The Software and Hardware Development of an Automated Microsphere/Cell Movement Device

Analysis of the Failure of Cellink's Infringed Patent

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for Degree
Bachelor of Science in Biomedical Engineering

By
Joshua Sanderson

September 22, 2022

Technical Project Team Members:
Kaden Hoffman, Jack Maschler, Remington Martinez

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.
Signed: Joshua Sanderson

ADVISORS

Benjamin Laugelli, Department of Engineering and Society
Christopher Highley, Department of Biomedical and Chemical Engineering

Introduction

3D bioprinting organs using an individual's own cells was an insurmountable challenge scientists faced until a breakthrough discovery; in 1999, a 3D-printed organ was successfully implanted into a human (Price, 2015). A bladder was printed, covered in the patient's cells, and transplanted. Due to the increase in drug development and disease modeling, the biotech industry began to look for technologies that progress research faster and more efficiently.

As a result, research and development efforts have been geared towards the field of organoids – three-dimensional cell cultures capable of mimicking the interaction between cells and their surrounding environment. Organoids are essential to building an accurate model of cell signaling pathways (Kapałczyńska et al., 2018). The current approach of moving organoids into a permissive biomaterial is done manually. In addition, existing bioprinting technology is not able to pick and place discrete cell spheroids/organoids, but generally relies on deposition from a reservoir on the device or from a needle that is preloaded with cells (Daly et al., 2021). The problem with the current approach is that it is time-consuming, it is imprecise, it creates limitations for seed formations, and it is difficult to use the approach for large-scale systems (Ren et al., 2021). To address the current challenges presented, I will propose the development of an automated biotech device capable of picking up and placing organoids in various formations within a biomaterial of choice.

While technical improvements to the efficiency of this method remain a primary driver for increasing scalability, there are important legal requirements that shape the development and implementation. These non-technical factors include the US patent and trademark office, corporate leadership, and competitors in the marketplace. Therefore, I will examine the court case Organovo, Inc. v. Cellink to understand both the technical and non-technical actors that resulted in a failed

patent. A lack of understanding regarding these social factors will limit the success of a product that could improve drug development and the study of diseases.

The technical and social aspects of the issue must be addressed concurrently to effectively develop a technology that will be able to pick up and place organoids in designated locations without human interaction. Using hardware and software, I will address the technical issue of manual organoid movement by developing an automation device. Furthermore, I will apply Actor-Network theory to a failed infringed patent by Cellink to determine what human and non-human actors affected the success of an innovative bioprinting technology.

Technical Project Proposal

Organoids are three-dimensional cell cultures constructed from stem cells that function to mimic human organs *in-vitro*. Human stem cells were first successfully harvested in 1998, however, the first true organoid was not developed until 2009 when Sato et al. derived the first organoid from a single adult stem cell (ASC) seeded in Matrigel, a hydrogel material (Sato et al., 2009). The landmark study in 2009 demonstrated that the key factor in the induction of ASC differentiation, and thus organoid formation was the biomaterial and environment in which it was seeded (Sato et al., 2009). Since then, many different organoids have been developed and used to study diseases, develop drugs, and even the preliminary development of transplantable organs (Magno et al., 2020). Although the range of organ tissues that can be mimicked *in-vitro* using organoids has increased dramatically, their use in research still remains limited by their lack of freedom of mobility (Ren et al., 2021).

ASCs are placed into biomaterials by hand using a pipette and once differentiated into organoids, moved to imprecise locations via vacuum aspiration (Daly et al., 2021). Although effective for small-scale studies where precision is less of an important variable, the current

organoid movement method is time-consuming, imprecise, and limits the scale and scope of potential studies (Ren et al., 2021). As with any procedure that relies heavily on human manual dexterity, the placement of organoids into specific locations within biomaterials is imprecise, thus introducing error and limiting study conclusions (Ren et al., 2021). Vacuum aspiration itself also introduces error through the accompaniment of media with organoid deposition. The extra media deposited with the organoid alters the desired extracellular environment, again limiting conclusions that can be made (Vonk et. al, 2020). By improving the current movement method of stem cells and organoids, new research could be conducted with higher degrees of accuracy with a faster turnaround time. Additionally, a more precise placement method would open the possibility for more abstract organoid arrangements to better mimic *in-vivo* conditions (Yin et al., 2016).

This technical project aims to design a device that precisely places organoids into a designated position in a permissive biomaterial using an automated set-it and forget-it approach. There are two major user needs the team intends to meet with the development of this device: the ability to designate organoid placement locations, and for the pick-up and placement to be done without human intervention.

To allow the user to designate organoid placement locations, a GUI will be created using Python that allows the user to input the desired placement location(s). Next, we will use this input to move both the 96-well plate containing the organoid(s) and the plate containing the permissive biomaterial using a premade multiaxis sled movement system powered by NEMA 23 motors controlled by the same Python program. Then, to pick up and place the organoids, a 2020 Nano-liter injector, also controlled by Python, will be attached to the vertical axis of the multiaxis sled movement system. To attach the Nano-liter injector, new components will be designed and

fabricated using 3D printing and/or laser-cutting. In conjunction, the aforementioned components will move plates and Nano-liter injector to pick up and place the organoid(s) in the user-inputted location.

To fully automate the pick-up and placement of the organoids, a Basler Ace Camera will be attached to the vertical axis of the multiaxis sled movement system. Using image detection in Python, this camera will be able to detect the presence of organoids within wells in the 96-well plate allowing for the aforementioned components to work seamlessly without user interaction.

Finally, to verify the device is working as intended, nanospheres and organoids will be loaded randomly into a 96-well plate and various placement patterns and locations will be input into the GUI. The resulting biomaterial containing organoids and nanospheres will be analyzed to determine if the organoids were placed in the desired locations. Additionally, the biomaterial will be compared to a biomaterial containing human-placed organoids to quantify the improvement in precision, scalability, and time consumption.

STS Project Proposal

In July of 2021, Organovo INC filed a complaint for patent infringement against Cellink, two corporations focused on the development of 3D bioprinters for drug therapy and profiling within the United States (Organovo, Inc. V. Cellink, 2021). While Cellink successfully produced and launched the BIO X bioprinter with an estimated market value of $1.5 billion, Organovo's first intellectual properties (IPs) date back to 2015 (Amato and Partners, LLC, 2022). Specifically, the main design component in question was the printer head of BIO X, that consisted of multiple heads capable of printing 3D structures which were already patented. Thus, Organovo sought to regain control of its technology as well as control of the bioprinting market. In 2019 Organovo sent a letter of notice to Cellink in hopes of reaching a licensing agreement, but Cellink continued

to sell its product for over two years (Amstutz, 2021). Although Cellink accrued over $20 million, its ephemeral success costs them roughly $1.5 million and royalties ranging from 1-10% of the licensed products' net sales (Manufactur3d, 2022).

While the failure of Cellink is often associated with its unsuccessful patent lawsuit against Organovo, the key stakeholders such as the corporation's C-suite staff and advisory board members as well as the US Patent and Trademark Office contributed to the defeat of a company with bioprinting potential. For instance, the executives of the company failed to address the patent infringement in 2019 and engage in a license agreement with Organovo before the repercussions became detrimental. In addition, the US Patent and Trademark Office misled Cellink by approving Organovo's IPs that were allegedly broad in scope, causing the company to disregard the filed documentation (Hanaphy, 2021). Such lack of attention to detail not only impacted Cellink's product's validity but also impacted the organization's relationship with its shareholders. Therefore, we need to set forth measures to understand how non-technical actors can influence the outcome of a project rather than devoting our attention solely to the technical actors involved. Given the consequences of Cellink's actions, it is imperative that future biotechnology companies take into account the interest of its shareholders in order to uphold a mutually beneficial relationship.

I argue that Cellink's infringement of Organovo's IPs while developing and selling the BIO X printer in conjunction with economic pressures from the C-suite, board of directors, shareholders, and the misleading approvals by the US Patent and Trademark Office led to the failure of Cellink's sole ownership of its product. Actor-Network theory can be utilized to describe the activity of a network builder who assembles a network that includes both human and non-human actors that seek to accomplish a particular goal (Callon, 1987). Furthermore, I will use

Callon's concept of translation which refers to the process of forming and maintaining an actor network. By using this concept, I aim to examine the roles of non-human and human actors within Cellink's network to determine who must be accounted for when developing future bioprinters that are planned to be sold to the public market. In order to develop an understanding of the project, I plan to analyze legal documentation, public shareholder announcements, interviews with executive leadership, and filings with the US Patent and Trademark Office.

Conclusion

The deliverable for the technical problem discussed in this paper will be the full development of a bioprinter capable of picking up and placing organoids into discrete formations within permissive biomaterials such as matrigel. The STS research paper will aim to determine why Cellink failed to be the sole proprietor of a bioprinter developed by its organization. This will be accomplished by applying Actor-Network theory using network building to explain how human and non-human actors shape the commercialization of bioprinting technology. The combined results of this technical report will serve to address the breakthrough bioprinting technologies from a socio-technical perspective, highlighting key considerations for the success of biotech companies and proposing the adoption of promising organoid-based bioprinting technology.

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