system functions alter over time, this method provides a detailed overview of its interactions. Subsequently, it pointed towards barriers that hindered the development and performance of 3D-BOIS (Wieczorek & Hekkert, 2012). The findings from the event analysis have been compiled into a comprehensive storyline about the 3D-BOIS of both California and the Netherlands. As explained in the *Theoretical framework* ([section 2.1](#)), a total of five system functions were explored being *Entrepreneurial Activities (System Function 1)*, *Knowledge diffusion (System Function 3)*, *Guidance of the Search (System Function 4)*, *Market formation (System Function 5)*, and *Support from advocacy coalitions (System Function 7)* as 3D bioprinting organs is currently in the stage of 'take-off' (Hekkert et al., 2011). This is because new visions about bioprinting organs in terms of societal goals are being formed while companies drive the early adoption of 3D printing machines (Choudhury et al., 2018; Carolo, 2020).

The second part of the research focused on the Institutional Readiness of hospitals regarding bioprinting organs and the relation between the IR categories and the system functions (see [section 2.3](#)). The input was derived from conducting semi-structured interviews with two types of experts. The first one has experience with organ transplantations within the UCSF Medical Centre and the UMCU and hence provided insight into barriers concerning the IR within UCSF and UMCU. The second type of experts refers to employees from patient organizations, such as the Dutch Transplant Foundation or the Dutch Kidney Patients Association, who provided insights into the dynamics surrounding the organ transplantations, such as procedures that can hinder a transition to 3D-BOIS or other rising technologies that appear to be promising for solving organ shortage.

3.2 Data collection

The following sections explain the data collection techniques that have been used for the desk research and interviews.

3.2.1 Desk research

The qualitative event analysis is a well-known and applied research approach to operationalize system functions (Hekkert et al., 2007; Suurs & Hekkert, 2009). Firstly, data was collected for both California and the Netherlands between January 2009 and December 2020 from (professional) journals, articles, patents, reports, and websites (see Table 3 on the next page). Each of these publications is called an

² Extrusion: Materials are loaded into the cartridges and extruded from a nozzle, which can be done via pneumatic or a mechanical system (Jiang et al., 2019).

'event' and was found using search terms similar and related to the one presented in Table 4 below. The (initial) set of search terms stemmed from logical reasoning and the keyword network map of 3D bioprinting, developed by Garcia-Garcia & Rodriguez-Salvador (2018). They provided an overview of keywords that occur and are applied the most in articles and websites for bioprinting organs. These keywords were combined using the Boolean operators 'AND' and 'OR,' for example, "bioprinting" AND "human organs," to ensure that relevant combinations appear in the sources. Through a snowball method, additional search terms were added. Furthermore, a total of 3796 found events was used to create an Excel database. Hereby, the event categories as used by Kooijman et al. (2017) and Suurs & Hekkert (2009) were adjusted to fit the context of 3D bioprinted organs ([Appendix 1](#)). Additionally, the event categories were applied to categorize the events in each of the five system functions. The database consisted of the following information for each of the collected events: *event description, date of the published article, country, or region in which the event occurred, source, event category, and a positive (noted as "+") or negative (noted as "-") influence of the events on the functions. During the desk research, Knowledge diffusion (System Function 3) appeared more often than expected. This was possibly due to the heterogeneous context in which 3D bioprinted organs is, which involves interlinkages between the development of 3D bioprinting organs and the government, competitors, and the market (Hekkert et al., 2007). Subsequently, system function 3 (Knowledge Diffusion) was also included in this research.*

Table 3: Example of used literature sources to find events for 3D-BOIS (*Own table*)

(Professional) journals	Websites	Search engines
<ul style="list-style-type: none"> • American Journal of Biochemistry and Biotechnology • American Research Journal of Biotechnology • International Journal of Molecular Sciences • International Journal of Bioprinting • Technological Forecasting and Social Change 	<ul style="list-style-type: none"> • US news • Penn Medicine • Washington post • WHO • Euro transplant • ScienceDirect • Nature 	<ul style="list-style-type: none"> • Scopus • Web of Science • Google Scholar • PubMed • LexisNexis • EPO/ USPTO

Table 4: Initial search terms for 3D-BOIS in California and The Netherlands (*Own table*)

Keywords / Search terms	
Additive manufacturing	Human organs
Bio ink	Inkjet printing
Bioengineering	Organ transplants
Bioprinting	Organovo
Bioprinting techniques	The Netherlands
California	Tissue engineering
Donor transplantations	Utrecht

3.2.2 Interviews

Interviews complemented the desk research to obtain in-dept insights about the Institutional Readiness for bioprinting organs in hospitals in California and the Netherlands. The interviews were also used to triangulate the data for the events found for the chosen system functions through desk research, in order to ensure no aspects were left behind. A semi-structured approach was applied to leave room for a discussion that may lead to unidentified aspects (Adams, 2015). The interviewees were selected according to a purposive sampling strategy through desk research (Dudovskiy, 2019). Hereby, experts were chosen if they are actively involved in any activities around organ transplantations or innovations in the field of organ donations. In order to ensure that the interviewees had sufficient knowledge about this topic, a requirement of at least five years of experience in this field was applied (Forbes, 2019). After agreeing to an interview, prior to the interview each interviewee signed an information sheet ([Appendix 2](#)). Furthermore, after each interview, the interviewee was asked to refer to contacts who can be interviewed (snowballing technique). [Appendix 3](#) outline the interview guide that was used in this research. In order to guarantee a representative overview, the researcher aimed for a minimum of 15 interviews in each of the selected hospitals in California and the Netherlands, namely UCSF and UMCU. However, due to Covid-19 related higher work pressure on the hospitals, only 11 interviews in the Netherlands and 6 interviews in California could be conducted. [Appendix 4](#) shows an overview of the interviewees and how they are referred to further into this research, while [Appendix 5](#) displays a complete list of contacts that were reached out to without success. The held interviews took place in English and were conducted via Zoom due to the restrictions to visit hospitals because of the current COVID-19 situation.

3.3 Operationalization

In order to perform the event analysis for 3D-BOIS, the system functions on which the event analysis is based were operationalized along with the Institutional Readiness categories (Table 5 on the next page). The operationalization of the system functions was based upon Hekkert et al. (2007), which provided a general operationalization for these system functions. However, as the scope is upon bioprinted organs, the description of Hekkert et al. (2007) was attuned to 3D-BOIS. Each of the events found from desk research resulted in either a positive (+) or negative sign (-). Also, F4 (*Guidance of the search*) was split into two 'categories,' namely *Positive guidance of the search* and *Negative guidance of the search*. Through this division, the expectations concerning 3D bioprinting can be indicated more clearly in the pattern analysis discussed in section 4. Moreover, the Institutional Readiness categories relate to specific organizational and institutional aspects that are challenging to quantitatively measure. Hence, the IR of UCSF and UMCU regarding 3D bioprinting organs was only assessed qualitatively. Hereby, Webster and Gardner's (2019) operationalized IR framework was applied with an altered interpretation of the IR categories to fit the scope of 3D bioprinting organs technology.

Table 5: Operationalization of the system functions and Institutional Readiness categories (Own table)

System function		
Name of function	Indicator	Measurement
Entrepreneurial Activities	<ul style="list-style-type: none"> • New project started • Innovation reached market • Actors engaging to develop a product (e.g. bioprinter) • Entrepreneurial support for bioprinting organs • Project abandoned • Lack of support/investors/contractors 	+ + + + - -
Knowledge diffusion	<ul style="list-style-type: none"> • Conferences on innovations surrounding organ transplantations • Collaborations between actors • Information exchange on organization or governmental website 	+ + +
Guidance of the search	<ul style="list-style-type: none"> • Positive expectations raised on the possibility of bioprinting organs • Market growth expected • Promising outcome of a study performed on bioprinting organs • Mission or target set by government to global organ shortage • Positive expectations expressed in articles • Doubt, uncertainty expressed in articles • Negative expectations raised on the ability of bioprinting organs 	+ + + + + - -
Market formation	<ul style="list-style-type: none"> • Start tax programs • Financial benefits enabling new market (research) opportunities • Policies/initiatives by government leading to new market opportunities • Industry standards that foster the development for bioprinting organs • Stop of tax programs 	+ + + + -
Creation of legitimacy	<ul style="list-style-type: none"> • Lobby actions from patient groups and/or health-related organizations • Support from professional institutions or organizations • Governmental support • Expressed resistance against bioprinting organs 	+ + + -
Institutional readiness category		
Name of category	Indicator	Measurement
Demand for new technology	<ul style="list-style-type: none"> • Capabilities for detecting new technology 	Qualitatively
Strategic focus	<ul style="list-style-type: none"> • Comparing 3D bioprinting to other technologies 	Qualitatively
Relative need and benefit of new technology	<ul style="list-style-type: none"> • Ability to adequately evaluating the adoption of 3D bioprinting 	Qualitatively
Evaluation processes in place	Sharing of evaluation results within the organization. <ul style="list-style-type: none"> • Agreement upon effectiveness of 3D bioprinting 	Qualitatively
Enacted IR	<ul style="list-style-type: none"> • Presence of, or ability to swiftly acquire, employee(s) that can support the adoption of 3D bioprinting 	Qualitatively
Receptivity	<ul style="list-style-type: none"> • Capability for organisational changes before adoption of 3D bioprinting 	Qualitatively
Adoptive capacity	<ul style="list-style-type: none"> • Ability to cope with unforeseen challenges 	Qualitatively
Sustainability	<ul style="list-style-type: none"> • Ability for long term adoption and evaluation of 3D bioprinting 	Qualitatively

3.4 Data analysis

In the following subsections, the approaches that were used to analyze the retrieved data from the desk research and interviews are described.

3.3.1 Desk research

After the database with events was created, see [section 3.2.1](#), the events were chronologically arranged. Then a visualization in the form of graphs was made to obtain insights into the systems functions and their changes over the years (trend analysis) (Suurs & Hekkert, 2009). The charts revealed patterns and trends of 3D-BOIS both in California and the Netherlands. Ultimately, the focus was on identifying barriers in the emerging 3D-BOIS on an organizational level in California and the Netherlands. The second method, interaction patterns analysis (Suurs & Hekkert, 2009), involved chronologically ordering the events to create a storyline. This enabled the analysis of the content of the events as the evolution of the 3D bioprinting organs innovation system is outlined.

3.3.2 Interviews

For the interviews' analysis, qualitative content analysis was performed based on Strauss and Corbin's (1994) coding method. The approach generated an overview of all data that is collected and consists of three steps. The first one refers to summarizing the given answers into concepts. Hereafter, these concepts are combined into categories, which in this case corresponded with the IR categories. Usually, the last step encompasses connecting the created categories into a theoretical model. However, in this study, linkages were made between the IR categories and the system functions as described in [section 2.3](#). Hence, the last step encompassed formulating a summary of the event, which was used in the storyline ([section 4](#)). In order to conduct this analysis, a qualitative data analysis tool, NVivo, was used for the coding process to examine each interview line-by-line (NVivo, 2020). This approach ensured internal validity, as coding rules were followed, and it enabled the researcher to identify IR categories that are perceived as significant. Subsequently, this led to a more holistic understanding of institutional barriers regarding hospitals. Ultimately, through this method, an answer could be formulated as to what preparedness in Californian and Dutch hospitals are concerning the adoption of 3D bioprinting organs. Hereby, also barriers can be observed for which solutions can be developed. The results were incorporated in the event analysis ([section 4](#)) and used to formulate recommendations ([section 7](#)).

3.5 Quality of the research

The data collection method assures validity and internal reliability through data triangulation of document analysis with expert interviews. As a single person conducted this research, investor triangulation was met by validating the desk research by data retrieved from interviews with experts. Moreover, by following the coding process of Strauss & Corbin (1994), the researcher was obligated to follow the rules, which reduced a biased perspective. Regarding the generalization (external validity), the scope is explicitly centered in hospitals two regions, namely California and The Netherlands. Hence, it encompasses a specific situation and is not recommended to be generalized.

4. Findings

This chapter describes the 3D bioprinted organs innovation systems (3D-BOIS) in California and the Netherlands between 2009 and 2020. The generated database, which includes a total of 3796 events concerning 3D bioprinting organs, was first explored to see if all five functions were essential for the analysis to obtain insights into the innovation dynamics of 3D bioprinted organs over the period 2009 – 2020. This was done by constructing a frequency distribution (Hekkert & Negro, 2009). As shown in figure 4, each of the five system functions (*System functions 1, 3, 4, 5, and 7*) is present in the generated database. Hence, all five system functions need to be included in this analysis (Hekkert & Negro, 2009). Subsequently, events were outlined in a historical event analysis, which was used to narrative the system functions' dynamics over time. This analysis enhanced the understanding of how the system functions influenced the 3D-BOIS in California and the Netherlands over time. Hereby, the period of 2009 – 2020 is separated into three episodes, being 1) 2009 – 2013, 2) 2014 – 2017, and 3) 2018 – 2020. The division of the years into three episodes was made based upon the identified developments surrounding 3D bioprinting organs. For instance, a successful outcome of a research conducted by 3D bioprinting organs, was often followed by favorable expectations arising on 3D bioprinted organs. These events were attempted to cluster in the same episode to make the content more reader-friendly and easy to follow. After each episode, a recap of the most prominent system functions is given in a brief analysis part (light brown box).

Moreover, the IR framework was applied to obtain more insights into the Institutional Readiness for 3D bioprinting organs on a micro-organizational level of hospitals. In order to do so, a total of 7 interviews in California and 11 interviews in The Netherlands were held. In the following two subsections, first, the historical event analysis for the emerging 3D bioprinting organs innovation system is outlined for California ([section 4.1](#)) and the Netherlands ([section 4.2](#)). Hereafter, the findings of the interviews are outlined in a narrative form for both California ([section 4.1.4](#)) and the Netherlands ([section 4.2.4](#)), before a case comparison is discussed in [section 5](#).

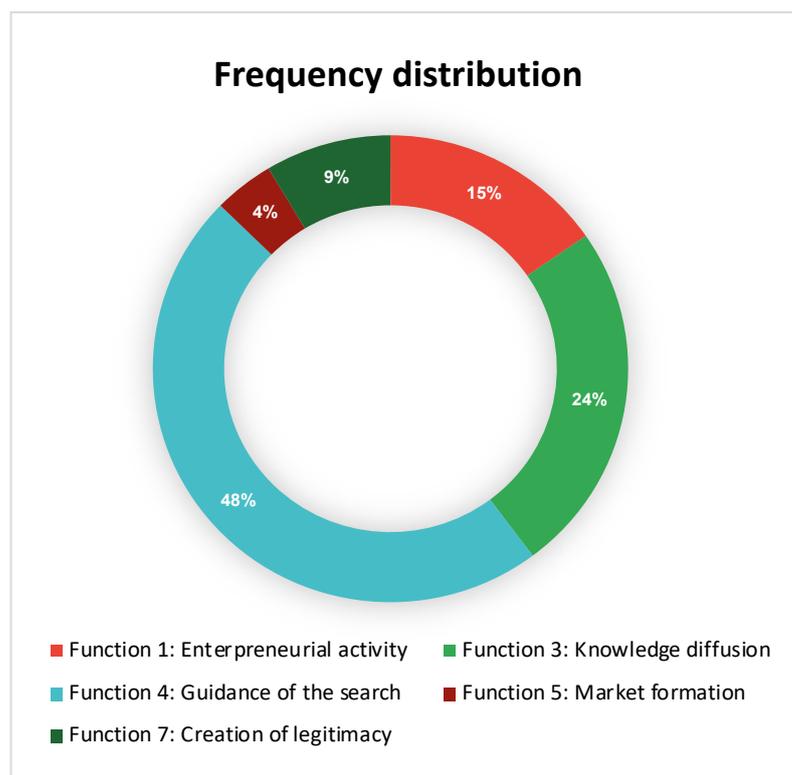


Figure 4: Frequency distribution (in percentages) for The Netherlands and California

4.1 Innovation system of bioprinted organs: California

The following three subsections describe significant events for each system function for the 3D-BOIS of California, whereafter the Institutional Readiness for 3D bioprinting organs of the UCSF hospital is described in [subsection 4.1.4](#). An overview of the distribution of the system functions per year is displayed in figure 5.

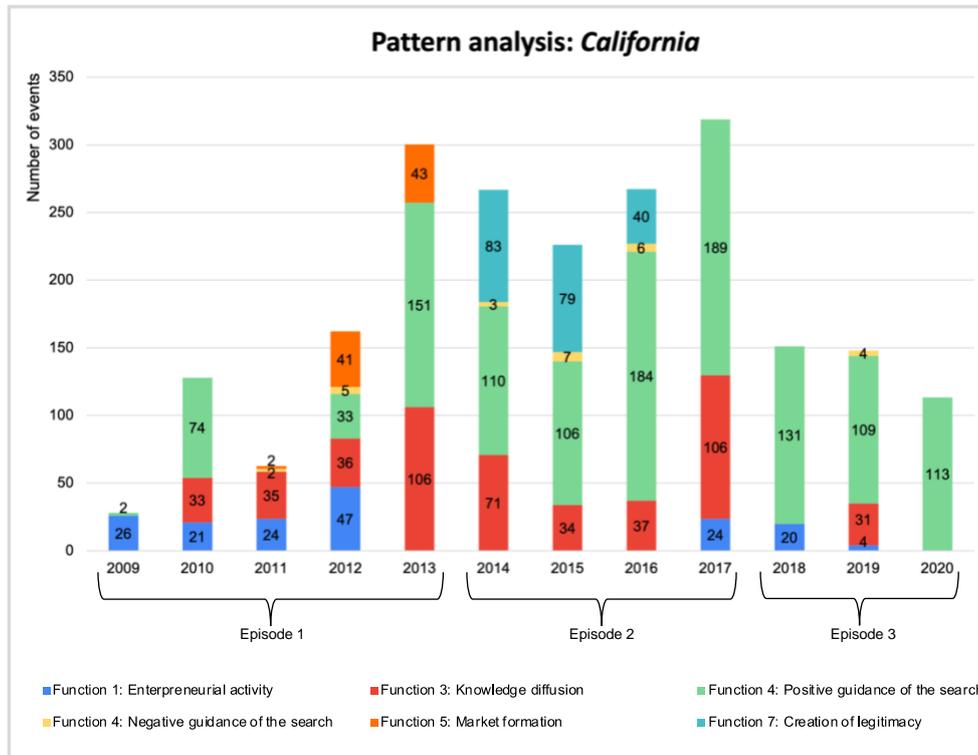


Figure 5: Pattern analysis for the 3D-BOIS in California in the period of 2009 until 2020

4.1.1 2009 – 2013: A flying start for 3D bioprinting in California

In 2009 an important patent expired, involving layering materials to create an object, namely the *fused deposition modeling*³ (FDM) patent. It was owned by Stratasys, an American Israeli manufacturer of 3D printers and 3D production systems. This milestone was considered a real turning point for 3D printing as the prices for a 3D printer declined over 75% from 15,000 EURO (EUR) (Siebert & Eldon, 2016; Creax, 2015). The same year several companies and projects reported activities related to 3D printing in healthcare (*System function 1: Entrepreneurial activities*). An example is Organovo, a Californian medical laboratory and research company, which collaborated with American biotech company *Invetech* to develop a bioprinter and commercially launch it by the end of the year. *Invetech* specifically focuses on the product design, instrument development, and manufacturing of 3D bioprinters (*Invetech*, 2021). In fact, *Invetech* stated to have a positive outlook upon 3D bioprinting human organs (*System function 4: Positive guidance of the search*): "*Building human organs cell-by-cell was considered science fiction not that long ago*" (Business Wire, 2009, para. 2). At the beginning of 2010, each bioprinter was scheduled to be sold, first within the USA and then internationally, for 200,000 United States Dollar(USD) (Xconomy, 2010).

³"Fused deposition modeling (FDM) is a technology where the melt extrusion method is used to deposit filaments of thermal plastics according to a specific pattern. Similar to 3DP, the layout for FDM consists of a printhead able to move along X and Y directions above a build platform" (Walker & Santoro, 2017)

4.1 Innovation system of bioprinted organs: California

Another new collaboration was between Silverstone Solutions, a Californian-based company that develops medical software that matches organ donors to patients, and the American non-profit medical charity Methuselah Foundation (*System function 3: Knowledge diffusion*). The collaboration aimed at reducing the organ shortage, as Methuselah Foundation, stated the following: "*Their [Silverstone's] innovative approach is exactly what is needed in the organ transplant world, and the medical field in general*" (Methuselah Foundation, 2010, para. 4). Moreover, in the second quarter of 2010, more positive articles appeared that highlighted the abilities of 3D bioprinting organs (*System function 4: Guidance of the search*). For instance, 3D bioprinting organs could enable the use of patients' cells, which would reduce the risk of an organ being rejected by the patient's body to nearly zero (The Medical Quack, 2010). By the end of 2010 Organovo released their data on their fully bioprinted blood vessel. (*System function 4: Positive guidance of the search*). Hereby, the cells from patients were used, making it the world's first artery of its kind (Business Wire, 2010).

During the American Association for the Advancement of Science (AAAS) annual meeting in February 2011, 3D bioprinted human tissue was positively highlighted again (*System function 3: Knowledge diffusion; System function 4: Positive guidance of the search*). However, concerns were raised regarding its security as 3D bioprinting was potentially at risk for bio crimes (*System function 4: Negative guidance of the search*) (AAAS, 2011). Nevertheless, in July 2011, the US National Institutes of Health granted NanoSort around 698,000 USD in the context of innovation research (*System function 5: Market formation*). NanoSort is a startup that develops a biomedical technique to analyze and sort cells. Around the same time, Organovo found a market for their 3D bioprinting technology, namely with Advanced BioHealing. This American company creates bio-engineered skin (*System function 1: Entrepreneurial activities*) (Xconomy, 2011). As the traction concerning 3D bioprinting organs increased, several prominent actors, such as Harvard Biosciences, were involved by the Biotech Showcase in January 2012 (*System function 3: Knowledge diffusion; System function 4: Positive guidance of the search*) (Marketwire, 2012). Harvard Biosciences is an American company, which is a global developer, manufacturer, and marketer of life sciences equipment that supports research and drug discovery. The prospects that were expressed had a beneficial effect on the market. For instance, Organovo obtained 6.5 million USD through private placement in February 2012, which even soared to a gross of 15.8 million USD. This capital was used to refine the existing 3D bioprinter but also to continue research in the following years (*System function 1: Entrepreneurial activities; System function 5: Market formation*) (Organovo, 2012; Market News Publishing, 2012). Moreover, Shaochen Chen, a professor of nano-engineering at the University of California, highlighted the improvements regarding 3D bioprinting (*System function 4: Positive guidance of the search*). For instance, Organovo was able to 3D print tissue ranging from blood vessels to lung tissue. The details with which these were printed provided a promising outlook for the medical sector, which has been coping with organ shortage (*System function 4: Positive guidance of the search*) (Newstex, 2012). Toward the end of 2012, pharmaceutical companies, such as Pfizer and United Therapeutics, also expressed their interest in 3D bioprinting (MedCityNews, 2012) (*System function 4: Positive guidance of the search*).

4.1 Innovation system of bioprinted organs: California

In the first quarter of 2013, Organovo announced its collaboration with Zen-BIO, a biotech company based in North Carolina that provides advanced cell-based solutions (*System function 3: Knowledge diffusion*). Through this partnership, Organovo aimed to develop functional features of human tissue. As they indicated, “Together, we can create new tissues [...] and [we] will fill unmet needs for medical research and surgical therapies” (Newswire, 2013a, para. 1). In April 2013, Organovo already reported their first success with a 3D bioprinted mini liver (*System function 4: Positive guidance of the search*). The tissue was built up with liver cells and blood vessels that could supply the cells with oxygen, similar to an ‘in-body liver. The ability to add the blood vessels enables the tissue to stay alive for a minimum of five days (MailOnline, 2013). Subsequently, Organovo was invited to talk at the 12th Annual Healthcare Conference, a recognized conference for investors to share the latest information within biotechnology and medical technology (*System function 3: Knowledge diffusion*) (Newswire, 2013b). The positive development led to the Methuselah Foundation offering a grant of approximately 500,000 USD for public and private research concerning 3D bioprinted organs (*System function 5: Market formation*) (MedCityNews, 2013). The end of 2013 finished with a promising outlook as Organovo revealed to have achieved a greater tissue thickness, enabling human tissue to survive longer in a functional state. Supposedly, it could stay alive for a minimum of 40 days (*System function 4: Positive guidance of the search*) (Mashanyare, 2013).

Analysis

In 2009 – 2013, after the expiration of the fused deposition modeling (FDM) patent 2009, the interest in 3D bioprinting organs immediately peaked in California and was continuously present until 2013. As a result, several actors swiftly launched projects (*System function 1: entrepreneurial activities*), such as the Californian medical laboratory Organovo (Invetech, 2021). Interestingly, in this first episode, Organovo also appears to be a leading company regarding improvements for 3D bioprinting organs. Moreover, relatively swiftly, namely in 2010, the first positive expectations about study outcomes on 3D bioprinted organs appeared in California (*System function 4: Positive guidance of the search*). This was due to, for example, Organovo, who reported success with a 3D bioprinted blood vessel.

Additionally, System function 3 (Knowledge diffusion) appeared to be significant as the number of collaborations gradually increased from 2010 onwards and even tripled by 2013 (Figure 4 on page 23). Further, in California, financial benefits enabled new market (research) opportunities for 3D bioprinting organs research in 2012 and 2013 (*System function 5: Market formation*). For example, the aforementioned medical laboratory Organovo obtained 6.5 million dollars in funding to advance their research on 3D bioprinting organs and to refine 3D bioprinters (Organovo, 2012; Market News Publishing, 2012). Lastly, although some concerns were raised, such as bio crimes by the American Association for the Advancement of Science (AAAS), it appears that the positive expectations about 3D bioprinted organs among American biotech companies and pharmaceutical companies, like Pfizer, prevailed. This was mainly due to the advancement being made by, for example, Organovo or Zen-BIO (*System function 4: Positive Guidance of the search*). Interestingly, new research opportunities upon 3D bioprinting organs were mainly created for Organovo by investments from venture capitals (*System function 5: Market formation*).

4.1.2 2014 – 2017: Collaboration, collaboration and collaboration

In the first quarter of 2014, the biotech company Organovo partnered up with the US National Institute of Health to improve 3D bioprinting technology (*System function 3: Knowledge diffusion*). With this collaboration, they aimed to develop a more reliable tool for tissue engineering on a faster time track (Newswire, 2014). However, to ensure everyone could keep up with the quick improvements concerning bioprinted organs, Nano3D Biosciences, a biomedical research company from Texas, launched an awareness campaign for 3D bioprinting technology (*System function 3: Knowledge diffusion*) (Business Wire, 2014). Shortly after this, regulatory questions were raised by the American Supreme Court due to unclarity. For example, it was vague what changes to American National Organ Transplant Act (NOTA), which ensures a national system to match organs and individuals, would be necessary if 3D bioprinted organs were recognized as personal property. More specifically, questions were raised about the Transplantation of Human Organ Act (THO) of 1994, which was created to streamline organ donation and transplantation activities. American researchers indicated that THO was outdated and did not cover emerging technologies, such as tissue engineering, which relates to 3D bioprinting organs (Shroff, 2009; Seedhouse, 2014). Additionally, several actors, such as bioethicists and biotech companies, expressed to be 'uncomfortable' if organs indeed would be acknowledged as personal property (*System function 4: Negative guidance of the search*) (Wagner, 2014). Nevertheless, the positive expectations for 3D bioprinting were overhand (*System function 4: Positive guidance of the search*). For instance, the director of innovation of the Museum of Science and Industry, Anthony Pelaez, indicated his enthusiasm for printed organs as he stated: "3D printing has been around a few years, but we're now starting to see some amazing applications of the technology. There's a lot of excitement about it, especially in bio-printing" (Loft, 2014, para. 2). Another example is the BIO International Convention in 2014, which highlighted the capabilities 3D bioprinting held for organ shortage (*System function 3: Knowledge diffusion*). They expected a continuous flow of innovations and developments for 3D bioprinting, especially since a two-year-old boy's life was saved by using a 3D printer for his defective heart (*System function 4: Positive guidance of the search*) (Xconomy, 2014; Moore, 2015). By the end of 2014, the Yale School of Medicine indicated collaborating with Organovo as they would like to contribute research-wise to the fast-growing field of tissue engineering to tackle the transplant shortage (*System function 3: Knowledge diffusion*) (Newswire, 2014).

Nevertheless, at the start of 2015, the challenges of 3D bioprinters were stressed again (*System function 4: Negative guidance of the search*). For instance, researchers from California pointed towards the regulatory aspects. They had doubts whether the US government would be convinced of the efficacy of bioprinted tissues (Johnson, 2015). However, by May 2015, Organovo accelerated its timeline for 3D bioprinting as they would like to automate the 3D bioprinting organs process by 2020 (*System function 4: Positive guidance of the search*). (Mendoza, 2015). Concurrently, the California State University (CSU) focused on 3D printing technology with their engineering students (*System function 7: Creation of legitimacy*). In fact, the students were encouraged to display their work at the mechanical engineering exhibition, which was held at the end of the year by California State University (California State University, 2015). Moreover, Frost & Sullivan, an international business consulting

4.1 Innovation system of bioprinted organs: *California*

firm, released a market analysis that portrayed 3D bioprinting as a promising technology worldwide: "*It [3D bioprinting] can unlock unprecedented opportunities by pushing advancements in tissue engineering and biomaterials that will eventually enable the development of human organs*" (para. 2) (*System function 4: Positive guidance of the search*). Nevertheless, the report also stressed that it is essential for other countries to accelerate the commercialization of 3D bioprinting to make a significant change in the healthcare sector, especially for human organs (Targeted News Service, 2015).

Furthermore, 2016 was off to a good start for bioprinted organs as researchers from the University of California announced successfully developed a 3D bioprinted tissue (*System function 4: Positive guidance of the search*). The material was almost similar to a human liver and was praised for its structure and function (Health Daily Digest, 2016). In the second quarter of 2016, Organovo announced its collaboration with the University of California San Francisco (USCF) to accelerate breakthroughs in the field of 3D bioprinting (*System function 3: Knowledge diffusion*) (Contify Life Science News, 2016). While positive news kept appearing around 3D printed tissues, concerns were also highlighted (*System function 4: Negative guidance of the search*). For instance, researchers within Organovo and journalists from 3Dprint, a news organization focused on the 3D printing industry, worried that a black market of 3D bioprinted organs would emerge as the organ shortage continued worldwide (Organovo Holdings, 2016). Despite this concern, 3D-printed organs appeared in the *Top 18 Technologies Fueling Growth Opportunities in Global Healthcare*, published by Frost & Sullivan's (*System function 4: Positive guidance of the search*) (PR Newswire Europe, 2016, para. 3).

Moreover, in the first quarter of 2017, the department of Engineering in Medicine from the University of California highlighted the advances in 3D bioprinting while also pointing to one major bottleneck, namely connecting the organs with blood vessels in order for the tissue to survive (*System function 4: Positive guidance of the search*). UCSF's Nanoengineering professor, Shaochen Chen, focused on this issue and developed a way to produce microstructures. However, the printed blood vessels could not yet transfer nutrients (States News Service, 2017). In April 2017, 3D systems, an American company that manufactures and sells 3D printers, collaborated with the American biotech company United Therapeutics to improve 3D bioprinting (*System function 3: Knowledge diffusion*). As they stated: "*Our partnership with 3D Systems is a major step forward in creating an unlimited supply of tolerable transplanted organs*" (FinancialWire, 2017, para. 1). Furthermore, Frost & Sullivan's 2017 market report stated that the healthcare sector appeared to be a keen adopter of 3D printed technology (*System function 4: Positive guidance of the search*). However, regulatory issues and cybersecurity matters needed to be clarified further before the niche of 3D bioprinters grows into mass production (*System function 4: Negative guidance of the search*) (The Saudi Gazette, 2017). Luckily the FDA published a guidance report called '*Technical Considerations for Additive Manufactured Medical Devices*' in December 2017, in which the FDA stated that 3D bioprinting was viewed as a medical device (*System function 7: Creation of legitimacy*). This was a response to the concerns surrounding the management of health information with 3D bioprinters. The FDA referred to the rule of *Individually*

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Identifiable Health Information (Privacy Rule) enforced by the American Department of Health and Human Service (HHS) in December 2001. This rule encompassed all the requirements applicable to medical devices of which 3D bioprinting became a part (FDA, 2017). Moreover, the FDA also acknowledged the advantages of 3D bioprinting (*System function 4: Positive guidance of the search*). For instance, the following is stated: "Another advantage is the ease in fabricating complex geometric structures, allowing the creation of engineered porous structures, tortuous internal channels, and internal support structures that would not be easily possible using traditional (non-additive) manufacturing approaches" (FDA, 2017, p.3). Nonetheless, some regulatory specifics for bioprinting remained vague (*System function 4: Negative guidance of the search*). For example, in the case that a functional 3D bioprinted heart was developed, it was unclear which regulation applied to it, as it would go beyond the jurisdiction of the FDA. For instance, either the rules of the National Organ Transplant Act could be applied, which specifically focus on the organ donation shortage and improvement of the organ matching and placement process, or additional rules for functional 3D bioprinted organs would need to be created (Mendis & Rutschman, 2020; HHS, 2013; Law Revision Counsel, n.d.). Nevertheless, 2017 ended with a bright outlook for 3D bioprinting organ developments as researchers from the University of California reported that they had refined the structure of 3D bioprinted tissue for human organ placement (*System function 4: Positive guidance of the search*) (Targeted News Service, 2017).

Analysis

For this second period, 2014 – 2017, the high number of positive expectations is noticeable for California (*System function 4: Positive guidance of the search*). Also, a sudden rise of System function 7 (*Creation of legitimacy*) between 2014 and 2016 can be seen in California. In fact, in this period, in California, support for 3D bioprinting arose from the California State University, which encouraged its students to work on 3D bioprinting (*System function 7: support from Creation of legitimacy*). Another development around this time was the research conducted by the FDA on the guidelines for 3D bioprinting, which was published in 2017. Their report stated that 3D bioprinting could be seen as a medical device, hence shedding light on which regulations healthcare actors and medical companies would need to follow when bioprinting organs. Lastly, in California, it could be seen that events related to System function 3 (*Knowledge diffusion*) occurred every year from 2014 through 2017. In fact, in California, the first awareness campaigns started in 2014. These were held to stimulate the adoption of 3D bioprinting once the technology could 3D bioprint viable organs. Overall, the positive expectations regarding 3D bioprinting organs by biotech companies and national authorities, namely FDA (*System function 4: Positive guidance of the search*), prevailed in California, and, presumably, this was a driving factor for further development concerning 3D bioprinting organs.

4.1.3 2018 – 2020: The future looks bright

In the first quarter of 2018, the principal of the Advisory Services International department from the international audit firm, Klynveld Peat Marwick Goerdeler (KPMG), Steve Bates, expressed his fascination for 3D bioprinting and the incredible advantage of no-wait list transplantation (*System*

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function 4: Positive guidance of the search). He pointed towards the advances made concerning 3D bioprinting in recent years, especially with functional human tissue (Zima, 2018). Not surprisingly, the global bioprinting market forecast for 2025 was optimistic due to the perceived increased demand for organ transplants and the growing funding available for R&D regarding 3D bioprinting worldwide (*System function 4: Positive guidance of the search*) (BIS Research, 2018). Shortly after this, the University of California Los Angeles (UCLA) announced to have adapted a 3D bioprinter to enable the construction of multiple muscle layers of which an organ exists. This was considered an essential scientific breakthrough as the complexity of an organ still was an obstacle to 3D bioprint viable human organs (*System function 4: Positive guidance of the search*) (UCLA, 2018). Moreover, June 2018 appeared to be a propitious month as Prellis Biologics, a Californian 3D printer company that focuses on human tissue, announced to have "*paved the way for important medical advances and, ultimately, functional organ replacements*" (*System function 4: Positive guidance of the search*) (Business Wire, 2018, para. 3). The company was able to develop human tissue with vessels in a shorter period. Although vessels could already be printed, it was at a slower pace and lacked the resolution to allow them to be viable. With this breakthrough, the company drastically reduced the organ transplantation list and foresaw that functional 3D bioprinted organs would become available by 2023 (Business Wire, 2018; Hooven, 2018). The positive expectations regarding opportunities for 3D bioprinting organs continued in the first months of 2019, with American healthcare institutions, such as UCSF, exploring 3D bioprinting due to the rising need for organ transplants worldwide (*System function 1: Entrepreneurial activities*) (O.G. Analysis, 2019).

Nevertheless, restrictions on products based upon biomaterials and the low pace of automation in institutions and organizations posed challenges for the healthcare industry, thereby negatively impacting the market for 3D bioprinting (*System function 4: Negative guidance of the search*) (ReleaseWire, 2019). Furthermore, in May 2019, Organovo announced to collaborate with Leiden University (The Netherlands) to explore and develop a stem-cell-based bioprinted tissue therapy (*System function 3: Knowledge diffusion*). Organovo's CEO, Taylor J. Crough, stated the following: "*Partnerships with world-class institutions can accelerate groundbreaking work*" (Organovo, 2019, para. 2). By September 2019, Prellis Biologics announced to have discovered how to develop human organs (*System function 4: Positive guidance of the search*). Prellis Biologics improved a 3D bioprinter, resulting in a 100-fold higher resolution than other 3D bioprinters. In addition, one of the significant advantages is the speed at which the organ could be developed, as Prellis's method could develop the vessels of an organ in weeks instead of months. The company then announced to focus on the next challenge, namely growing the cells to, ultimately, develop into a functional organ. Prellis Biologics believed that the first lab-created kidney could be ready by 2023 (*System function 4: Positive guidance of the search*) (Fortson, 2019). In fact, they were not the only ones with a bright outlook for the future. For instance, Shahram Seyedin-Noor, founder of Civilization Ventures, a Californian venture capital firm, believed that the first 3D bioprinted organ clinical trials would begin in the upcoming decade. The company perceived 3D bioprinting as the future for organs and tissue replacements and the end of any waitlists (*System function 4: Positive guidance of the search*) (Medtech Insight, 2019).

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The positive beliefs regarding 3D bioprinting organs continued in 2020. However, this was not without any reason as researchers from the Terasaki Institute for Biomedical Innovation in Los Angeles developed an oxygen-realizing bio-ink that could be used to 3D print functional organs. Up until now, the 3D printed cells lacked oxygen, causing them not to be viable. Although another method was being explored, namely one that involves creating blood vessels in pre-made constructions, this took more time and, hence, was less favorable (*System function 4: Positive guidance of the search*) (Hastings, 2020). Further positive news was reported by the biotech company Organovo towards the end of 2020. The research team reported having uncovered a method to develop a large number of tissue for kidneys, namely by using stem cells from patients with genetic kidney disease (*System function 4: Positive guidance of the search*). A smaller kidney could be generated, which could then be modified for the patient itself. Organovo reported that the precision with which the biophysical aspects could be adapted in the kidney would influence the functionalities of the printed organs. This discovery led them a step closer to printed organs for transplants (GDP, 2020).

Analysis

In this last episode, 2018 - 2020, predominantly positive expectations regarding 3D bioprinted organs could be observed due to many breakthroughs (*System function 4: Guidance of the search*). This refers to both scientific breakthroughs and regulatory frameworks, for example, the FDA that indicated that 3D bioprinting organs could be perceived as a medical device (*System function 7: Creation of legitimacy*). Also, collaborations occurred between actors to further spur developments of 3D bioprinting organs (*System function 3: Knowledge diffusion*). For instance, the Californian medical biotech company Organovo joined forces with Leiden University (The Netherlands). Interestingly, 2020 was marked by only positive results concerning 3D bioprinting organs (*System function 4: Guidance of the search*).

4.1.4 Institutional readiness for 3D bioprinted organs in University of San Francisco Medical Center (*California*)

This subsection describes the results of interviews conducted in California to identify the Institutional Readiness (IR) for 3D bioprinting organs in the University of San Francisco (UCSF) Medical Center. As described in [section 3.1](#), UCSF ranks third in the top 10 American hospitals in terms of organ transplants performed between 1988 and 2019 (Michas, 2020). Further, as mentioned in [section 2.2](#), there are 8 IR categories: 1) Demand for new technology, 2) Strategic focus 3) Relative need and benefit of new technology, 4) (E)valuation processes in place, 5) Enacted IR 6) Receptivity, 7) Adoptive capacity and 8) Sustainability.

Firstly, UCSF appears to be able to identify new technologies to tackle organ shortage (**C1: Demand for new technology**), mainly due to the several dedicated innovation and research labs at UCSF. For instance, IV13 explained: “Besides the many collaborations we have, with for example with Organovo, UCSF is also home to several labs. To give you an example, there is Edge Labs. This is a research division

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that offers 3D printing. We [UCSF] also have the Makers Lab, which offers the UCSF community access to 3D tools. This creates an environment that fosters interdisciplinary collaboration, but more importantly, discovery". Moreover, IV14, a 3D printing engineer, further indicated: "I am part of the UCSF Center for Advanced 3D+ Technologies, which ensures that labs at UCSF have enough resources. But we also provide support in terms of research groups, which I am part of as well. We look at the current developments and explore the possibilities for these technologies, especially, to improve healthcare". Concerning the possibilities to solve organ shortage, it appears that not 3D bioprinting organs is not the only focus for UCSF (**C2: Strategic focus**). For instance, IV15 mentioned: "Yes, 3D bioprinting is everywhere these days and, it is advancing, but there are other trends we see in tissue engineering. An example is organ-on-a-chip or sometimes called human on a chip". Nevertheless, each innovation is thoroughly explored to combat the organ shortage. As IV14 described: "We can't jump up on the first technique that appears to be promising. It is fairly costly, and new techniques are continuously being developed. This indicates that the identification of new technologies relates to the positive outcomes (*System function 4: Guidance of the search*) and financial support (*System function 5: Market formation*). Moreover, IV15 explained: "Here [in USA], each hospital wants the so-called first-mover advantage in order to have prestige. Of course, we won't just buy a 3D bioprinter because one researcher screams that it is good. We do keep our eye upon it and evaluate it based on articles and researchers. But the sooner such innovation is placed in the hospital, the better". Before any innovation is implemented, like 3D bioprinting organs, UCSF assigns the assessment of the technology to a different chain of key actors (**C3: Relative need and benefit of new technology**), which start with researchers and ends with multiple departments as IV16 stated: "Well, I believe this sector is highly multidisciplinary but ultimately we always start with researchers. They go through every aspect of it [a new technology] and draw a report on that. Sometimes this is published publicly, but sometimes it is only for internal use. Then it is discussed among so-called first rang departments, which for example, involves the financial department. If the pros outweigh the cons, meaning there is sufficient evidence that the technology will be of added value to solve a medical issue, then an action plan is drawn up". Because this process takes place in steps, not each employee of UCSF is informed about 3D bioprinting at the same time (**C4: (E)valuation processes in place**). Nonetheless, this does not appear to pose an issue within UCSF, as IV11 nicely summarized: "I think that the research groups here are more objective and open to apprehend and basically to evaluate whatever the outcome is and to then see how much potential is out there for this technology." Also, regarding the effectiveness of 3D bioprinting, the different employees of UCSF appear to agree, as all of them mentioned that it would take at least another 15 years before 3D bioprinting could be implemented (*C4: (E)valuation processes in place*). However, should 3D bioprinting organs be adopted in UCSF, employees who acquire knowledge to support this implementation would not appear to be an issue (**C5: Enacted IR**). Namely because "UCSF this year [2021] again ranked high among all public and private institutions nationwide. In fact, we ranked third I believe. This already indicates that we are a prominent hospital, which also reflects on the type of people we hire. Per my knowledge, we hardly have an issue with finding new employees" (IV16).

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Moreover, due to the several already existing research groups and innovation teams within UCSF that focus upon (recent) promising medical technologies, UCSF does not perceive the need to restructure a lot (**C6: Receptivity**). As IV16 explained: *“Our innovation labs are well organized, and we have a process to implement new technologies. In the case of 3D bioprinting specifically, maybe the patient rooms or monitoring would need to be taking up a notch. But that is something that would be discussed during the assessment early on in the process already as they [the researchers or innovation team] include members from other departments, such as human resources. In that way during the analysis of 3D bioprinting organs it is already discussed what organizational problems can arise”*. Additionally, this statement also appears to suggest that UCSF has knowledge about potential challenges that could arise for technology, in this case 3D bioprinting organs (**C7: Adoptive capacity**). This is confirmed by IV17: *“We [UCSF] are bound to financial resources, hence during the assessment we appraise the technology. As you can imagine, this surely involves any challenges we might stumble upon in the future”*. Furthermore, looking ahead, namely towards the scenario whereby 3D bioprinting is adopted, assessment for an extended time is essential. For this, employees of UCSF indicated to have a process: *“[...] during the assessment period we [UCSF] already explore indicators. Before any technology, whether it be 3D bioprinting or another innovation, is implemented we always agree upon indicators, think employees, financial resources etc., that are being keeping track of. Who is in charge of this, depends on what technology we are talking about”* (IV17). Hence, UCSF seems to be capable of assessing 3D bioprinted organs once it would be implemented (**C8: Sustainability**).

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The following three subsections highlight the most significant events for each of the five system functions for the Dutch 3D-BOIS, whereafter the Institutional Readiness is described in [subsection 4.2.4](#). Also, the distribution of these system functions per year is displayed in figure 6 below. Again, after each of the three subsections an analysis (light brown box) can be seen, which provides a brief analysis of the prominent system functions.

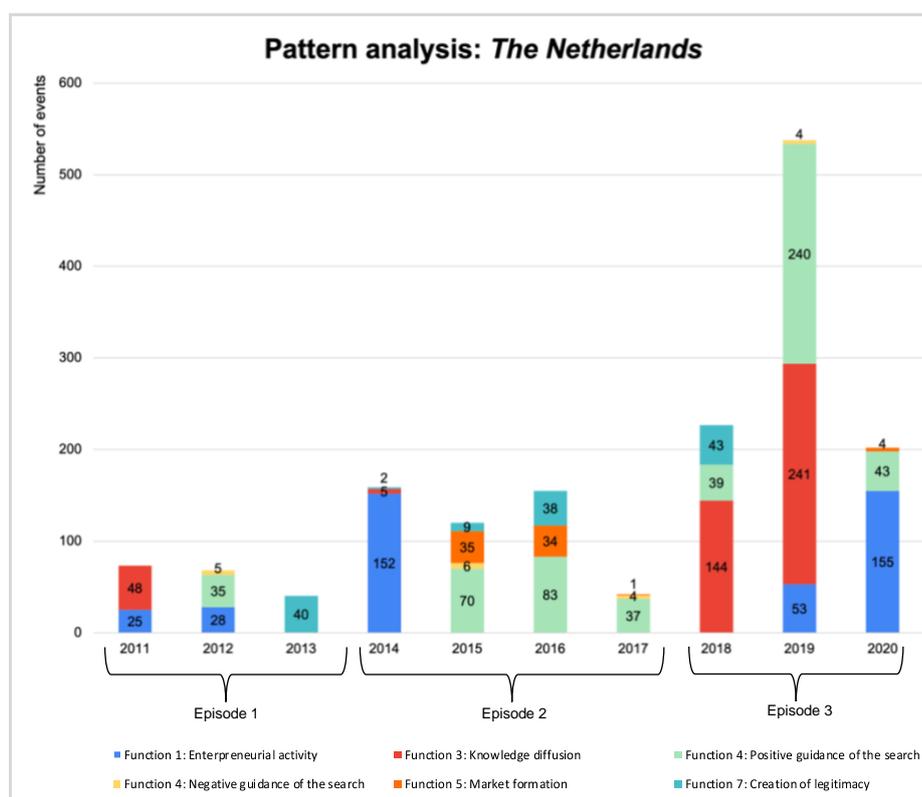


Figure 6: Pattern analysis for the 3D-BOIS in The Netherlands in the period of 2009 until 2020

4.2.1 2009 – 2013: The start of a Dutch organ transplantation revolution

In 2009 an important patent expired, namely the *fused deposition modeling*⁴ (FDM) patent. This milestone was considered a real turning point for 3D printing due to declining prices for a 3D printer (Siebert & Eldon, 2016; Creax, 2015). Nevertheless, as shown in figure 6, it was not until 2011 that interest in 3D bioprinted organs occurred in The Netherlands. One of the companies that was founded in 2011 is Ultimaker (*System function 1: Entrepreneurial activities*), which aimed to develop 3D printers in general and not specific within healthcare. After their establishment in Utrecht, the company quickly sold 3D printers among technicians. In fact, they grew into a significant international player regarding 3D printers in the following years (Intermediair, 2017; RTL Nieuws, 2018), which stimulated the refinements of 3D printers and, thereby, indirectly stimulated the advancements for 3D bioprinting that could be used to 3D bioprint organs.

In the following year, 2012, Shapeways, a Dutch-founded 3D printing startup company, released their research on consumers' perspectives towards innovative products. It showed a high demand for personalized products as consumers were not content with the produced items on a mass scale (*System function 4: Positive guidance of the search*) (Libbenga, 2012). Although companies admitted that 3D printers were still in the beginning stage, as only one material and color was technically possible, its potential was appealing for many. In 2012, the Dutch bank ABN AMRO released a report "*Hype, haarlemmerolie of harde waardecreatie?*" in which the value creation of 3D printing technology from the point of view of a typical Dutch entrepreneur was explored. The findings showed that 3D printing held great potential for the medical sector. More specifically, the technology could be implemented for leg prostheses and printed human tissue in the future as 3D printers became better and more cost-effective (*System function 4: Positive guidance of the search*). In addition, the time in which the 3D printers could produce the tissue and prostheses decreased. However, in terms of different materials that could be used, technicalities still required some improvement at that time (*System function 4: Negative guidance of the search*) (ABN AMRO, 2012). Coincidentally, in June 2012, an unprecedented operation succeeded that ushered the implementation of patient-specific parts that were 3D bioprinted (*System function 4: Positive guidance of the search*). Namely, a 3D printed lower jaw was successfully placed onto an 83-year-old woman's face in Orbis Medical Centre in Sittard-Geleen (The Netherlands) (BBC, 2012). Nevertheless, concerns regarding the required ink for the 3D printer remained as materials needed to be ordered, such as the liquid titanium used with the jaw operation. Waiting on these materials could endanger a patient that requires its tissue swiftly (*System function 4: Negative guidance of the search*) (Carter, 2012).

Besides the technical constraints of 3D bioprinters, there were also concerns among Dutch regulatory authorities, namely the Dutch Association for the Judiciary. For instance, during the annual conference of the Dutch Association for the Judiciary in 2012 (*System function 3: Knowledge diffusion*), 3D bioprinting was mentioned as one of the essential new fields to focus upon. Due to its innovative nature, they pointed to the potential need to renew legislation to ensure safety for the society (*System function 4: Negative guidance of the search*) (Grimmelikhuisen, 2012). Although it was unclear

⁴ "Fused deposition modeling (FDM) is a technology where the melt extrusion method is **used to deposit filaments of thermal plastics according to a specific pattern**. Similar to 3DP, the layout for FDM consists of a printhead able to move along X and Y directions above a build platform" (Walker & Santoro, 2017)

4.2 Innovation system of bioprinted organs: *the Netherlands*

whether 3D bioprinters could be perceived as a medical device, no limitations on the growth of the 3D bioprinting market were perceived (*System function 5: Market formation*). In fact, in 2013, the Dutch 3D printing market was estimated to be worth approximately 2.74 billion EUR (*System function 4: Positive guidance of the search*) (Kemps, 2015). However, it was still mainly the startups that reported positive outlooks on the possibility of 3D bioprinting organs. More specifically, the regions of Brabant, North Holland, and Utrecht were perceived as 3D hubs, which also encompass 3D bioprinting (ABN AMRO, 2013). The larger Dutch corporations followed the developments around 3D bioprinting closely but were waiting for further developments that enhanced 3D printing (Kemps, 2013). In September 2013, the Ministry of Economic Affairs published its letter to the Dutch House of Representatives (*Dutch: Tweede Kamer*), highlighting the changes needed for intellectual property (IP) rights because of 3D bioprinting. They pointed to technological advancements, such as the rise of 3D printers and biotechnology, that required law amendments (*System function 7: Creation of legitimacy*) (Ministerie van Economische Zaken, 2013).

Analysis

In this first episode, 2009 - 2013, it can be observed that after the *fused deposition modeling* (FDM) expired, in contrast to California, it was not until 2011 that projects concerning 3D bioprinting were launched in the Netherlands (*System function 1: Entrepreneurial activities*). Also, in the Netherlands, two years later than California, namely in 2012, positive outlooks were reported about 3D bioprinting organs (*System function 4: Positive guidance of the search*). For instance, the Dutch bank ABN AMRO released its report on the value of 3D bioprinting, in which they highlighted its great potential for healthcare. Furthermore, the Dutch government, more specifically the Dutch House of Representatives (*Dutch: Tweede Kamer*), acknowledged the rise of 3D bioprinting, as they published a letter indicating what changes needed to be made to intellectual property (IP) rights due to the rise of 3D printers and biotechnology (*System function 7: Creation of legitimacy*). In addition, also similarities can be observed between the 3D-BOIS in the Netherlands and California in this period. For instance, from the moment 3D bioprinting organs reached interest entrepreneurial activities (*System function 1*) took place and were continuously present until 2013. In addition, in both California and the Netherlands, a slight increase of negative expectations arose concerning 3D bioprinted organs in 2012 (*System function 4: Negative guidance of the search*), namely concerns regarding possible changes required to the National donor law, which researchers and judiciary expressed.

4.2.2 2014 – 2017: The tide is turning for 3D bioprinting organs

In the first quarter of 2014, the National Institute for Public Health and the Environment in The Netherlands (*Dutch: RIVM*) and Netherlands Knowledge Centre on Alternatives to Animal Use (NKCA) jointly released a report on 3D printing, named '*3D-printing, een nieuwe dimensie voor de 3V's*' as the potential applications increased and 3D printing gained traction (*System function 3: Knowledge*

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diffusion). The study described the positive outlook of the use of 3D printing for tissue engineering. For example, the following was reported: "*The technology can play a crucial role in solving the problem in the long term of the shortage of donor tissues and organs*" (p.8) (*System function 4: Positive guidance of the search*). Nevertheless, they acknowledged that the 3D bioprinting technique was still being refined, and more insights needed to be gained in this innovative research (*System function 4: Negative guidance of the search*). Hereby, the regulatory aspects were also mentioned as an aspect that required more clarity. For instance, it was unclear whether 3D bioprinting could be classified as a medical device (NKCA, 2014). In March 2014, the UMCU released details of a successful medical operation on a 22-year-old woman. She suffered from a chronic bone disorder and would not have survived as no other procedure was available for her condition. In fact, 3D bioprinting provided a lifesaving opportunity (*System function 4: Positive guidance of the search*) (Tufnell, 2014). Roughly two months later, Dutch researchers reported working on creating beef. Since a human organ is quite complex, the researchers aimed first to uncovering the structure of similar tissues, such as beef (*System function 1: Entrepreneurial activities*) (The Technician: North Carolina State University, 2014). To further spur improvements of 3D bioprinting to reduce the organ shortage, a non-profit organization, FabLab Amsterdam, dedicated an entire lab to this cause (Sher, 2014). FabLab Amsterdam was created by Waag, which is a Dutch research institution that focuses on the intersection of art, science, and technology (*System function 5: Market formation*) (Waag, 2021).

Nevertheless, by 2015, the Dutch 3D printing market was still relatively at the beginning stage. Therefore, the former Minister of Economic Affairs, Henk Kamp, offered a subsidy scheme for R&D focused on 3D printing. The aim of this was to sway entrepreneurs across several sectors, among which the healthcare sector, to enhance 3D bioprinting to reduce the organ shortage (*System function 5: Market formation*) (Kooijman, 2015). This was quickly followed by positive publicity surrounding research into the use of 3D printing to print human skin, tissue, and organs (*System function 4: Positive guidance of the search*) (Basulto, 2015). Also, educational institutions, such as Dutch Universities, began to focus on 3D bioprinting organs (*System function 4: Positive guidance of the search*). For example, the faculty of Medicine at Utrecht University launched a new course, '*3D Printing and Biofabrication*', for their summer school. The course provides insight into the opportunities of additive manufacturing technologies and 3D (bio)printing (*System function 7: Creation of legitimacy*) (Utrecht Summerschool, 2021). However, with the optimistic view also, concerns were raised regarding the safety of 3D bioprinting. For instance, as human tissue was involved, fear for biocrime rose, and safety measures were needed. Moreover, while the creation of cellular structures was not a radical innovation, its combination with the 3D printing method demanded a new approach from the regulatory perspective. This was needed, for example, to know what procedures need to be followed once a functional organ was printed (Tran, 2015). For instance, in The Netherlands, the Embryo Act was in effect since 2002, which prohibited individuals' cloning through embryo splitting, cell nuclear transfer, or using the nuclear transfer to grow organs or tissue (*System function 4: Negative guidance of the search*) (Blom, 2016).

4.2 Innovation system of bioprinted organs: *the Netherlands*

By the end of 2015, several major players, such as TNO, were investing in 3D printers for printing organs and other benefits. However, there were no manufacturers of printers in The Netherlands yet, which prevented the Dutch from making significant steps (Kemps, 2015). In February 2016, Elsevier, which is one of the leading providers of scientific literature, announced a new journal that would focus upon novelty across all areas of 3D bioprinting. This was after the success of their other newly added journal *additive manufacturing* in which the significance and need for 3D bioprinting research were stressed (*System function 7: Creation of legitimacy*) (Elsevier, 2016). Towards the end of the year, the positive outlook upon 3D printing in the Dutch healthcare industry became more apparent. It was even perceived as revolutionizing since more complex tissue could be printed than before (*System function 4: Positive guidance of the search*) (LIFE, 2016). In order to further stimulate breakthroughs within 3D bioprinting, Training4CRM, a program that focuses upon training students across several disciplines, announced to focus upon additive manufacturing. More specifically, the field would include several techniques for developing organs, among which 3D bioprinting (*System function 7: Creation of legitimacy*) (Syndigate, 2016). Nevertheless, 2017 was not off to a good start for 3D bioprinting organs, as doubtful articles about the advancements of the 3D bioprinting technique appeared. For example, the expectation was that the forecast set in 2000 concerning revolutionary manufacturing stemming from 3D bioprinting in the healthcare industry would not be met. In fact, the perception was that the attention for 3D bioprinted organs would slowly decrease (*System function 4: Negative guidance of the search*) (Bakker, 2017). Presumably, the Dutch Ministry of Economic Affairs (EZK) also noticed this as approximately 10 million euros of subsidy was made available in the following months for innovative companies in all sectors (*System function 5: Market formation*). Hereby, InnovationQuarter, an investor focused on the Dutch province of 'South-Holland,' advised the EZK on which projects are feasible. Surprisingly, one-third of the subsidy projects involved 3D printing (van der Wal, 2017).

Analysis

For this second period, a remarkable rise of System function 1 (*Entrepreneurial activities*) in the Netherlands could be seen in 2014. This could potentially be driven by a report published by the Dutch House of Representatives in 2013, which pointed to the changes need for IP rights due to the emergence of 3D bioprinting organs. Also, System function 5 (*Market formation*) was present in the Netherlands, primarily in 2015 and 2016 and slightly in 2017. This was presumably because of the subsidy given by the Dutch Ministry of Economic Affairs for innovative companies focusing on 3D bioprinting R&D, which benefited new research opportunities for 3D bioprinting. Also, in this episode, 2014-2017, it can be seen that *Guidance of the search* (System function 4) was significant for the Dutch 3D-BOIS to attract other prominent actors to engage in developments focused on 3D bioprinting organs, such as TNO, the scientific literature *Elsevier* and the Utrecht University (*System function 7: Creation of legitimacy*).

4.2.3 2018 – 2020: The niche of 3D bioprinting is transitioning into a trend

In May 2018, the *Bioprinting 3D-Printing in the Life Sciences* Conference was held in Rotterdam, which focused on novel technologies, such as 3D printing in the life science field (*System function 3:*

Knowledge diffusion). Hereby 3D bioprinted organs was mentioned to be a promising technology due to the advancements and attention in recent years (*System function 4: Positive guidance of the search*). Some believed that printed organs were no longer too far in the future and should be perceived as a serious solution to the organ shortage worldwide (Select Biosciences, 2018; M2 PressWIRE, 2018). This aligned with the new market report published shortly after by BIS Research, which provides market intelligence on technologies that can cause a disruption in the market in the upcoming years (*System function 4: Positive guidance of the search*). Hereby, a grow over 3.8 million EUR by 2025 was expected for the global bioprinting market. One of the main drivers mentioned for this was the increased funding for 3D bioprinting research coupled with an increased demand for organ transplants worldwide (BIS Research, 2018). Also, the European Commission got wind of the rising popularity of 3D bioprinted organs as they announced an investigation into the legal aspects of 3D printing (*System function 7: Creation of legitimacy*). This was, for example, because it was unclear which organization can be held liable for the viable 3D bioprinted organs, which resulted in uncertainty among manufacturers about what they can expect (Europees Parlement, 2018). Nonetheless, the research and collaborations with a focus on 3D bioprinting continued. In fact, in December 2018, Aspect Biosystems, a biotechnology company based in Canada, partnered up with the Institute for Technology-Inspired Regenerative Medicine at Maastricht University (*System function 3: Knowledge diffusion*). The collaboration aimed to use Aspects' bioprinter to develop a kidney tissue (Maastricht University, 2018).

Moreover, during the conference *Europe Biofabrication & Biomanufacturing* in February 2019 in Rotterdam, the emphasis was laid upon advanced techniques and approaches of 3D printing (*System function 3: Knowledge diffusion*). Although 3D bioprinting was mentioned again as a viable solution for organ replacements, other techniques such as organ-on-a-chip also gained a fair share of attention (*System function 4: Negative guidance of the search*) (PR Newswire, 2019; Select Biosciences, 2019). Nevertheless, a detailed report of Future Market Insights, released around April 2019, mentioned that an increasing number of healthcare workers are looking into 3D bioprinting due to its decreased risk during longer surgeries. They also pointed towards the growing integration of IT in healthcare that enhances the 3D bioprinting technique (*System function 4: Positive guidance of the search*). However, the ban on products that are based on biomaterial can pose a severe challenge to the growth of the 3D bioprinting market (Future Market Insights, 2019). Fortunately, several actors continued to collaborate and refine 3D bioprinting technology (*System function 3: Knowledge diffusion*). For instance, Leiden University announced its partnership with the Californian biotech company *Organovo* to create a 3D bioprinted tissue (Medical Xpress, 2019). In August 2019, Utrecht University, which collaborated with the École Polytechnique fédérale de Lausanne School of Engineering, developed a 3D printing technique to generate viable cells faster (*System function 4: Positive guidance of the search*). This discovery was perceived as a gamechanger, as the complex yet sophisticated human tissue structure could be created now (ENP Newswire, 2019). The techniques even opened the doors for personalized human organs to tackle the organ shortage (FICCI, 2019).

4.2 Innovation system of bioprinted organs: *the Netherlands*

In the first quarter of 2020, Maastricht University, along with the University College of London in the United Kingdom (UK), published an elaborated review of the capabilities of 3D bioprinting (*System function 4: Positive guidance of the search*). Hereby, the precision at which organs could be 3D bioprinted was highlighted as a unique feature (Tissue Engineering, 2020) (*System function 4: Positive guidance of the search*). Moreover, in 2020 several startups in the Netherlands arose that focused on addressing gaps in the niche of 3D bioprinting (*System function 1: Entrepreneurial activities*). In fact, many believed that the niche for 3D bioprinting would soon gain further in popularity due to the swift advancements that were being made (*System function 4: Positive guidance of the search*). An example is the startup FELIXprinters, a Dutch 3D printing technology supplier, who saw that researchers had trouble obtaining a 3D bioprinting machine due to the pricing. Hence, they developed an add-on that could be attached to their existing printer, after which it converts into a 3D bioprinter. In fact, it was the first machine of its kind in the Netherlands and positioned itself attractive among the research labs (Listek, 2020). By September 2020, the prospects for 3D bioprinting became even more favorable in the Netherlands as the University of Twente reported developing a process for storing tissue-specific gels (*System function 4: Positive guidance of the search*). These gels are needed for the structure of organs created by 3D bioprinters. The coming years will need to prove how this project evolves. However, they stated, "if successful, 'off-the-shelf' 3D-printed tissue could soon become the norm" (Universiteit Twente, 2020, para. 3). Also, Utrecht University launched new research, which involved developing a faster 3D technique to print living cells (*System function 4: Positive guidance of the search*). Researchers at Utrecht University even received a startup grant of 1.8 million EUR for their VOLUME-BIO project plan from the European Research Council (*System function 5: Market formation*) (CORDIS, 2020).

Analysis

For the last period, 2018 – 2020, similar to California, also positive expectations regarding 3D bioprinted organs could be observed in the Netherlands (*System function 4: Guidance of the search*), which is the result of advancements within 3D bioprinted organs (*System function 1: Entrepreneurial activities*). For example, the 3D bioprinting development by the Utrecht University and EPFL School of Engineering to generate viable cells faster. Nonetheless, the European Commission pointed towards regulatory unclarity, such as who could be held liable for the 3D bioprinted organs, resulting in an investigation of the European Commission (*System function 7: Creation of legitimacy*). Moreover, in the Netherlands, *Knowledge diffusion* (*System function 3*) appears to be present in 2018 and 2019. For instance, the medical conference 'Europe Biofabrication & Biomanufacturing' in Rotterdam focused on novel healthcare technologies, specifically 3D bioprinting. Furthermore, interestingly 2020 was mainly marked by new projects launched concerning 3D bioprinted organs (*System function 1: Entrepreneurial activities*), such as the Volume-bio project by Utrecht University.

4.2.4 Institutional readiness for bioprinted organs in University Medical Center Utrecht (*The Netherlands*)

This subsection outlines the results from the conducted interviews in the Netherlands to identify the Institutional Readiness (IR) for 3D bioprinting organs in University Medical Center Utrecht (UMCU). As described in [section 3.1](#), UMCU ranks in third place nationally in terms of organ transplantations (NTS, 2020c).

The **demand for new technology (C1)** regarding bioprinted organs appears to be developed in UMCU as, for example, IV2 stated: *“We have a 3D lab at Utrecht. Every department of the hospital can contact the 3D Lab with questions about 3D technology in healthcare. They basically look at the demand. Based on the demand, they look at what is possible and how they can help”*. This separate innovation unit within UMCU specifically researches new 3D technologies that can fulfill unmet medical needs, namely organ shortage. Nonetheless, this is not without any restrictions as IV5, a coordinator at the 3D Lab of UMCU, mentioned: *“What I have to deal with the most, because everything I do has something clinically applicable so there must be dtc, meaning diagnosis, treatment, combination. If there is none, that means that actually no money can be released for it”*. Additionally, IV5 also indicated a difference between the 3D Lab and research being done by UMCU upon 3D printed organs, namely: *“If you look at the clinic, too little is being done about financing. If you look at research, quite a lot is being done”*. Nonetheless, there are methods to obtain enough funding, for instance: *“There is an application towards the Ministry of Health, which is called Promising care. Zorginstituut Nederland implements the subsidy scheme together with ZonMw. Of course, on behalf of the Ministry of Health, Welfare and Sport. You can use this for techniques that are not yet applied, like 3D bioprinting [...] and, if you go through, it will be financed by the health insurer, what really helps your case”* (IV5). The presence of the ability and knowledge and competencies about potential solutions if 3D bioprinting would need to be adopted reflects positively upon UMCU’s capacity to assess the adoption of 3D bioprinting organs (C3: *Relative need and benefit of new technology*).

However, 3D bioprinting organs is not the only promising technique on the radar of healthcare actors (C2: *Strategic focus*). For instance, IV2 mentioned a recent development called ‘heart-in-a-box,’ which is a collaboration between doctors from the UMCU, University Medical Center Groningen (UMCG), and Erasmus Medical Center (Erasmus MC). This technique enables the heart of a deceased patient to beat outside the body, which is an important step, as IV2 stated: *“[...] heart donation is only possible with a brain-dead donor. But unfortunately, more than half of the donors’ hearts stop pumping, so it is not possible to transplant their hearts anymore. This innovation could really help to lower the waiting list for heart donors”*. Another technique is organ-on-a-chip, which was mentioned by five interviewees within UMCU. They mentioned that organ-on-a-chip could be seen as a steppingstone and perhaps, even be combined with 3D bioprinting. For instance, IV8 indicated: *“What immediately comes to mind is your topic, 3D bioprinting and also organ-on-a-chip. I believe the latter could be quite important for organ shortage as it also develops human tissue. Combine that with 3D bioprinting and something promising could be coming out of that”*. Nevertheless, as IV2 stated: *“It is all about the financial cost.*

4.2 Innovation system of bioprinted organs: *the Netherlands*

Without financial support, we can only research so much. Luckily there is enough attention for 3D bioprinting organs, however, there are other techniques that appear to be promising to solve the issue of organ shortage. Because of this, you don't know what the future holds.". Also, IV5 mentioned *"We often post on our internal network website about new projects. This is not only about the outcomes of these projects, but also how it is progressing"*. Hence, this indicates that the identification of new technologies relates to the positive results (System function 4) but mainly financial support (System function 5). Nonetheless, UMCU appears to be able to identify promising technologies that can tackle the organ shortage and compare these to 3D bioprinting (**C2: Strategic focus**).

Furthermore, it also seems that UMCU has competent key actors to assess the adoption of 3D bioprinted organs (**C3: Relative need and benefit of new technology**). In fact, UMCU has a large laboratory that researches 3D bioprinting (IV2) and also has quarterly meetings as IV2 stated: *"We have these meetings, you can call it webinars, quarterly. Hereby the innovation team, and sometimes another laboratory we [UMCU] collaborates with, give an update on existing and new project. It is quite interesting actually, because that is also how I learned about 3D bioprinting organs"*. Interestingly, not every employee is simultaneously informed about the progress of this technique. For example, IV1 explained: *"We [UMCU] have an innovation team that works closely with the researchers. If there is an innovation, they will thoroughly explore it before bringing it to our attention. If they do, well then, we further assess to see where it fits and if it can be of added value"*. Additionally, IV2 further pointed towards the involvement of the necessary actors by stating: *"Depending on the knowledge and input one can provide, they are involved. It really depends on which step in the process we are. There is no use of informing the head of operations, if professors are still researching how beneficial a new technique truly is."* It appears that within UMCU, a common agreement is that the key actors, being researchers, should be the ones to assess innovations first before other departments. As IV1 politely explained: *"[...] there are a lot of innovations about which is being published. If for example, it would be you or I, we tend to be more positive looking towards it. Researchers stay more objective, allowing them to assess it better. So the outcomes of studies and reports upon 3D bioprinting organ also indicate how effective and safe the innovation can be"*. Moreover, they also seem to share the same expectation of 3D bioprinting as each of the employees at UMCU stated that they believe that 3D bioprinting organs is promising but that it will not be implemented for another 10 – 15 years (**C4: (E)valuation processes in place**).

Nonetheless, if 3D bioprinted organs were to be implemented, there would be no issue to find suitable employees that can support the required procedures for 3D bioprinting organs (**C5: Enacted IR**) as IV2 explained: *"We always have enough employees. And there is not much to incentive I believe. Utrecht always want to innovate and improve and whoever applies for a job here has the same ambitions"*. Also, the need to restructure in order to adopt 3D bioprinting organs (**C6: Receptivity**) does not appear to be an obstacle due to the existence of a separate innovation team, which IV1 also mentioned: *"We have a separate focus on innovation, so I don't believe a whole department would need to be changed in Utrecht."* Moreover, all of UMCU's employees stated that in-depth analysis is done on each

4.2 Innovation system of bioprinted organs: *the Netherlands*

technology system, allowing them to have knowledge about potential challenges that could arise in the future (**C7: Adoptive capacity**). For instance, IV1 explained: *“We always make an assessment. So when we analyze different aspects, we also look at the risks and potential challenges. We take this into account, also with the costs to be prepared. Although it drives up the investment, you always need to consider all risks because if it happens, you need to have the resources for it”*. This ability to assess not only the added value of 3D bioprinting organs but also whether there are enough resources appears not to be an issue for UMCU. Both IV2 and IV5 indicated that the teams assigned for the assessment often report an update during department meetings. In fact, they also report when the preset indicators are not met and if other irregularities appear. Hence, it is assumed that UMCU can assess 3D bioprinting organs once it is implemented (**C8: Sustainability**).

5. Analysis: Case comparison

This chapter will present an initial pattern of connections among the system functions and IR categories, so-called motors of change (explained in section 2.1), for California ([section 5.1](#)) and The Netherlands ([section 5.2](#)). This involves the functioning of the 3D-BIOS and the Institutional Readiness (IR) for bioprinting organs in Californian and Dutch hospitals, respectively UCFS and UMCU. Hereafter, a comparison between California and the Netherlands is outlined in [section 5.3](#).

5.1 Motors of change 3D-BOIS: California

This section describes the observed linkages between the system functions in the 3D-BOIS in California and Institutional Readiness within the University of California San Francisco (USCF) Medical Centre.

From Figure 7 below, it can be seen that *the Guidance of the search (System function 4)* is a prominent system function in the 3D-BOIS in California as it is linked to all of the other four system functions. For example, positive expectations surrounding 3D bioprinting can result in support from actors such as the US government or biotech companies based in California (*System function 7: Creation of legitimacy*). In turn, System function 7 (*Creation of legitimacy*) will lead to an increased number of projects being launched that focus on 3D bioprinting organs (*System function 1: Entrepreneurial activities*) and also further enhances positive expectations surrounding 3D bioprinting organs (*System function 4: Guidance of the search*). Consequently, *the Guidance of the search (System function 4)* also enhances the availability of financial resources for research on 3D bioprinting organs (*System function 5: Market formation*) and information exchange upon 3D bioprinting organs or collaborations to improve 3D bioprinting technology (*System function 3: Knowledge diffusion*). Nevertheless, the feedback loop can also indicate a negative influence on the development of 3D bioprinting organs. For instance, a lack of information exchange or collaborations focused on 3D bioprinting (*System function 3: Knowledge diffusion*) can result in a decline of positive expectations being raised about 3D bioprinting organs (*System function 4: Guidance of the search*). This will, in turn, negatively influence both *Creation of legitimacy (System function 7)* and *Entrepreneurial Activities (System function 1)*.

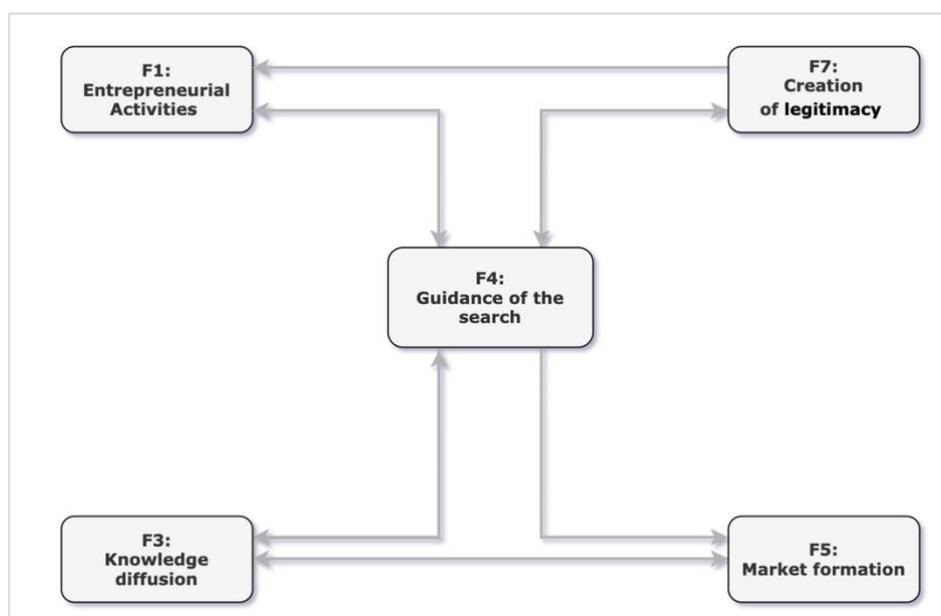


Figure 7: Pattern analysis of the system functions for the innovation system of 3D bioprinted organs in California

Figure 8 below displays the observed link between the system functions (SF) and Institutional Readiness (IR) categories. For instance, if there are positive expectations raised concerning 3D bioprinted organs (*System function 4: Guidance of the search*), a hospital is more likely to identify 3D bioprinting technology as a solution to the organ shortage (*C1: Demand for new technology*). It appears that, in turn, *C1 (Demand for new technology)* further enhances the optimistic outlook and expectations upon 3D bioprinting organs (*System function 4*). In fact, *C1 (Demand for new technology)* appears to have a reciprocal relation with *System function 4 (Guidance of the search)*. Besides this system function, *C1* appears to be influenced by both *System function 1 (Entrepreneurial activities)* and *System function 3 (Knowledge diffusion)*. This is because, for example, Californian hospitals often have their own innovation research lab or collaborate with one. Therefore, as 3D bioprinting is recognized to potentially solve the medical need of organ shortage (*C1: Demand for new technology*), entrepreneurial projects are launched to research this (*System function 1: Entrepreneurial activities*), and/or collaborations are set up (*System function 3: Knowledge diffusion*) to study 3D bioprinted organs.

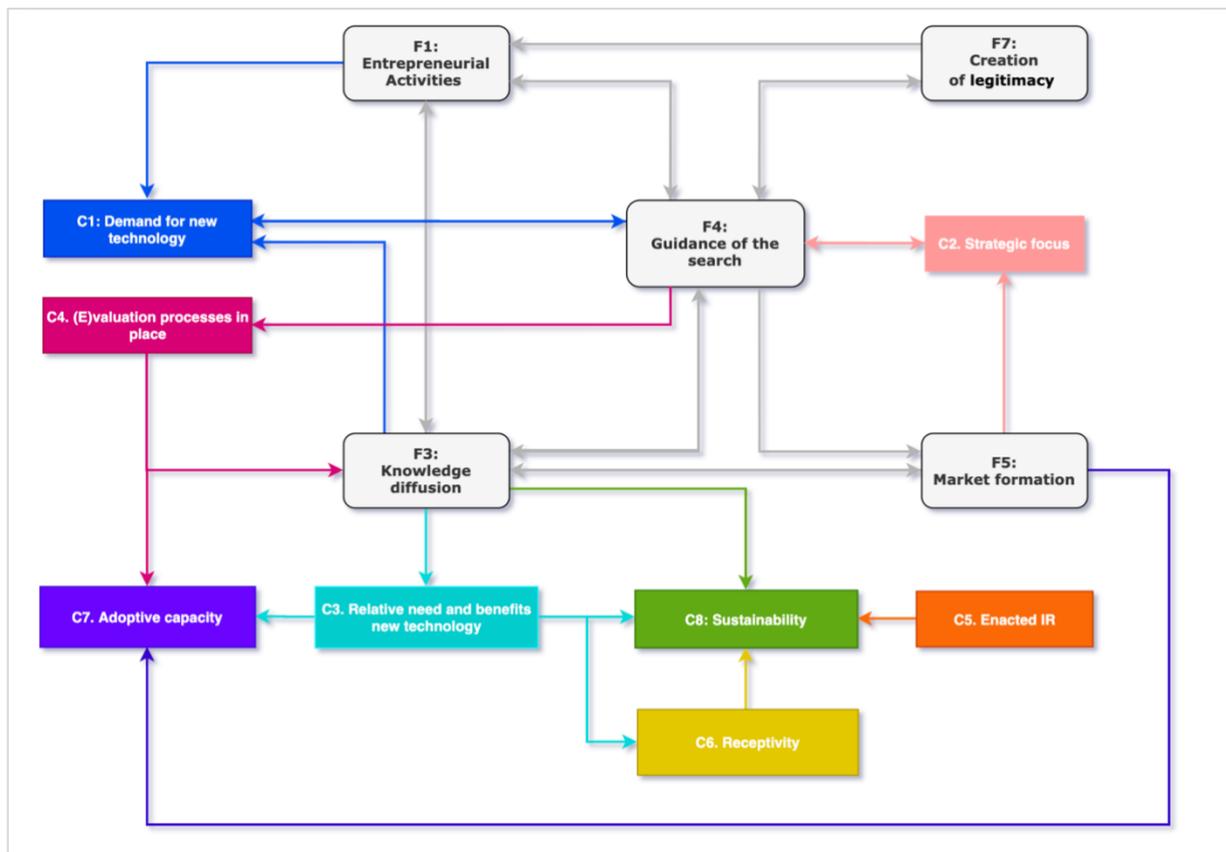


Figure 8: Linkages between system functions and Institutional Readiness categories for the innovation system of 3D bioprinted organs in California (University of California San Francisco Medical Centre)

Moreover, it appears that **C2 (Strategic focus)** is influenced by both *System function 4 (Guidance of the search)* also *System function 5 (Market formation)*. This is due to the fact that discovery and research into innovative medical technology by UCSF is restricted by financial benefits being offered (*System function 5: Market formation*) as well as the reported outcomes of other studies performed

on 3D bioprinting organs (*System function 4: Guidance of the search*). Furthermore, the presence of competent key actors within Californian hospitals, namely UCSF, that assess the 3D bioprinting technology (**C3: Relative need and benefits new technology**) appears to be influenced by the information being exchanged about 3D bioprinting organs through various forms, among which medical innovation conferences and in-depth analysis conducted by researchers of the hospital itself (*System function 3: Knowledge diffusion*). In fact, there is a chain of actors involved within the hospitals, starting with researchers and ending with the financial and operations department, that first assess 3D bioprinting before it can be adopted. In turn, the presence of key actors concerning 3D bioprinting organs within the hospital affects three IR categories. The first one being, the ability of the hospital to cope with organizational challenges before adopting 3D bioprinting organs (**C6: Receptivity**). Suppose the key actors are knowledgeable and capable of making an adequate assessment about the adoption of 3D bioprinting organs. In that case, the Californian hospital will be more informed about the requirements and associated challenges surrounding 3D bioprinted organs. Nevertheless, several employees from UCSF indicated that information regarding 3D bioprinting organs is not equally shared across the hospital but depends on the stage in which the 3D bioprinting organs is in. Moreover, the second IR category influenced by *C3 (Relative need and benefits new technology)* is **C7 (Adoptive capacity)**. The extent to which the key actors within the hospital conducted an in-depth analysis of 3D bioprinting organs (**C3: Relative need and benefits new technology**) affects the hospital's ability to cope with unforeseen challenges when adopting 3D bioprinting technology (**C7: Adoptive capacity**). Lastly, the hospital's capability to assess 3D bioprinting organs in the long-term concerning required resources and adequate knowledge (**C8: Sustainability**) is influenced by the analysis conducted by the key actors (**C3: Relative need and benefits new technology**).

Moreover, the agreement among hospital staff upon the effectiveness of 3D bioprinting organs (**C4: (E)valuation processes in place**) is affected by the positive expectations on 3D bioprinting organs expressed by, among others, researchers and healthcare actors (*System function 4: Guidance of the search*). In turn, the level to which hospital staff believes that 3D bioprinting technology can solve the organ shortage influences both the extent to which they communicate information about 3D bioprinting organs (*System function 3: Knowledge diffusion*) and the hospital's ability to cope with unforeseen challenges (**C7: Adoptive capacity**). Furthermore, it appears that the presence of employees that can support the adoption of 3D bioprinting organs within the hospital (**C5: Enacted IR**) and the extent to which the hospital is capable of coping with organizational challenges (**C6: Receptivity**) influences the long-term assessment a hospital can conduct, for which besides financial resources also human resources are needed (**C8: Sustainability**). Moreover, the hospital's capability to cope with unforeseen challenges concerning the adoption of 3D bioprinting organs (**C7: Adoptive capacity**) is influenced by the financial resources available by the US government or venture capitalist (*System function 5: Market formation*). Lastly, **C8 (Sustainability)** is beside the aforementioned *Enacted IR (C5)*, *Receptivity (C6)*, and *Relative need and benefits new technology (C3)* also influenced by a system function, namely *Knowledge diffusion (System function 3)*. This is because the availability of

financial benefits can ensure that the effectiveness of 3D bioprinting organs can be assessed in the long term by adequate personnel (*System function 3: Knowledge diffusion*).

5.2 Motors of change 3D-BOIS: *The Netherlands*

This section outlines the observed linkages between the system functions in the 3D-BOIS in the Netherlands and Institutional Readiness within the University Medical Centre Utrecht (UMCU).

From Figure 9, it can be seen that *Guidance of the search* (*System function 4*) is a significant system function in the 3D-BOIS in the Netherlands since it is connected to all of the other four system functions. For example, optimistic expectations about 3D bioprinting organs will positively influence the availability of financial benefits offered by either the Dutch government or an organization (*System function 5: Market formation*). In turn, a collaboration between actors, such as Universities and medical biotech companies that research 3D bioprinting organs, is positively stimulated (*System function 3: Knowledge diffusion*). In fact, *System function 3 (Knowledge diffusion)* further enhances the positive expectations about 3D bioprinting organs (*System function 4: Guidance of the search*) and the availability of financial support (*System function 5: Market formation*). Nevertheless, the feedback loop can also negatively influence the development of 3D bioprinting organs in the Netherlands. For instance, a lack of projects that research and develop 3D bioprinted organs technology (*System function 1: Entrepreneurial activities*) can negatively influence the expectation about 3D bioprinting organs in the Netherlands (*System function 4: Guidance of the search*).

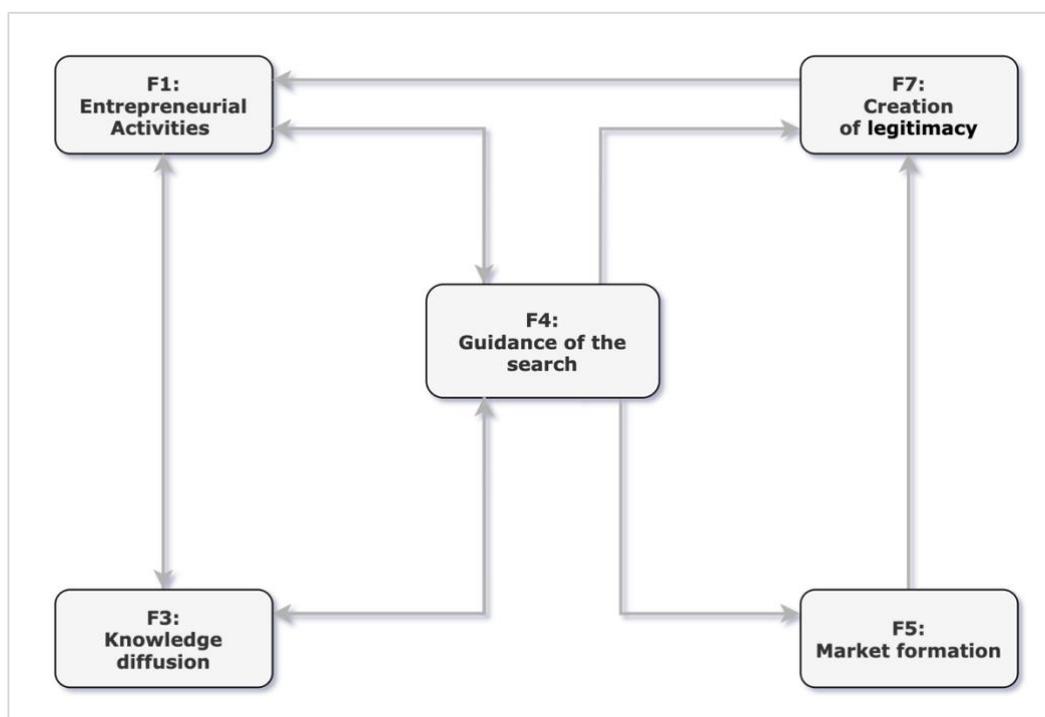


Figure 9: Pattern analysis of the system functions for the innovation system of 3D bioprinted organs in The Netherlands

Figure 10 below shows the observed links between the system functions (SF) and Institutional Readiness (IR) categories for the 3D-BOIS in the Netherlands. Firstly, it appears that **C1 (Demand for new technology)** is influenced by four system functions, namely *System function 1 (Entrepreneurial activities)*, *System function 4 (Guidance of the search)*, *System function 5 (Market formation)*, and *System function 7 (Creation of legitimacy)*. Employees within UMCU already indicated that it is essential that research is being conducted upon 3D bioprinting organs (*System function 1: Entrepreneurial activities*) in order for the technology to be identified as a possible solution to organ shortage. Additionally, the availability of financial resources to research 3D bioprinting organs (*System function 5: Market formation*) also influences a hospital's capacity to identify 3D bioprinting organs. In fact, a lack of available financial support can delay or even halt the developments concerning 3D bioprinting technology, thereby causing a hospital to not perceive 3D bioprinting organs as a solution that can fulfill the medical need of organ shortage. Also, the positive expectation expressed about 3D bioprinting (*System function 4: Guidance of the search*) and support from the Dutch government (*System function 7: Creation of legitimacy*) can positively affect a hospital's ability to identify 3D bioprinting technology as a solution for the organ shortage. However, it appears that **C1 (Demand for new technology)**, in turn, can further enhance the outlook that exists around 3D bioprinting organs. As explained earlier, a positive or negative feedback loop can arise. Suppose Dutch hospitals do not identify 3D bioprinting organs as a solution to the organ shortage, then fewer positive expectations concerning 3D bioprinting technology will occur.

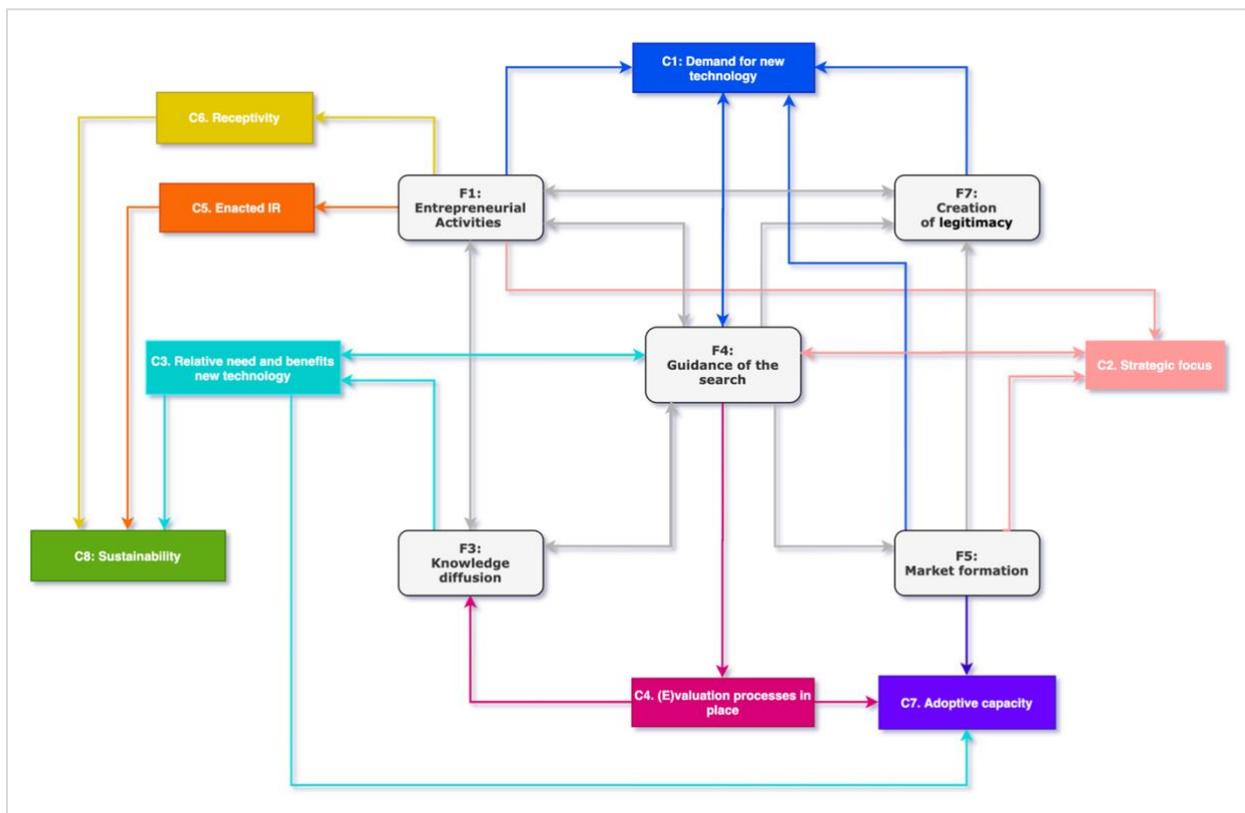


Figure 10: Linkages between system functions and Institutional Readiness categories for the innovation system of 3D bioprinted organs in The Netherlands (University Medical Centre Utrecht)

Moreover, concerning **C2 (Strategic focus)**, System function 4 (*Guidance of the search*) appears to influence the ability of hospital staff to identify other technologies that can solve organ shortage besides 3D bioprinting organs, such as organ-on-a-chip. Also, projects launched by biotech companies and UMCU's innovation teams (*System function 1: Entrepreneurial activities*) play a significant role in observing technologies that can solve the organ shortage. Additionally, financial support (*System function 5: Market formation*) affects **C2 (Strategic focus)** because discovery and research into innovative medical technology in UMCU are restricted by the offered financial benefits. Similar to **C1 (Demand for new technology)**, **C2 (Strategic focus)** also appears to further boost the outlook around 3D bioprinting organs. Furthermore, the presence of key actors that can assess the adoption of 3D bioprinting organs within the hospital (**C3: Relative need and benefits new technology**) appears to be affected by the expectations that exist about 3D bioprinting organs (*System function 4: Guidance of the search*) and the level of information communicated among involved actors, such as hospital staff, on 3D bioprinting technology (*System function 3: Knowledge diffusion*). In turn, the availability of adequate key actors can positively influence the ability of a hospital to cope with unforeseen challenges that might arise when adopting 3D bioprinting technology (**C7: Adoptive capacity**). Additionally, the hospital's ability to evaluate 3D bioprinting organs in the long-term, which requires resources and adequate knowledge (**C8: Sustainability**), is affected by **C3 (Relative need and benefits new technology)**.

Further, the extent to which information is shared within the hospital about the value of 3D bioprinting organs and the level to which staff members agree upon the effectiveness of 3D bioprinting organs (**C4: (E)valuation processes in place**) is influenced by the expectations that exist on 3D bioprinting organs (*System function 4: Guidance of the search*). Positive expectations about 3D bioprinting organs can result in a higher level of agreement among hospital staff upon the efficiency of 3D bioprinting organs. In turn, **C4 ((E)valuation processes in place)** affects the number of collaborations, as UMCU's innovation team, such as 3Dlab, often partners up with other Universiteit and/or biotech companies (*System function 3: Knowledge diffusion*). Also, again, the capability of a hospital to cope with unforeseen challenges regarding the adoption of 3D bioprinting is influenced (**C7: Adoptive capacity**). Moreover, both the availability of employees that can support the adoption of 3D bioprinting organs (**C5: Enacted IR**) and the extent to which a hospital is capable of coping with organizational challenges (**C6: Receptivity**) appears to be influenced by the projects that UMCU launches concerning 3D bioprinting technology (*System function 1: Entrepreneurial activities*). In fact, a Transplant coordinator (IV2) from UMCU stated that projects of UMCU display the innovative character of the hospital, which is appealing to many, thereby ensuring sufficient availability of prospective candidates (**C5: Enacted IR**). In turn, the presence of ample employees (**C5: Enacted IR**) and the ability to cope with organization challenges (**C6: Receptivity**) can be beneficial to the required assessment of 3D bioprinting organs in the long term (**C8: Sustainability**).

Moreover, **C7 (Adoptive capacity)** is influenced by System function 5 (*Market formation*), apart from the aforementioned **C4 ((E)valuation processes in place)** and **C3 (Relative need and benefits new**

5.3: Motor of change 3D-BOIS: California vs The Netherlands

technology). UMCU indicated that the availability of financial resources is important for and during the adoption of 3D bioprinting technology. Lastly, as mentioned previously, **C8 (Sustainability)** is affected by three IR categories, being *C3 (Relative need and benefits new technology)*, *C5 (Enacted IR)*, and *C6 (Receptivity)*.

5.3 Motors of change 3D-BOIS: California vs. The Netherlands

This section describes a comparison between the innovation system of 3D bioprinted organs within California and the Netherlands for which the Technological Innovation System (TIS) approach (Hekkert et al., 2007) was complemented by the Institutional Readiness (IR) categories (Webster & Gardner, 2019) (see [section 2.3](#)). Two hospitals were chosen as illustrative cases, namely University of California San Francisco (USCF) Medical Centre and University Medical Center Utrecht (UMCU) and University of California San Francisco (USCF) hospitals. Both hospitals were chosen due to their high ranking concerning the number of organ transplantations within, respectively, USA and Europe as well as their innovative character. It appears that in most regards, the 3D-BOIS and IR of hospitals within California and The Netherlands are similar. In fact, figure 11 shows that *Guidance of the search* (F4) is a prominent system function in both the 3D-BOIS of California and the Netherlands. In fact, the highest number of events retrieved related to System function 4 (Guidance of the search). In contrast, the lowest number of events found in California and the Netherlands relates to financial support (*System function 5: Market formation*). Nonetheless, some differences are observed regarding links between, and among, system functions and institutional readiness categories within the 3D-BOIS of California and The Netherlands. Table 6 on the following page displays an overview of the observed links within the 3D-BOIS of California and the Netherlands.

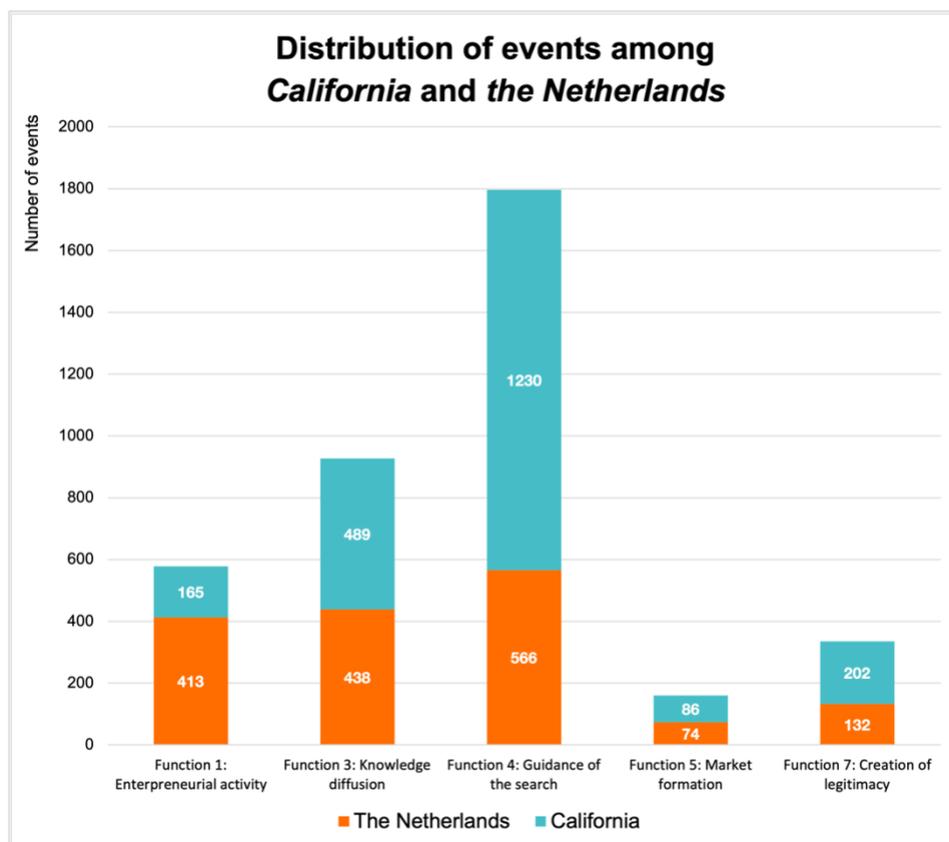


Figure 11: Overview of the distribution of events in California compared to The Netherlands

5.3: Motor of change 3D-BOIS: *California vs The Netherlands*

Table 6: Overview of the observed links between Institutional readiness categories and system functions in the 3D-BOIS of California and the Netherlands (Own table)

Institutional readiness category	Observed link within the 3D-BOIS of California	Observed link within the 3D-BOIS of the Netherlands
C1: Demand for new technology	<ul style="list-style-type: none"> System function 1: Entrepreneurial activities System function 3: Knowledge diffusion System function 4: Guidance of the search 	<ul style="list-style-type: none"> System function 1: Entrepreneurial activities System function 4: Guidance of the search System function 5: Market formation System function 7: Creation of legitimacy
C2: Strategic focus	<ul style="list-style-type: none"> System function 4: Guidance of the search System function 5: Market formation 	<ul style="list-style-type: none"> System function 1: Entrepreneurial activities System function 4: Guidance of the search System function 5: Market formation
C3: Relative need and benefit of new technology	<ul style="list-style-type: none"> System function 3: Knowledge diffusion C6: Receptivity C7: Adoptive capacity C8: Sustainability 	<ul style="list-style-type: none"> System function 3: Knowledge diffusion System function 4: Guidance of the search C7: Adoptive capacity C8: Sustainability
C4:(E)valuations processes in place	<ul style="list-style-type: none"> System function 3: Knowledge diffusion System function 4: Guidance of the search C7: Adoptive capacity 	<ul style="list-style-type: none"> System function 3: Knowledge diffusion System function 4: Guidance of the search C7: Adoptive capacity
C5: Enacted IR	<ul style="list-style-type: none"> C8: Sustainability 	<ul style="list-style-type: none"> System function 1: Entrepreneurial activities C8: Sustainability
C6: Receptivity	<ul style="list-style-type: none"> C8: Sustainability 	<ul style="list-style-type: none"> System function 1: Entrepreneurial activities C8: Sustainability
C7: Adoptive capacity	<ul style="list-style-type: none"> System function 5: Market formation 	<ul style="list-style-type: none"> System function 5: Market formation
C8: Sustainability	<ul style="list-style-type: none"> System function 3: Knowledge diffusion 	-

5.3: Motor of change 3D-BOIS: California vs The Netherlands

A total of four connections appears to be absent within the 3D-BOIS of California compared to the 3D-BOIS of the Netherlands. Firstly, it appears that among Californian hospitals, the identification of 3D bioprinting organs as a solution to cope with the rising organ shortage (*C1: Demand for new technology*) is not dependent on financial benefits (*F5: Market formation*). In contrast, within the Netherlands, subsidies offered by the Dutch Ministry of Health for research upon 3D bioprinting technology appear to be a driving factor in perceiving 3D bioprinting organs as a valuable technology to solve organ shortage. Additionally, within the 3D-BOIS of the Netherlands, *C1 (Demand for new technology)* also appeared to be influenced by System function 7 (*Creation of legitimacy*). In general, governmental institutions involve organizational bureaucracy, hence a (high) dependency of Dutch hospitals on governmental institutions can potentially delay a transition to a 3D-BOIS (*System function 7: Creation of legitimacy*). Secondly, in the 3D-BOIS of the Netherlands, the ability of Dutch hospitals to identify other technologies (*C2: Strategic focus*), such as a heart-in-a-box which can also help to solve the organ shortage issue, is influenced by the projects launched by the Dutch hospitals themselves (*System function 1: Entrepreneurial activities*). However, within Californian hospitals, this link appears to be missing. The absence of this information stream within Californian hospitals about current projects that focus on organ shortage and medical technologies, such as 3D bioprinting organs, affects the ability of employees to compare the technique of 3D bioprinting to other technologies (*C2: Strategic focus*).

Furthermore, within the 3D-BOIS of California, *C3 (Relative need and benefits new technology)* appears to be not affected by the expectations that exist about 3D bioprinting organs (*System function 4: Guidance of the search*). However, since the capacity of a Californian hospital to have competent key actors evaluating the 3D bioprinting technology affects the ability to incorporate the organ 3D printing technology in the long term (*C8: Sustainability*), see Table 6 on the previous page or figure 8 on page 44. It is essential to understand how the 3D bioprinting technology is positioned in the market and among the hospital staff as well as perceived by the society, which includes patients (*System function 4: Guidance of the search*). The last observed absent link within the 3D-BOIS of California relates to System function 1 (*Entrepreneurial activities*). Within the 3D-BOIS of the Netherlands, the number of actors involved in projects focused on 3D bioprinting organs influences both the availability of hospital employees that can support the adoption of 3D bioprinting technology (*C5: Enacted IR*) and the ability of the hospital to cope with organizational challenges (*C6: Receptivity*). In fact, employees from UMCU indicated that the projects that UMCU launched on innovations, such as 3D bioprinting organs (*System function 1: Entrepreneurial activities*), enhances the presence of prospective candidates (*C5: Enacted IR*). Also, the projects for which the dedicated innovation teams are in charge of, such as 3Dlab, result in no significant restructuring necessary to adopt 3D bioprinted organs (*C6: Receptivity*). Hence, it might also be beneficial for Californian hospitals to be aware of projects on 3D bioprinting organs to use it to attract promising prospects (*C6: Receptivity*) and also to reduce the need to (unnecessary) restructure departments for the adoption of technologies.

5.3: Motor of change 3D-BOIS: California vs The Netherlands

Moreover, there are three connections absent within the 3D-BOIS of The Netherlands, compared to the 3D-BOIS of California. Firstly, within California, financial resources from mostly venture capitalists (*System function 5: Market formation*) have a reciprocal link with the number of actors collaborating to research 3D bioprinted organs (*System function 3: Knowledge diffusion*). Instead, within the Netherlands, most financial support comes from the Dutch government in the form of subsidies (*System function 7: Creation of legitimacy*). Secondly, within the Dutch 3D-BOIS, a link appears to be absent between *Receptivity (C6)* and key actors within the hospital that will assess the adoption of 3D bioprinted organs (*C3: Relative need and benefits new technology*). It is essential to have employees with sufficient knowledge and competencies evaluating the adoption of 3D bioprinted organs to ensure no organizational barriers arise. Lastly, within the Dutch 3D-BOIS, compared to the 3D-BOIS in California, the ability of a hospital to assess 3D bioprinted organs in the long term (*C8: Sustainability*) is not influenced by the level of information exchange about 3D bioprinted technology (*System function 3: Knowledge diffusion*). In fact, employees from UCSF reported that all factors that could impact the adoption of 3D bioprinted organs, such as required financial and human resources, are being tracked and communicated. This ensures that the long-term assessment of 3D bioprinting can be conducted as accurate as possible (*C8: Sustainability*).

The following [section 6](#) will discuss the theoretical relevance as well as limitations of this research, whereafter the research question is answered in [section 7](#).

6. Discussion

This research aimed to map the emerging innovation system of 3D bioprinted organs and the Institutional Readiness of UCSF and UMCU between 2009 and 2020. Hereby the TIS framework (Hekkert et al., 2007) and IR framework (Webster & Gardner, 2019) were applied. Firstly, [section 6.1](#) discusses the theoretical relevance of this research, whereafter [section 6.2](#) reflects on the limitations of this study and the research methods used. Lastly, in [section 6.3](#), suggestions for further research are discussed.

6.1 Theoretical relevance of the research

This research has three significant contributions to literature. Firstly, the technological innovations systems literature is commonly used for sustainable technologies in the energy sector. However, there is a lack of TIS incorporation in the life science sector. Researchers such as Kukk et al. (2016) aimed to pinpoint the specific barriers that arise for innovations in the healthcare sector, but the challenges are yet mainly unknown. This research displays the interactions within a TIS framework essential for developing the innovation system of 3D bioprinting organs, which is yet in the take-off phase. Additionally, this research also displayed that while the technology of 3D bioprinting is in the take-off phase, *Knowledge diffusion* (System function 3) appears to be important. This system function is not commonly mentioned as essential during the take-off phase (Hekkert et al., 2011). *Nevertheless, in Hekkert et al. (2007), it is explained that System Function 3 (Knowledge Diffusion) is vital in a heterogeneous context, whereby the development of the technology is linked with government, competitors, and the market. This is the case for 3D bioprinted organs both in California and the Netherlands. In fact, a high number of collaborations between actors, such as medical biotech laboratories and biotech companies, is observed. Hence, this could supposedly indicate that besides the system functions commonly indicated to be essential in the take-off phase. Also, System function 3 (Knowledge diffusion) should be included for healthcare innovations within the take-off phase.*

Secondly, this thesis contributes to the Institutional Readiness (IR) literature in two manners. Firstly, while Webster and Gardner's (2019) IR framework was initially developed for regenerative medicine, this thesis focused upon the Institutional Readiness for a specific rising technology, namely 3D bioprinting of organs. Webster and Gardner (2019) indicated that no other novel field of biomedicines coped with the challenges of stabilizing living tissues. Interestingly, this challenge appeared for researchers aiming to 3D bioprinted a viable human organ, thereby indicating that there are perhaps common barriers for regenerative medicines and 3D bioprinting organs. Secondly, Webster and Gardner (2019) suggested that the IR framework could also be applied to other contexts from which insights could be gained. In this research, two prominent hospitals were chosen, namely UCSF and UMCU. Consequently, the lessons learned from these hospitals can be applied to other novel medical technologies for which hospitals will be the primary organization to implement the innovation in question.

Lastly, this thesis assumed a link between Webster and Gardner's (2019) Institutional Readiness categories and the system functions from the Technological innovation system (Hekkert et al., 2007). This assumption was based upon earlier work that researched barriers specific for the healthcare sector, such as Kukk et al. (2016) and Moors et al. (2018), and general knowledge. The findings of this study corroborate a connection between the system functions and IR categories. Nevertheless, it also appears that not all of the assumed relations between the system functions and Institutional Readiness categories occurred ([see section 2.3](#)). For example, IR category 1 (*Demand for new technology*) was assumed to be related to System function 1 (*Entrepreneurial activities*), System function 3 (*Knowledge Diffusion*), System function 4 (*Guidance of the search*), and System function 5 (*Market formation*). However, for the 3D-BOIS of California, it appeared that C1 (*Demand for new technology*) is not influenced by System function 5 (Market formation). Concerning the 3D-BOIS of the Netherlands, System function 7 (*Creation of legitimacy*) instead of System function 3 (*Knowledge Diffusion*) appeared to influence IR category 1 (*Demand for new technology*). Another example is C2 (*Strategic focus*), which, in both the 3D-BOIS of California and the Netherlands, besides the assumed System function 4 (*Guidance of the search*), was also linked to System function 5 (*Market formation*). In fact, within the Dutch 3D-BOIS, also a third system function was related to C2 (*Strategic focus*), being System function 1 (*Entrepreneurial activities*). In [Appendix 6](#), a complete overview of the assumed link between the Institutional Readiness categories and system functions as well as those observed within the 3D-BOIS of California and the Netherlands can be seen. Although this research is explorative of nature, and hence these identified relations might not be complete, this research is an adequate first step to develop a refined, integrated framework for interactions between TIS and IR.

6.2 Limitations and reflection

This chapter outlines the limitation of the theoretical framework, research methods, and results. Also, the validity and reliability of this research are discussed.

The theoretical framework of Technological Innovation System (TIS) and Institutional Readiness (IR) was chosen because they were assumed to complement each other. Namely, as the TIS only focuses on barriers at a systemic level, institutional challenges on the micro-level within an organization can be overlooked. Hence, the IR framework complemented the TIS by obtaining insights into hampering aspects and challenges on an organizational level within hospitals in California and The Netherlands. Although the findings corroborate a relation between system functions and Institutional readiness, the IR framework is relatively new. This might have caused aspects to be overlooked that could be important for innovation within the healthcare sector, such as agreements between the government, hospitals, and insurance companies about what part of the cost for medical treatments is covered. Moreover, triangulation took place, namely by validating the data obtained from desk research with interviewees. Nevertheless, no investor triangulation occurred, which may have caused biases from the researcher, affecting the descriptive validity. However, it should be noted that the findings were also discussed with an external supervisor during the research process. In addition, reliability is

ensured by including the interview guide ([Appendix 3](#)) and the list of interviewees ([Appendix 4](#)) to provide transparency regarding the data collection.

Furthermore, fewer interviews could be conducted than expected within California (UCSF) and the Netherlands (UMCU) due to the COVID-19. As more interviews took place for The Netherlands (11 interviews) than California (7 interviews), the interpretation of the organizational readiness within UCSF can be affected. Additionally, this research focuses on a specific medical technology, namely 3D bioprinting organs, and two academic hospitals. Hence, the findings cannot be generalized for the United States of America and the Netherlands but rather are restricted to San Francisco (California) and Utrecht (Utrecht). Moreover, concerning the scope, namely California and the Netherlands, most interviewees were employees from, respectively, UCSF and UMCU. Hence, incorporating different viewpoints could have presented a more comprehensive representation of the development of the 3D bioprinting organs innovation system in California and the Netherlands. Although the researcher attempted to contact several organizations, for example, a participant from an insurance company in the Netherlands or the Dutch government is missing. Concerning California, an interviewee could be added that is an employee at, for example, a patient advocacy organization, FDA, or the United States Secretary of Health and Human Services.

6.3 Future research

As mentioned before, this thesis provides a good starting point to developing an integrated framework to analyze barriers at both systemic and organizational level, respectively, by incorporating the TIS and IR. Hence, a few directions for future research that support the further development of 3D bioprinting organs are outlined.

Firstly, it appears that some Institutional Readiness categories are influenced by, and are affecting, the same system functions and Institutional Readiness categories. For example, within the 3D-BOIS of the Netherlands, both C5 (*Enacted IR*) and C6 (*Receptivity*) are influenced by System function 1 (*Entrepreneurial activities*) and affecting C8 (*Sustainability*). Hence, it would be interesting to explore whether some Institutional Readiness categories can be clustered. More specifically, this would shed light on whether all eight IR categories are important for innovations within the health care sector. Additionally, the observed links among system functions and Institutional Readiness categories could be explored among private hospitals and smaller (local) hospitals within California and the Netherlands to identify similarities or differences.

Secondly, the Dutch government appears to have five Health & Care Missions upon which they focus, for which the targets are set for 2040. However, according to Marsman (2021), these missions are rigid, and as a result, medical innovation is often not the priority. Therefore, it could be interesting to also include a Mission-Oriented Innovation System (MIS). The MIS supports the idea that transformative change is achieved by mobilizing and coordinating actors to innovate to reach clearly defined targets in broad societal areas (Hekkert et al., 2020), which in this case would be the healthcare

sector. Further research could reveal, for example, how the set mission that “By 2040, all Dutch people will live at least five years longer in good health [...]” (Ministerie van Economische Zaken en Klimaat, 2019, p.49) affects the developments of medical innovations, such as 3D bioprinted organs.

Moreover, as this research merely focused on the innovation system of 3D bioprinting organs, the Multi-Level Perspective (MLP) framework could also be included. The MLP is a framework consisting of three levels. The first one is called ‘*landscape*,’ which refers to exogenous factors, such as wars, or in this case, the pressure resulting from the increasing organ shortage. The second level is the ‘*sociotechnical regime*,’ which relates to the existing rules and practices around organ transplantations. The last level is ‘*niche*’ in which new technologies are developed (Geels, 2002). This research focused on the upcoming innovation system of 3D bioprinting organs, which is situated between the niche and sociotechnical regime. Further research can also include the *sociotechnical regime* to explore how the current practices of organ transplantations affect the development of 3D bioprinting organs, either positively or negatively. Thus, a more comprehensive view can be obtained, which might also indicate unobserved barriers.

Lastly, as the scope of this research is on two different geographical areas, namely California and the Netherlands, for which differences are already observed ([section 5.3](#)), the literature upon Entrepreneurial ecosystems could also be included. As Spigel (2017) stated: “*Entrepreneurial ecosystems have emerged as a popular concept to explain the persistence of high-growth entrepreneurship within regions*” (p.1). Both California and the Netherlands appear to be in the top 5 geographical locations with established biotech companies, respectively, within the USA and Europe. Also, researchers from both locations are active regarding developments upon 3D bioprinted organs. Therefore, it would be intriguing to explore the entrepreneurial ecosystems and how this affects the types of resources that American and Dutch entrepreneurs can obtain to develop 3D bioprinting organs. The research findings could reveal how entrepreneurial ecosystems within California and the Netherlands affect the entrepreneurship process surrounding 3D bioprinting organs. Additionally, it can also point towards policy recommendations that can strengthen the 3D bioprinting organs ecosystem.

7. Conclusion

Globally the shortage of organs is becoming a pressing issue as the number of patients on the donor waiting list is increasing. In order to fulfill this medical need, 3D bioprinting of organs appears to be a suitable solution, primarily due to the technological advancements that have been made in the past decade, especially since 2009. In this thesis, two geographical locations have been chosen based on their developments regarding bioprinting organs, being California and The Netherlands. The former was chosen as the Californian medical laboratory Organovo managed to bioprint a heart in 2009, which was perceived as a significant breakthrough in 3D bioprinting of organs. Hence, this signals that the Americans were a frontrunner regarding 3D bioprinting organs. The Netherlands was chosen as researchers of the University Medical Centre Utrecht (UMCU) developed a 3D technique that can supposedly reproduce parts of the human body within minutes. Hence, it appears that the Dutch are catching up and can potentially learn from the Californian front-runner case. Nevertheless, besides technical abilities, it is also essential to focus on barriers for the implementation of the technology. This is because a lack of acceptance of bioprinted organs within hospitals can delay the adoption of 3D bioprinting organs. This research was developed to explore the barriers within the innovation system of bioprinted organs (3D-BOIS) in California and the Netherlands to stimulate a transition from the current organ transplantation to 3D-BOIS. In order to explore this, the following research question was formulated:

What are the barriers and potential solutions concerning hospitals' Institutional Readiness for 3D bioprinting organs in California and The Netherlands based on the emerging 3D bioprinting organ innovation system throughout 2009 – 2020?

In order to answer this question, a conceptual framework was developed which combined the Technological Innovation System (TIS) approach with the Institutional Readiness (IR) approach. The former provides insights into the barriers of 3D bioprinting organs on a systemic level, whereas the latter focuses on the obstacles of 3D bioprinting organs at an organizational level, namely hospitals. In order to obtain more in-depth insights at the organizational level, two illustrative cases were studied, namely the University of California San Francisco (UCSF) Medical Center and University Medical Center Utrecht (UMCU). Both hospitals rank within, respectively, the American and European top five hospitals that focus on organ transplantations. Data was obtained through desk research and 18 interviews with experts regarding organ transplantations and 3D bioprinting innovation, namely 7 interviews within California and 11 within the Netherlands. For the 3D bioprinting organs innovation system (3D-BOIS), several barriers regarding the Institutional Readiness of hospitals in California and The Netherlands over the period 2009 – 2020 were identified. The following paragraphs outline these identified barriers within the 3D-BOIS in California and the Netherlands.

Firstly, both California and the Netherlands appeared to cope with two common barriers. The first barrier relates to the absence of a clear regulatory framework around 3D bioprinting organs (*System function 7: Creation of legitimacy*). In 2009 – 2020, the U.S. Food and Drug Administration (FDA) aimed

to clarify and issue guidance on 3D bioprinting organs. This report classified 3D bioprinting as a medical device, which clarified what regulations and procedures could be followed. Nevertheless, it also resulted in further questions. For instance, it was unclear which regulations would need to be followed once a functional organ was printed. In the Netherlands, legal clarity on how 3D bioprinting organs are classified has yet to be provided by the European Medicines Agency (EMA). Although the Dutch House of Representatives indicated that changes would need to be made to intellectual property (IP) rights, among researchers concerns about biocrimes increased. Moreover, since 2002 in The Netherlands, the Embryo act is in effect, which prohibits human tissue growth or cloning. Nonetheless, once 3D bioprinters can 3D bioprint functional organs, the regulatory framework must be in place. If the regulations differ in each country, it can hinder the commercialization of 3D bioprinting and further delay the transition to 3D-BOIS. More importantly, within the 3D-BOIS of California and the Netherlands System function 7 (*Creation of legitimacy*) appears to be linked with the number of actors that are researching 3D bioprinting organs (System function 1: Entrepreneurial activities), which in turn affects the ability of the hospital to perceive 3D bioprinted organs as a solution to solve the organ shortage (*Institutional Readiness 1: Demand for new technology*). Hence, both the Dutch and Californian governments must construct clear regulations surrounding 3D bioprinting to enhance market access to the technique in the near future while also considering the ethical questions and concerns on biocrimes. Hereby, primarily the FDA and the EMA should explore the regulations and procedures once a functional human organ has been printed. Even though 3D bioprinting is still being refined, the regulations are essential so that healthcare actors and medical companies can quickly adapt their processes accordingly. Ultimately, this will prevent further delays in the transition to a 3D-BOIS.

The last common barrier relates to the effectiveness of 3D bioprinting, for which a discrepancy was found between desk research and interviews (*System function 4: positive guidance of the search*). Whereas several reports and articles mentioned that 3D bioprinting organs might occur no later than the next decade, interviewees from UCSF and UMCU believe that it is too early for 3D bioprinting organs, and advancements still need to be made. This could potentially pose a barrier as both Californian, and Dutch hospitals allocate their finances (*System function 5: Market formation*) after a thorough analysis, which includes exploring the added value of the 3D bioprinting technology. In addition, a negative expectation upon 3D bioprinting organs might move them in the direction of other rising technologies, such as organ-on-a-chip or heart-in-a-box. Additionally, in both California and The Netherlands, positive expectations (*System function 4*) about 3D bioprinting organs appeared to be related to the ability of a hospital to identify 3D bioprinting as a solution to fulfill organ shortage (*C1: Demand for new technology*) and the agreement upon the effectiveness of 3D bioprinting (*C4: (E)valuation processes in place*). Hence, sufficient financial resources must be available to stimulate research in hospitals on 3D bioprinting organs (*System function 5: Market formation*). For this, in the Netherlands, the Dutch government should offer subsidies for public and private institutions and organizations, such as innovative medical companies, which engaged in a project focused on 3D bioprinting organs. In California, the situation appears to be slightly different due to the high number

of venture capital investments that are generally available. Hence, in California, it is essential that information is being exchanged about the capabilities of 3D bioprinting between the private or public institutions/organizations and the venture capitalist to obtain enough financial resources for the development of 3D bioprinting organs.

Moreover, also two specific barriers were observed within the 3D-BOIS of the Netherlands. The first one relates to a hospital's capacity to identify 3D bioprinting organs as a technology to solve the human organ shortage (*Institutional Readiness category 1: Demand for new technology*). Within the 3D-BOIS of the Netherlands, besides system functions 1 and 4, this IR category is influenced by support from professional institutions and Dutch governmental organizations (*System function 7: Creation of legitimacy*), such as the Dutch Ministry of Health, and financial benefits in the form of subsidies (*System function 5: Market formation*). As it is generally known that these governmental institutions involve organizational bureaucracy, the high dependency on these governmental institutions can delay a transition to a 3D-BOIS. For comparison, within California, besides system functions 1 and 4, the ability of a hospital to identify the technique of 3D bioprinting organs as a solution to the human organ shortage depends on the information exchange and conferences (*System function 3*). In fact, yearly conferences focus on novel medical technologies within California, and even awareness campaigns are launched to promote 3D bioprinted organs. Hence, in order to assure that Dutch hospitals can faster 'detect' the technique of and developments within 3D bioprinted organs and its potential to solve the human organ shortage, the Dutch government should collaborate with patient organizations, such as the Dutch Transplant Foundation, to organize (bi-)yearly conferences that focus on novel medical technologies for pressing unfulfilled medical needs. Additionally, Dutch hospitals can provide university students access to 3D tools, as is currently being done by UCSF Medical Centre. This will enhance interdisciplinary collaboration and increases the rate of discovery. Moreover, the Dutch hospitals can also launch an awareness campaign in collaboration with patient organizations and the Dutch Ministry of Health, as was done in California in 2014. The questions that will arise during the campaign from the patients can support the Dutch hospitals to prepare better for the procedures of 3D bioprinting organs and point towards unidentified aspects that need to be taken care of.

The second and last observed barrier in the 3D-BOIS in the Netherlands relates to the hospital's capacity to cope with organizational requirements to adopt 3D bioprinting organs (*Institutional Readiness category 6: Receptivity*). In both the Netherlands and California, this Institutional Readiness category appears to influence the hospital's ability to evaluate and adopt 3D bioprinting in the long term (*Institutional Readiness category 8: Sustainability*). Nevertheless, in Dutch hospitals, a link appears to be absent between *Receptivity (Institutional Readiness category 6)* and key actors within the hospital that will assess the adoption of 3D bioprinted organs (*Institutional Readiness category 3: relative need and benefits new technology*). As it is essential to have employees with sufficient knowledge and competencies evaluating the adoption of 3D bioprinted organs to ensure no organizational barriers arise, the Dutch can apply a similar approach as the Americans. This approach involves including a staff member from other departments, such as human resources and the

operational department, during the analysis of 3D bioprinting organs. Hereby, it is discussed whether departments would need to be restructured or organizational problems, such as lack of a staff, would occur during the adoption of 3D bioprinted organs.

Furthermore, also two barriers were observed specifically within the 3D-BOIS in California. For example, the strategic focus (*Institutional Readiness category 2*) within Californian hospitals is influenced by the expectations that exist about 3D bioprinting organs (*System function 4: Guidance of the search*) and the financial benefits offered to research 3D bioprinting organs (*System function 5: Market formation*). In the Netherlands, besides these two system functions, an additional system function influences the *strategic focus (Institutional Readiness category 2)*, namely entrepreneurial activities (*System function 1*). Within the Dutch hospitals, other technologies that can solve the organ shortage, such as organ-on-a-chip, are affected by the projects launched by the Dutch hospital itself (*System function 1: Entrepreneurial activities*). The absence of information about current projects that focus on organ shortage and medical technologies, such as 3D bioprinting organs, within Californian hospitals affects the ability of employees to compare the technique of 3D bioprinting to other technologies (*Institutional Readiness category 2: Strategic focus*). Additionally, the strategic focus of the hospital indirectly relates to the key actors within the hospital that needs to assess the adoption of 3D bioprinted organs (*Institutional Readiness category 3: relative need and benefits new technology*), which in turn influences the ability of a hospital to cope with unforeseen challenges (*Institutional Readiness category 7: Adoptive capacity*). Hence, it is of importance that the researchers have accurate information about potential technologies that can cope with organ shortage as they are the first ones in the chain to assess innovations, whereafter other departments are included to discuss the potential adoption of the innovation in question. In order to overcome this issue in Californian hospitals, for example, the internal computer network of Californian hospitals can be updated for exchanging information about medical innovations, as UMCU is doing. For this, a section on the website called 'current projects' can be included, whereby novel medical innovations are described, such as 3D bioprinting organs. This should involve not only information about new projects but also a brief update on existing projects. Consequently, this information stream within the hospital will be improved, and thereby positively affecting *Institutional Readiness category 2 (Strategic focus)*

The last observed barrier was related to *Institutional Readiness category 3 (relative need and benefits new technology)*, which is influenced by *Knowledge diffusion (System function 3)*. In contrast, in the Dutch 3D-BOIS, besides *Knowledge diffusion (System function 3)*, the presence of key actors that can assess the adoption of 3D bioprinting organs within the hospital (*C3: Relative need and benefits new technology*) is also affected by the expectations that exist about 3D bioprinting organs (*System function 4: Guidance of the search*). Both in California and the Netherlands, the availability of key actors evaluating the 3D bioprinting technology (*Institutional Readiness category 3: Relative need and benefits new technology*) influences the ability to assess the organ 3D printing technology in the long term (*Institutional Readiness category 8: Sustainability*). Hence, it is essential to understand how 3D bioprinting technology is positioned in the market in terms of developments and outcomes of studies.

As an organ donor coordinator from UMCU explained, the outcomes of studies and reports upon 3D bioprinting organs indicate how effective and safe the innovation can be. Subsequently, based on the information available on 3D bioprinting organs, it can be assessed whether the key actors, primarily researchers, are capable and knowledgeable enough to assess the adoption of 3D bioprinting organs. As within both UCSF and UMCU often innovation teams are in charge of novel technologies, UCSF can adopt UMCU's approach. This approach involves organizing quarterly webinars with the innovation team, department staff, such as transplant coordinators, and medical biotech companies with whom the hospital collaborates. During these webinars, both new existing and new projects on innovations can be discussed. These webinars can enhance the information exchange about study outcomes of 3D bioprinting organs with hospital members, thereby ensuring that the hospital can verify that they have competent actors that can assess the innovation in question, in this case, 3D bioprinting organs.

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Appendices

Appendix 1: Event categories

System function	Event Category	Sign
F1: Entrepreneurial activity	New project started	+
	Innovation reached market	+
	Actors engaging to develop a product (e.g. bioprinter)	+
	Entrepreneurial support for bioprinting organs	+
	Project abandoned	-
	Lack of support/investors/contractors	-
F3: Knowledge diffusion	Conferences on innovations surrounding organ transplantations	+
	Collaborations between actors	+
	Information exchange on organization or governmental website	+
F4: Guidance of the search	Positive expectations raised on the possibility of bioprinting organs	+
	Market growth expected	+
	Promising outcome of a study performed on bioprinting organs	+
	Mission or target set by government to global organ shortage	+
	Positive expectations expressed in articles	+
	Doubt, uncertainty expressed in articles	-
	Negative expectations raised on the ability of bioprinting organs	-
F5: Market formation	Start tax programs	+
	Financial benefits enabling new market (research) opportunities	
	Policies/initiatives by government leading to new market opportunities	+
	Industry standards that foster the development for bioprinting organs	+
	Stop of tax programs	-
F7: Creation of legitimacy	Lobby actions from patient groups and/or health-related organizations	+
	Support from professional institutions or organizations	+
	Governmental support	+
	Expressed resistance against bioprinting organs	-

Appendix 2: Information sheet



Utrecht University

**INFORMED CONSENT FORM for participation in:
Thesis on bioprinting organs**

You are invited to take part in a research study. Before I conduct the scheduled interview, I would like to inform you about the research that is being done and what it would mean for you. You are at any moment, before or during the interview, free to ask questions for further clarification.

The purpose of the research is to obtain insights in 1) the upcoming innovation system of bioprinting organs in California and the Netherlands and 2) what the current institutional readiness is in UMCU and UCSF Medical Centre. The study is done as part of my master thesis at Utrecht University.

Please place your signature below if you have no objections on the following points

I confirm that:

- I am satisfied with the received information about the research
- I have been given opportunity to ask questions about the research and that any questions that have been risen have been answered satisfactorily
- I had the opportunity to think carefully about participating in the study
- I will give an honest answer to the questions asked

I agree that:

- The data to be collected will be obtained and stored for scientific purposes
- The collected, completely anonymous, research data can be shared and re-used by scientists to answer other research questions
- Video and/or audio recordings may also be used for scientific purposes.

I understand that:

- I have the right to withdraw my consent to use the data.
- I have the right to see the research report afterwards.

Name of the participant

Date/ Place

Signature

Appendix 3: Interview guide*

Warm up questions

1. Can you please tell me about your role and experience with organ transplants?
2. How long have you been working in the healthcare sector, and specifically involved with organ transplants?

Questions

System function 1: Entrepreneurial activities

3. What would you say are key trends in the last decade in terms of innovations to combat the organ shortage?
 - a. How would you rank 3D bioprinting among those?
 - b. Who are the key drivers of these innovations?

System function 3: Knowledge diffusion

4. Have you observed any collaborations between (key) actors to combat organ shortage?
5. Do you believe there are sufficient events such as workshops and conferences that allow to diffuse knowledge on 3D bioprinted organs?

System function 4: Guidance of the search

6. What is your perception/expectation regarding 3D printed organs?

System function 5: Market formation

7. What aspects support or hinder the development of the 3D bioprinted market?

System function 7: Creation of legitimacy

8. Based on your experience, do you perceive resistance or acceptance of 3D printed organs?
 - a. Ethical challenges?

As a part of my thesis, I also specifically look at the organization itself. This is because within organizations there could factors that influence the extent to which they are 'ready' for 3D bioprinted organs. The following questions will be about this. If you are unable to answer one of the questions, feel free to indicate so.

9. C1/2: How do you identify new technologies/innovations that can fulfill unmet medical needs, such as the organ shortage?
 - a. Does this specifically involve people that have knowledge and resources to identify and compare these technologies?
10. C2/C3: How do you assess the value of 3D bioprinting for the organ shortage?
 - a. Which key actors are hereby involved?
 - b. C4: How is this information shared within the organization? Does this include all actors involved in the "chain"?
11. C5: How do you internally discuss the adoption of any innovation, but specifically 3D bioprinting?
 - a. C5/6: Which departments need to make changes in order to adopt the 3D bioprinting? Are they prepared to do so?

*For interview transcripts, please click [here](#)

12. C7: How do you prepare for unforeseen challenges, when adopting a new system?
13. C8: How do you monitor new systems?
 - a. How would this be done for 3D bioprinting?

Closing questions

14. From your view, what are the most significant differences between the development of 3D bioprinting in USA (California) and The Netherlands?
15. Are there specific actors or organizations that you think are relevant for this research that we haven't discussed yet?
16. Is there anything you want to add that has not yet been discussed?
 - a. Do you perhaps have any interesting documents to share with me?
17. Do you know someone from this field who I could contact and interview?
18. Can I contact you if I need clarification on any issue?

Appendix 4: Interviewee references

Interviewee	Location	Organization	Function
IV1	The Netherlands	University Medical Center Utrecht	Organ donor coordinator
IV2	The Netherlands	University Medical Center Utrecht	Transplant coordinator
IV3	The Netherlands	University Medical Center Groningen	Professor and Transplantation and Program Coordinator
IV4	The Netherlands	University Medical Center Utrecht	Head of Innovation and Associate professor Medical Technology
IV5	The Netherlands	University Medical Center Utrecht	Coordinator 3D lab
IV6	The Netherlands	University Medical Center Groningen	Program manager and Research Transplantations
IV7	The Netherlands	Dutch Transplant Foundation	Law and regulation manager
IV8	The Netherlands	Patient Federation Netherlands	Senior advisor Patient interest
IV9	The Netherlands	Dutch Kidney Patients Association	Senior policy officer
IV10	The Netherlands	Child and Hospital Foundation	Director
IV11	The Netherlands	Erasmus Medical Centre	Cardiologist
IV12	California	University of California San Francisco	Researcher Bioengineering
IV13	California	University of California San Francisco	Transplant nurse
IV14	California	University of California San Francisco	3D printing engineer
IV15	California	University of California San Francisco	Professor: Departments of Bioengineering & Therapeutic Sciences and Surgery
IV16	California	University of California San Francisco	Strategy & Operations
IV17	California	University of California San Francisco	Transplant Coordinator

Appendix 5: Contacted interviewees

Interviewee number	Location	Organization	Function
1	The Netherlands	University Medical Center Utrecht	Medical innovation manager
2	The Netherlands	University Medical Center Utrecht	Head of Innovation and Associate professor
3	The Netherlands	University Medical Center Utrecht	Professor of Translational Regenerative Medicine
4	The Netherlands	University Medical Center Utrecht	Nurse organ transplantation
5	The Netherlands	University Medical Center Utrecht	Professor of Molecular Cardiogenetics
6	The Netherlands	University Medical Center Utrecht	Biomedical engineer 3D Lab
7	The Netherlands	University Medical Center Utrecht	Cardiologist, Fellow Heart Failure
8	The Netherlands	University Medical Center Utrecht	Innovation manager Healthcare
9	The Netherlands	University Medical Center Utrecht	Innovation and Valorisation manager
10	The Netherlands	University Medical Center Utrecht	Nurse organ transplantation
11	The Netherlands	University Medical Center Utrecht	Assistant Professor - medical
12	The Netherlands	University Medical Center Utrecht	Researcher Bioengineering
13	The Netherlands	University Medical Center Utrecht	Transplant coordinator
14	The Netherlands	University Medical Center Utrecht	Nurse organ transplantation
15	The Netherlands	University Medical Center Utrecht	Assistant professor - Healthcare
16	The Netherlands	University of California San Francisco	Strategy & Operations
17	The Netherlands	University of California San Francisco	Transplant Coordinator
18	The Netherlands	OHRA (insurance company)	Service manager (Team Innovation)
19	The Netherlands	OHRA (insurance company)	Claims handler (Medical treatments)
20	The Netherlands	OHRA (insurance company)	Claims handler (Medical treatments)

21	The Netherlands	OHRA (insurance company)	Manager Sales Health Insurance
22	The Netherlands	Zilveren Kruis (insurance company)	Claims handler (Medical treatments)
23	The Netherlands	Zilveren Kruis (insurance company)	Service manager (Team Innovation)
24	The Netherlands	Zilveren Kruis (insurance company)	Claims handler (Medical treatments)
25	The Netherlands	Zilveren Kruis (insurance company)	Manager Sales Health Insurance
26	The Netherlands	Ministry of Health, Welfare and Sport	Coordinator Healthcare Systems
27	The Netherlands	Ministry of Health, Welfare and Sport	Policy Officer Organ and Tissue Donation
28	The Netherlands	Ministry of Health, Welfare and Sport	Management Team member Medicines and Medical Technology, Innovation and Security of Supply
29	The Netherlands	ZonMw (organization for health research and care innovation)	Consultant Strategy & Innovation
30	The Netherlands	ZonMw (organization for health research and care innovation)	SDG3 Health coördinator
31	The Netherlands	ZonMw (organization for health research and care innovation)	Program manager (Healthcare & Innovation)
32	The Netherlands	FELIXprinters (3D printing company)	Research Development Lead
33	The Netherlands	FELIXprinters (3D printing company)	Sales manager
34	California	Organovo (Biotech Company)	Technology development Lead
35	California	Organovo (Biotech Company)	Manager Sales
36	California	Prellis Biologics (Biotech Company)	Manager Product Management
37	California	Prellis Biologics (Biotech Company)	Lead Tissue Engineer
38	California	University of California, San Francisco Medical Centre	Living Donor Nurse Coordinator
39	California	University of California, San Francisco Medical Centre	Clinical Program and Research Coordinator
40	California	University of California, San Francisco Medical Centre	Lead Program Coordinator
41	California	University of California, San Francisco Medical Centre	Associate Professor

42	California	University of California, San Francisco Medical Centre	Manager of Health System Operations
43	California	University of California, San Francisco Medical Centre	Chief of Innovation
44	California	University of California, San Francisco Medical Centre	PhD Candidate (department of bioengineering)
45	California	University of California, San Francisco Medical Centre	Director, Clinical Innovation Center
46	California	University of California, San Francisco Medical Centre	Nurse organ transplants
47	California	University of California, San Francisco Medical Centre	Nurse organ transplants
48	California	University of California, San Francisco Medical Centre	Healthcare Management
49	California	University of California, San Francisco Medical Centre	Sr. Supervisor Transplantation Service
50	California	University of California, San Francisco Medical Centre	Liver Transplant Coordinator
51	California	University of California, San Francisco Medical Centre	Neonatology
52	California	University of California, San Francisco Medical Centre	Innovation manager Healthcare
53	California	University of California, San Francisco Medical Centre	Living Donor Nurse Coordinator
54	California	Anthem Blue Cross (insurance company)	Claims handler (Medical treatments)
55	California	Anthem Blue Cross (insurance company)	Service manager (Team Innovation)
56	California	Anthem Blue Cross (insurance company)	Claims handler (Medical treatments)
57	California	Anthem Blue Cross (insurance company)	Manager Sales Health Insurance
58	California	U.S. Department of Health and Human Services	Regional Strategy & Innovation manager (Healthcare)
59	California	U.S. Department of Health and Human Services	Regional Specialist for Innovation and Strategy
60	California	U.S. Department of Health and Human Services	Medicare & Medicaid Innovation manager
61	California	U.S. Department of Health and Human Services	Team member Center for Medicare and Medicaid Innovation
62	California	U.S. Department of Health and Human Services	Global Health Officer
63	California	U.S. Department of Health and Human Services	Health Security Professional

64	California	American Transplant Foundation	Program and Engagement Coordinator
65	California	American Transplant Foundation	Transplant Mentor
66	California	American Transplant Foundation	Patient Relations
67	California	American Transplant Foundation	Quality Manager, Kidney and Liver Transplant
68	California	American Transplant Foundation	Law and regulation manager
69	California	American Transplant Foundation	Senior advisor Patient interest
70	California	American Association of Kidney Patients	Advocacy & Patient Engagement
71	California	American Association of Kidney Patients	Law and regulation manager
72	California	American Association of Kidney Patients	Finance Consultant
73	California	American Association of Kidney Patients	Director of Office Operations

Appendix 6: Overview of the observed links in the 3D-BOIS of California and the Netherlands

Institutional readiness category	Assumed link with (See section 2.3)	Observed link within the 3D-BOIS of California	Observed link within the 3D-BOIS of the Netherlands
C1: Demand for new technology	<ul style="list-style-type: none"> System function 1: Entrepreneurial activities System function 3: Knowledge diffusion System function 4: Guidance of the search System function 5: Market formation 	<ul style="list-style-type: none"> System function 1: Entrepreneurial activities System function 3: Knowledge diffusion System function 4: Guidance of the search 	<ul style="list-style-type: none"> System function 1: Entrepreneurial activities System function 4: Guidance of the search System function 5: Market formation System function 7: Creation of legitimacy
C2: Strategic focus	<ul style="list-style-type: none"> System function 4: Guidance of the search 	<ul style="list-style-type: none"> System function 4: Guidance of the search System function 5: Market formation 	<ul style="list-style-type: none"> System function 1: Entrepreneurial activities System function 4: Guidance of the search System function 5: Market formation
C3: Relative need and benefit of new technology	<ul style="list-style-type: none"> System function 4: Guidance of the search 	<ul style="list-style-type: none"> System function 3: Knowledge diffusion C6: Receptivity C7: Adoptive capacity C8: Sustainability 	<ul style="list-style-type: none"> System function 3: Knowledge diffusion System function 4: Guidance of the search C7: Adoptive capacity C8: Sustainability
C4:(E)valuations processes in place	<ul style="list-style-type: none"> System function 5: Market formation 	<ul style="list-style-type: none"> System function 3: Knowledge diffusion System function 4: Guidance of the search C7: Adoptive capacity 	<ul style="list-style-type: none"> System function 3: Knowledge diffusion System function 4: Guidance of the search C7: Adoptive capacity
C5: Enacted IR	<ul style="list-style-type: none"> System function 4: Guidance of the search System function 7: Creation of legitimacy 	<ul style="list-style-type: none"> C8: Sustainability 	<ul style="list-style-type: none"> System function 1: Entrepreneurial activities C8: Sustainability
C6: Receptivity	<ul style="list-style-type: none"> System function 4: Guidance of the search System function 7: Creation of legitimacy 	<ul style="list-style-type: none"> C8: Sustainability 	<ul style="list-style-type: none"> System function 1: Entrepreneurial activities C8: Sustainability
C7: Adoptive capacity	<ul style="list-style-type: none"> System function 7: Creation of legitimacy 	<ul style="list-style-type: none"> System function 5: Market formation 	System function 5: Market formation
C8: Sustainability	<ul style="list-style-type: none"> System function 3: Knowledge diffusion 	<ul style="list-style-type: none"> System function 3: Knowledge diffusion 	-