Embedded 3D Bioprinting into a Yield-Stress Hydrogel Matrix as a Novel and Cost-Effective Approach to Regenerative Medicine

(Technical Paper)

More Than Money: The Lost Perspective of Low-Income Communities in the Quality, Accessibility, and Trustworthiness of the American Healthcare System

(STS Paper)

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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

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Introduction

According to the United States Centers for Medicare and Medicaid (2019), in the United States alone, healthcare is a multi-trillion-dollar industry. Within that is a massive network of insurance plans, hospitals, local medical practices, and patients. On top of providing healthcare, billions more go in to investments for medical research(Viergever & Hendriks, 2016, n.p.). Medical research is heavily funded because Americans place great value in living healthy and long lives. One of the fastest growing fields in the medical community revolves around three-dimensional (3D) printing of cells and tissues called 3D bioprinting. Bioprinting is similar to conventional 3D printing, yet instead of plastics or metals, cells are printed in hopes of building functional tissue. Despite many recent advancements, efforts are still held back by expensive and unreliable procedures that cannot consistently produce functioning tissues.

Despite recent technological advancement and the need for advanced medical care across all communities in the United States, especially those in lower-income areas, it has become apparent that poorer communities do not receive care to the same extent as wealthier communities (Reitman, 2016, n.p.; Ross, 2018, n.p.). A lot of medical expenditures are related to medical care for preventable conditions, and these conditions disproportionately affect those in worse socioeconomic conditions (Shaw, 2016, n.p.). Thus, it is the technical goal of this prospectus to develop a reliable and reproducible methodology for 3D bioprinting, while it is the STS goal to reframe the problems surrounding healthcare in the United States by attempting to include the often-overlooked perspective of members of low-income communities.

Technical Topic – Embedded 3D Bioprinting into a Yield-Stress Hydrogel Matrix as a Novel and Cost-Effective Approach to Regenerative Medicine

Bioprinting is a rapidly growing and changing field in medicine as it has wide reaching clinical and commercial value for both lab-based experimentation and medical implantation

(Kačarević et al., 2018, n.p.; Mason, Visintini, & Quay, 2016, n.p.). The field has the potential to revolutionize the medical industry with the abilities to fabricate new tissues and organs, customize prosthetics and implants, and provide alternative anatomical models for drug delivery and discovery (Klein, Lu, & Wang, 2013). It is projected that the bioprinting industry, and the medical devices associated with it, will be a multi-billion-dollar industry in the near future (Schubert, Langeveld, & Donoso, 2014, pp 159-161; Ventola, 2014, n.p.).

Currently a large portion of lab-based biological study is done on two-dimensional (2D) cell cultures, but 2D cultures are limited in that they do not mimic how tissues would respond to stimulus in a real 3D environment (Kapałczyńska et al., 2018, n.p.). Live organs and tissues have well-defined and ordered cellular structures that are not simulated completely in a 2D structure. This lack of proper tissue mimics and models derived from them has slowed drug discovery and modeling of diseases. (Centeno, Cimarosti, & Bithell, 2018, n.p.; Duval et al., 2017, n.p; Kapałczyńska et al., 2018, n.p.).

It is the goal of this project to combat this unaddressed issue by designing and optimizing a procedure for 3D bioprinting that is both reliable and reproducible. One of the main challenges to reproducibility and viability of bioprinted tissues comes from the need to create a highly ordered structure that can provide structural support while also creating an environment where cells can proliferate as they would in a body (Kačarević et al., 2018, n.p.; Ke & Murphy, 2019, n.p.). This is solved, to varying degrees of success, by first printing cells on to a biocompatible base matrix (Pati & Cho, 2017, n.p.; Rider, Kačarević, Alkildani, Retnasingh, & Barbeck, 2018, n.p.). Once the cells have grown and developed as they are intended, another major problem is finding a way to remove this non-essential base matrix. Some base matrices are degradable over time or can be digested by the body, yet this leaves behind harmful byproducts (Ashammakhi et al., 2019, n.p.).

The innovation to be made in this project is combining the relatively new and promising method of embedded 3D bioprinting (EMB3D) with a sacrificial yield-stress hydrogel, that can be liquified and removed easily following a targeted stimulus. Recently, promising results from Lewis and Stone following the use of EMB3D have made it a new avenue for further development of tissue mimics (Grosskopf et al., 2018, pp. 23353-23361). EMB3D's main difference from conventional bioprinting is that instead of depositing material on the surface of a matrix, cells are deposited **inside** a specially designed matrix material. An EMB3D schematic is presented below in Figure 1. By depositing inside the hydrogel instead of on top, the hydrogel can be used to provide support and structural orientation for cells while also limiting the amount of shear stress that cells would be subjected to from layered printing. Previously, lower layers of cells would have to hold up the next layer during the printing process which limits cell viability after printing is completed.

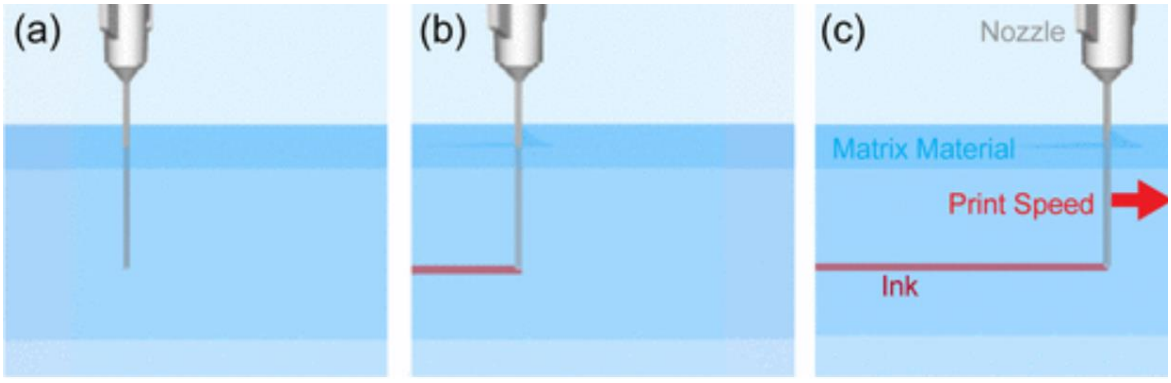

Figure 1. *Schematic of Embedded 3D Bioprinting (EMB3D)*. Instead of depositing material on the surface of a base layer or matrix, the print nozzle sticks inside and moves within the base layer. Material is deposited in the interior, as the

Alone, EMB3D is very promising, but the true innovation comes when it is combined with a sacrificial yield-stress hydrogel as mentioned above. A yield-stress hydrogel is a very viscous liquid that flows and acts similar to a very thick shampoo. These materials are called sacrificial when they exhibit a very specific property that causes them to liquefy following a targeted stimulus. They are used in a wide variety of applications, some as the base for cosmetics

and others as a means of creating tubing for vascularization in other polymer gels (Agarwal et al., 2012, n.p.; Liu, Zheng, Poh, Machens, & Schilling, 2015, n.p.; Xu, Luikart, Sims, & Allbritton, 2010, n.p.). When combined with EMB3D, a sacrificial hydrogel will provide the necessary support and can easily be removed when its job is done.

STS Topic – More Than Money: The Lost Perspective of Low-Income Communities in the Quality, Accessibility, and Trustworthiness of the American Healthcare System

In America, where healthcare is mostly privatized, higher income is associated with better medical care. With the introduction of Medicare, Medicaid and the Affordable Care Act, the goal was to ensure more people could afford medical care. Despite countless pieces of legislation surrounding healthcare spending and allocation within the United States, higher quality care is still disproportionately received by higher income people (Chernew, Cutler, & Keenan, 2005, n.p.; Schoen, 2013, n.p.). This contributes to a growing disparity in overall health between low, middle, and high-income communities.

When tackling complex technical projects like developing a method for 3D printing living tissue, it is first essential for engineers to understand that part of their job is understanding the perspective of those their working with and for. How can an engineer convince themselves that their project is meaningful if they cannot reconcile their solutions with the people who will actually be influenced by them? In his analysis of engineering curricula, Downey writes that the "key issue in defining the engineering problem at stake is not overcoming uncertainty but reconciling different perspectives." (Downey, 2005, pp. 592) This must be true when tackling the massive sociotechnical issue of providing healthcare to a nation. It is essential that the problem definition includes and is shaped by the people directly influenced by the potential solution. Otherwise, healthcare in the United States will continue to stagnate and the disparity between its wealthiest and poorest citizens will continue to grow.

When listening to any campaign speech or political talk-show, it is a guarantee that someone will say the key to healthcare in low-income areas is making it more affordable. However, if any attempt to actually include low-income community members in this discussion were to be made, the issues would shift beyond just affordability. Many of these issues can be broken down into three categories: *quality*, *accessibility*, and *trustworthiness*.

Higher quality healthcare is the goal for everyone, yet economic feasibility has contributed to a gap in quality of care directly related to a person's socioeconomic status. The Affordable Care Act was introduced to ensure that everyone had a healthcare plan, yet more access has not equated with higher quality care for all. Per the United States Department of Health and Human Services, black and Hispanic Americans consistently receive lower quality care. Even more striking, is that 70% of members of poor and low-income communities received worse medical care than high income community members (United States Department of Health and Human Services, 2016, n.p.). One potential explanation comes from a study that found that living in a low-income community was associated with "lower reliance on physicians offices" and a "greater reliance on community health centers" (Hussein, Diez Roux, & Field, 2016, pp. 1041). Despite being able to receive higher quality care from a trained physician at their practice, members of low-income communities are more likely to seek out the more comfortable and familiar out-patient nature of a community clinic. Recent legislation has helped lessen the economic burden of quality medical care, yet to ensure quality healthcare is sought out it is equally important that members of the community see the advantage of higher quality care on top of it being both socially and culturally-friendly.

Those who seek out healthcare receive lower quality care, yet some people do not even have the opportunity to seek out care at all because of other factors limiting its accessibility.

Members of low-income communities often work multiple jobs and do not have the luxury to take time off. As shown below in figure 2, in the United States, medical care is much more accessible to wealthy people than poor people. Studies show that the inability to take time off and lacking the economic means to find childcare if necessary are major barriers to low-income patients (Birs, 2016, n.p.). An even larger contributing factor is that many people rely on public transportation and are limited by their scheduling (Syed, 2014, n.p.). People in these communities thus have very high rates of missed appointments and struggle to schedule them in the first place. Even if people want to receive care, they do not have the means to go get it. If they were to seek out care, they would risk losing their jobs, leaving their children alone, and taking long hours to get to their destination. In order for any progress to be made towards improving healthcare in the United States, members of low-income communities must be included in finding ways to ensure everyone can actually reach their care provider.

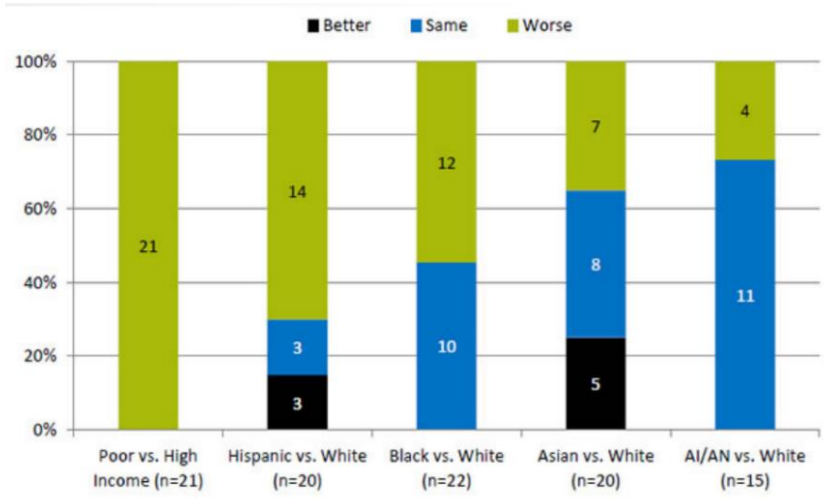

Figure 2: *Percentage of People who Experienced, Better, Same, Or Worse Access to Care.* In the United States, poor people have worse access to medical care than wealthier people. In general, white people had the best access to care, with hispanic and black people having the worst access. (United States Department of Health and Human Services.

Even when patients have the means to seek out care, many still do not due to cultural differences and lack of trust in the medical community. In the United States, many members of low-income communities are immigrants who are both documented and undocumented. In recent years, as the Immigration and Customs Enforcement Agency (ICE) has grown bolder, many undocumented immigrants are afraid to seek out medical care out of fear that they or their loved

ones will be deported (Machado, 2014, n.p.). One woman said that her family is “afraid of maybe getting sick or getting into an accident, but the fear of [her] husband being deported is bigger” while another is about to “forgo chemotherapy because [she] had a child that was not here legally” (Kennedy, 2018, n.p.) On top of the fear of harassment or even deportation, there often exist a potentially dangerous language barrier, as English is not a primary language for many immigrants. Studies have found that a considerable language barrier between healthcare providers and patients not only raises the chances for a misdiagnosis, but also contributes to lack of respect and amicability between parties (Meuter, 2015, n.p.). Improper diagnosis and a breakdown in communication leads to distrust in the medical community. Fear or a language barrier should never outweigh the desire to seek medical care, yet that consistently occurs in the United States. To combat this, those who are afraid or are struggling to communicate must not only be included but must also be a central focus of healthcare legislation so that they feel safe and respected by their care providers.

Conclusion

Despite the United States ranking at the top of lists for healthcare expenditures and research quality, the nation ranks consistently lower when it comes to quality of health. It is evident that a novel method of 3D bioprinting will provide alternative and cost-effective tissue mimics for continued medical research, yet these new avenues will be meaningless if their products do not reach the people who need them most. This is why a fresh look at the problems inherent to healthcare provision in low-income communities is essential. A new and more holistic perspective will help inform the next era of legislation and ensure that advances in technology also lead to advances in quality of life. [1891]

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