Prospectus

Utilization of 3D bioprinting to understand the effects of tumor heterogeneity on treatment resistance
(Technical Topic)

Configuring knee replacement implants and the implicit biases it portrays
(STS Topic)

By

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Introduction

"Over the past 50 years, engineering has been about controlling the external world; what biomedical engineering is really about is controlling the internal world," states Michael I. Miller, the director of the Johns Hopkins Department of Biomedical Engineering, "and [it's] going to change the way the world moves forward in the future" (Regan and Swaney, 2017). Biomedical engineering creates the future by anticipating the needs of clinical medicine and fostering collaboration among disciplines through building upon the basic concepts used in engineering and biology.

Due to the complex nature of many diseases, like cancer, often cures must be found through animal testing. This is both costly and raises ethical concerns. These models also do not reliably predict how certain therapies will translate into a human body and can lead to higher failure rates once it reaches clinical trials (Trachet, 2017). In response, I aim to create a three-dimensional (3D) model which would allow precise control over different parameters in order to better mimic the human *in vivo* environment. By representing the tumor environment more accurately, I may be able to better predict therapeutic responses in a more cost-efficient way as well as modify each treatment to a patient's specific diseased architecture.

While it is true that biomedical engineering aims to solve many of the problems that occur when our bodies ultimately fail, it is also known that many of these proposed solutions fail commercially. Often times these failures arise from a miscommunication between the engineers and the clientele; a solution to the problem was designed, but, then due to outside influences, is not actually wanted. In order for my model to succeed, I also need to acquire a better understanding about how the ideas that designers have about users get embedded into technology and constrain what users can and cannot do. To do so, I will analyze a specific case in which an

implant used for knee replacement surgery was reported better than the currently used model physiologically but had a higher dissatisfaction rate due to unforeseen human factors.

Without evaluating both social and technical implications of artifacts, I'll fail to understand how implicit and unintentional biases of the designer can affect the product's design and ultimately lead to its failure to be accepted by society. I argue that users and technology are co-constructed and therefore one can not be assessed without understanding how its been shaped by the other.

Utilization of 3D bioprinting to understand the effects of tumor heterogeneity on treatment resistance

Approximately 350,000 people worldwide die every year due to pancreatic ductal adenocarcinoma (PDAC), making it the one of the deadliest cancers (Siegel, Miller, and Jemal, 2016). Today, more than 70% of patients do not respond to treatment which in turn leads to a more invasive and resistant tumor (Juiz, Iovanna, and Dusetti, 2019). Recently, there has been an accumulation of evidence that intratumoral heterogeneity plays an important role in tumor recurrence, therapeutic response, and survival in patients with PDAC. Intratumoral heterogeneity encompasses the diverse gene expression within a patient's tumor which then expresses itself through a variety of spatial patterning and functionalities. This heterogeneity has been shown to directly correlate to drug resistance and, therefore, a better understanding of tumor heterogeneity is essential for the development of a better prognosis for PDAC (Dagogo-Jack and Shaw, 2018). However, conventional 3D

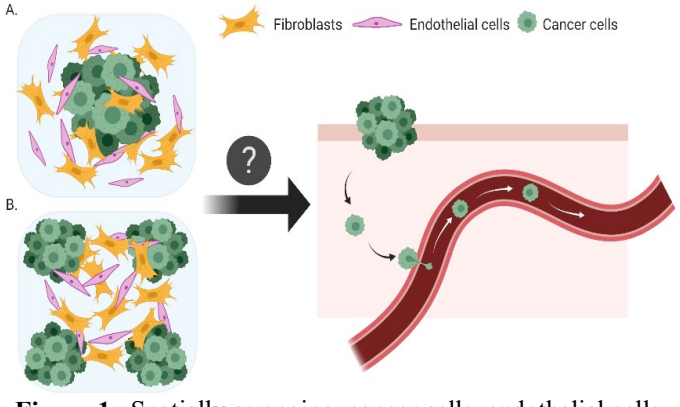

Figure 1. Spatially arranging cancer cells, endothelial cells, and fibroblasts using 3D bioprinting in differing orientations, like A. and B., to better understand how the tumor-stromal cell interactions correlate with metastatic phenotypes resistant to therapy.

models used to study tumorigenesis and cell interactions, like spheroids and organoids, lack the ability to precisely position cellular subsets within matrices to recapitulate the conditions under which heterogeneous tumors arise and develop in humans.

Previous work in our lab has shown that murine PDAC cells printed using an alginate-derived hydrogel comprising of 1% alginic acid sodium salt powder and 6% gelatin maintain 87% cell viability (Jiang *et al.*, 2018). Langer *et al*. (2019) have shown that Alginate Lyase can be used to dissolve the alginate-derived scaffold after 48 hours, resulting in scaffold-free tumor tissues with defined architecture. I propose a 3D bioprinting approach to create multi-cell tumor models with the capability to precisely position subsets of cells in order to recapitulate various spatial patterning seen in heterogeneous tumor microenvironments in a reproducible manner. As shown in figure 1, this method could be used to study the effects of spatial arrangement of subsets of cells on tumor-stromal cell interactions and how this correlates with both drug resistance and metastatic tumor phenotypes. In order to identify the optimal approaches to tumor therapy, a more representative *in vitro* model will be constructed using 3D bioprinting from the following two methods: 1. Design a printing protocol that allows for subsets of cells to be precisely positioned while maintaining high cell viability and 2. Identify relationships between cancer therapies and spatial arrangements of varying cell types.

To accomplish these methods, I will utilize a RegenHU 3DDiscovery bioprinter which can print multiple cell types, like PDAC cells, endothelial cells, and fibroblasts, in specifically programmed patterns as shown in Figure 1A and 1B. Being able to elucidate the interaction between therapeutic response and tumor spatial arrangement will more accurately model *in vivo* tumors in comparison to current methods. In the future, this research can be expanded to better

mimic a single patient's tumor in order to create a personalized approach to cancer therapy, thus hopefully developing a better prognosis for this lethal disease.

Configuring knee replacement implants and the implicit biases it portrays

When biomedical engineering was first developed, many scientists were satisfied with generalizing a problem and creating a solution that could be applied to a widespread population. However, as many of us know from a shopping trip to our local shoe store, when it comes to the body, this 'one size fits all' approach typically does not provide a sufficient solution. As a result, many current research topics involve creating a customized or patient-specific remedy to better a device that has already been engineered. For example, White and Ranawat (2016) set out to create a patient-specific knee implant to replace the currently used "off-the-shelf implants." To do so, patients underwent a CT scan which was used to engineer a one-of-a-kind implant based on the patient's distinctive knee structure (White *et al.*, 2016). All patients returned at six-weeks and at two-years postoperatively for a follow-up and, through a series of surveys and tests, patients were assessed for pain, inflammation, and functionality. Interestingly, White *et al.* (2016) found that patients with the customized knee were reporting more pain and less functionality than those with the standard implants despite there being lower amounts of inflammation and therefore no physiological reason for these reports (White *et al.*, 2016). Exclusive reliance on how the engineered technology functions fails to analyze the intricate co-constructed relationship between the technology and the users. By exploring White *et al.*'s (2016) ideas about the customized knee implant equating to a "more natural knee" were embedded into the implant, I'll gain a better understanding of the way unintentional and implicit bias can affect the product's success. I argue that White *et al.*'s (2016) customized knee failed

not due to a breakdown in the artifact's design but rather due to the designers' ideas about its improved functionally becoming embedded into the artifact.

When new technologies are introduced, parameters are often set which attempt to configure the user to the designers' ideas about the imagined user. These configurations carry ideological underpinnings, reflecting the biases and assumptions of designers, which adjusts the technology to the perceived needs of certain groups of users while other needs and users are excluded (Suchman, 1987). As a result, the eventual users' actual needs may not be reflected in such technologies (Grimes, 2015). Through the concept of "configuring the user," I have identified two potential reasons why patients in White *et al.*'s (2016) study were dissatisfied with the patient-specific knee: 1. Incorporating implicit biases in the technologies which appeared within discursive representations, such as advertising and 2. Misidentifying the functional needs of the users.

White *et al.* (2016) believed that the proposed benefits of its customized knee implant could translate to improved satisfaction, shorter lengths of stay, reduced cost, and more normal joint kinetics. As a result, these perceived benefits from the designer were passed down to the patient due to the product being marketed as both "patient-specific" and offering a "more normal feeling knee," which likely caused these patients to have higher expectations with this design compared to others, thus skewing the data (White *et al.*, 2016). During this study, White *et al.* (2016) also designed the customized implant to increase the users' range of motion in order to allow for a more active lifestyle. However, they failed to consider that most patients receiving knee replacements are age 50-80 and, therefore, may not desire or benefit from this feature (Foran, 2015).

Conclusion

As I develop a model to better mimic the PDAC tumor microenvironment, I plan to use my knowledge of user configuration to ensure that no user is suppressed by my design. From the case with White *et al.* (2016), I have learned that customized treatments do not always equate to better results and, if that bias gets designed into my model, it may actually be what causes its demise. Ultimately, I aim to design a method in which lethal diseases, such as PDAC, can be studied in a more cost-efficient and effective way without excluding the impact of sociotechnical factors.

Using user configuration to consider how human factors contributed to the poor satisfaction rates of what was supposed to be a novel technology to improve knee implants highlights the importance of how certain expectations and ideals about the engineered product are reflected and reproduced, while others are suppressed or excluded all together. My analysis of the customized knee implant draws on the science, technology, and society (STS) concept of user configuration to draw attention to White *et al.*'s (2016) negligence in considering how outside influences shaped its engineered product and, as a consequence, its product performed worse that the standard "off-the-shelf implants."

Through evaluating both technical and social frameworks, I've learned that in order to anticipate the needs of clinical medicine I must not only encourage collaboration among disciplines, but also foster more effective communication between patients and scientists. Overall, I anticipate that this communication would allow the scientist a better understanding of the patient's needs as well as better regulate the patient's expectations so that they are not unrealistic. Going forward, I plan to use both user configuration as well as my assessment of the

failure of White *et al.*'s (2016) knee implant to ensure that I do not overlook any of the social implications that my model may occur.

Word count: 1803

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