Manufacturing of a Recombinant Protein-based COVID-19 Vaccine

(Technical Paper)

Exploration of Digital Technology on the Break-Down of Democracy

(STS Paper)

A Thesis Prospectus Submitted to the

Faculty of the School of Engineering and Applied Science

University of Virginia • Charlottesville, Virginia

In Partial Fulfillment of the Requirements of the Degree

Bachelor of Science, School of Engineering

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Fall, 2021

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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

Coronavirus disease 2019 (COVID-19), the highly contagious infectious disease caused by the novel SARS-CoV-2 virus, remains a major global health concern. To date, there have been over 240 million confirmed cases and 4.8 million deaths worldwide (World Health Organization, 2021a). Nevertheless, 6 billion doses of vaccines have been administered, with many well-developed nations, including the United States, UK, and members of the EU, having vaccination rates that exceed 50% (World Health Organization, 2021b; Mwai, 2021). However, only 2.5% of people in low-income countries have received at least one vaccine dose (Ritchie et al., 2020). Furthermore, 50 countries have not met the 10% vaccination target set by the World Health Organization (World Health Organization, 2021b) for the end of September 2021 (Mwai, 2021). A majority of these countries are located in Africa, where the overall vaccination rate is less than 5% (Mwai, 2021). To reach a target of 70% vaccination worldwide, an estimated 11 billion doses are required. COVAX, an organization co-led by CEPI, Gavi, and WHO, aims to donate enough vaccine doses to vaccinate 20% of low-middle income countries (World Health Organization, 2021b). By vaccinating 20% of low-middle income countries, health care workers and high-risk citizens can acquire protective immunity against COVID-19. However, a low supply of vaccines has prevented COVAX from reaching their initial goal (Paton & Bloomberg, 2021). More vaccine doses are sorely needed for low-income nations.

COVID-19 vaccines currently on the market notably include Pfizer-BioNTech's and Moderna's mRNA-based vaccines. Although these vaccines have efficacies over 90%, they present a problem to supply chains in their requirement for extremely cold storage: between -50 °C and -15 °C for Moderna and between -90 °C and -60 °C for Pfizer (Centers for Disease control and Prevention, 2021). This frozen storage is not an issue for developed countries that have the

resources and infrastructures to accommodate a low temperature-controlled supply chain. However, it is an issue for the 3 billion people in locations where cold chain storage is not easily accessible (Hinnant, 2020). Currently, Sanofi and GSK are developing a recombinant protein vaccine in phase 3 clinical trials with 95% efficacy after the 2nd dose (Sanofi, 2021). This vaccine is manufactured using the baculovirus expression vector system and can be stored at normal refrigeration temperatures, providing considerable potential for low-income nations (Sagonowsky, 2020). This project seeks to design a process to manufacture the COVID-19 vaccine based on the Baculovirus expression vector system (BEVS) to immunize millions living in areas where vaccine distribution and ultra-cold supply chain is limited.

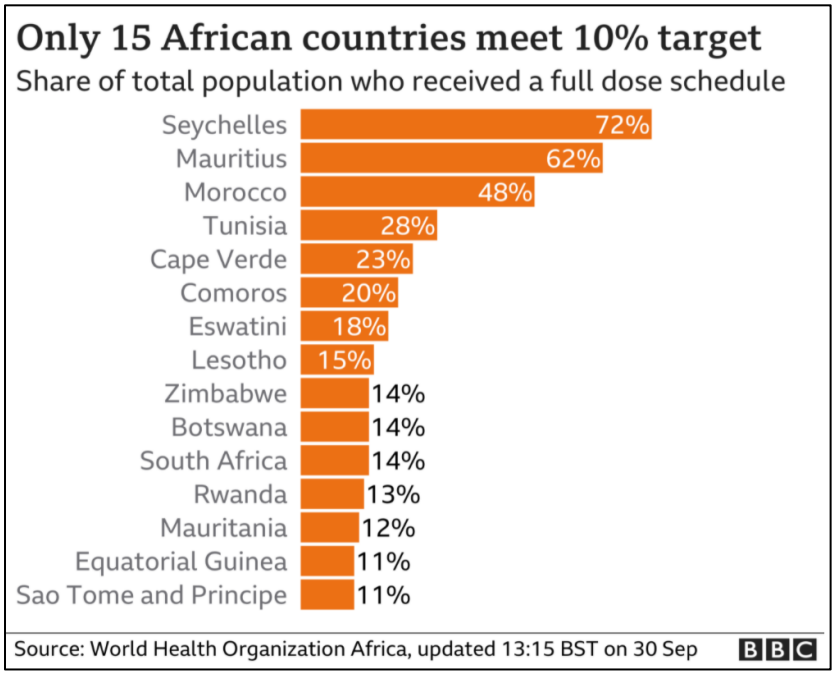

Figure 1. African countries that meet WHO's 10% vaccination rate goal (Mwai, 2021)

Technical Topic

Baculoviruses are a family of viruses that are known to infect insects. The baculovirus expression vector system (BEVS) is an important biotechnology tool because it can be used to insert protein-coding DNA into insect cells (Felberbaum, 2015). Once infected, the insect cells are instructed to reliably produce the antigen protein which, when inserted in the human body, initiates an immune response, producing antibodies that protect against future infection. A key feature of BEVS is its flexibility to be engineered with features that can increase product immunogenicity and facilitate purification (Deschuyteneer, 2010; Chen et al., 2013). Additionally, products made from BEVS are free of pathogens, proteins, and other chemicals that can be undesirable or allergenic (Caubet, 2014). The BEVS platform also has safety features built-in. Baculoviruses are very selective in their choice of hosts to infect; they cannot infect mammals, plants, fish, or non-target insects (Hu, 2005). Unlike many other vaccine production processes, BEVS does not require the handling of live, potentially-dangerous pathogens, reducing the biocontainment requirements (Felberbaum, 2015). Compared to other biopharmaceutical manufacturing platforms, such as those used in the production of mRNA- and viral vector-based vaccines, BEVS is associated with lower manufacturing costs and easier scalability. Insect cells are grown in suspension and are only limited by the size of the bioreactor (Felberbaum, 2015). As such, utilizing the existing global bioreactor capacity can reduce initial investment costs for BEVS facilities (Felberbaum, 2015). These facilities can manufacture multiple types of vaccines using the same cell line and equipment (Josefsberg, 2012). Furthermore, genetic and fermentation-based approaches exist that are known to improve product yield (Cox, 2012). There are currently four BEVS-derived products approved for human use including the Flublok® vaccine for seasonal influenza and the Cervarix® vaccine

to prevent certain types of cancer-causing human papillomavirus (HPV). For these reasons, BEVS is an appealing option for the manufacture of a high-efficacy COVID-19 vaccine.

The goal of this project is to design a rapid, safe, and cost-effective production process for a recombinant spike protein-based SARS-CoV-2 vaccine using the baculovirus expression vector system. Thirty-six percent of the global population is fully vaccinated, and there are 22 authorized vaccines in use currently (Zimmer et al., 2020). In order to provide enough vaccines for the rest of the population, this process will be designed to produce 400 million vaccine doses per year. The process will be divided into upstream and downstream processing and will be modelled at the industrial scale for mass production of a single-use injectable. Upstream processing will include a multistep seed train, in which *Spodoptera frugiperda* (Sf9) insect cells will be grown from a master cell bank and scaled up from flasks to bioreactors. Cell growth kinetic data will be obtained from a study by Rhiel et al. (1997). A similar scale-up procedure will be used to amplify the recombinant baculovirus in inoculated insect cells and produce the desired active pharmaceutical ingredient (API). Downstream processing will include a series of unit operations to recover, purify, and formulate the bulk API. Membrane filtration, namely diafiltration and virus filtration, will be performed to remove cell debris and concentrate the target spike protein. To selectively isolate the protein of interest, affinity chromatography and ion-exchange chromatography will be conducted, since this combination of chromatography techniques is common in literature (O'Shaughnessy & Doyle, 2011). A viral inactivation step will be performed to prevent viral contamination of the API. In the final formulation stage, the API will be combined in an aqueous solution with adjuvant, stabilizers, and preservatives. The vaccine will be formulated with the Adjuvant System 03 (ASO3) manufactured by GlaxoSmithKline (GSK), which reduces the amount of API needed by enhancing the immune response. Finally, the product will be filled into single-use vials with 10 µg of the API.

Since each stage of this process must be performed in a sterile environment, a reverse osmosis-based system to produce Water For Injection (WFI) will be designed. Sequencing of the spike protein gene and the genetic modification of the baculovirus are beyond the scope of this project.

The technical design team will investigate the COVID-19 vaccine production process during the fall and spring semesters in CHE4474 and CHE4476, respectively. The team will meet weekly to review the progress of the project and assign tasks for the following week. Additionally, the team will meet periodically with our faculty advisor, Prof. Eric Anderson, to receive feedback and guidance as the project progresses. Throughout the technical project design, the team will rely on the expertise from the University of Virginia's Chemical Engineering department faculty: Professor Michael King, an industry expert on vaccine production, and Professor Giorgio Carta, who is very experienced with the downstream bioseparation process. Relevant data will be gathered from prior research on the COVID-19 vaccine and other vaccines manufactured using BEVS to inform the technical design. We will also draw insight from clinical trial data for the Sanofi-GSK BEVS COVID-19 vaccine.

Digital Technology effects on Democracy

Next, I will be exploring how the rise of digital technology has undermined democracy seen through recent political divisiveness, election interference, and insurrection. Digital technology are electronic systems that generate, store, or process data, such as social media, phones, and artificial technology. On January 6th, 2021, a political rally broke into the U.S. Capitol Building protesting that the 2020 US election had been stolen, despite there being a lack of evidence. Five people died and at least 138 police officers were injured (Schmidt, 2021). Although it's easy to blame the protestors or Trump for spreading false information, I also believe technology bears some responsibility. Parler, a "free speech" social media platform, was the shared space where the insurrectionists spread fake news and organized the event (Munn, 2021). To protect our democracy, we as a society must understand how these tools, though seemingly harmless, can be deadly.

The January uprising was just one out of many recent events that illustrate the pernicious effects of digital technology. In the 2016 US Election campaign, a Russian advertisement agency called the Internet Research Agency (IRA) paid Facebook to show divisive ads to Americans before and after the election results (Ribeiro et al., 2019). The United States House Intelligence Committee recovered 3,517 ads that were shown to American Facebook users. Facebook's advertisement platform allowed the IRA to target specific demographics of U.S. citizens, building off of their political beliefs or casting doubt in order to sway their political vote. Eighty-nine percent of these ads were found to contain some piece of false information. Payment for these advertisements was accelerated in the months before the election and right after Trump won, interfering with the Presidential election and worsening the political divide.

Other foreign interests also use social media. From 2014 to 2017, the Islamic State of Iraq and Syria (ISIS), a militant Islamist group, initiated a massive social media campaign to recruit and gain sympathy for its fight in the Middle East (Awan, 2017). They produced Youtube videos and Facebook profiles to target potential sympathizers for recruitment. From 2014-2017, ISIS recruited 750 British citizens, effectively attracting people over digital media. Moreover, Facebook whistleblower France Haugen claimed that Facebook knew of its harmful effects on children and political discourse (Allyn, 2021), yet it still acted in ways that maximized profit. Facebook's algorithm, run by complex Artificial intelligence, curates videos and media to maximize user engagement time in order to sell advertisements. However, the algorithm tends to show controversial or fake content to users because it maximizes engagement. As of October 2021, there has been a bipartisan push to regulate Facebook, showing that the US government sees this as a pressing issue. Understanding the relationships between technology, society, and politics is pivotal in making decisions that will protect people and democracy around the world.

Figure 2. Example of an Ad paid by the IRA (Ribeiro et al., 2019)

To analyze these events, I plan on utilizing STS frameworks from Pinch and Bijker (1984) and Winner (1980). Because artificial intelligence is still a new technology, regulation

will be a topic of immense discussion with major impacts in politics, society, and industry. Pinch and Bijker's work emphases that technology is iterated through societal negotiation, with different social groups competing for their perspective to be considered. Therefore, society shapes digital technology, and Facebook's examination by the public is a positive process that will lead to change. Winner's paper believes that technologies are inherently political due to unavoidable conditions it brings to human relationships. Whether it is repressive or liberating, democratic or authoritarian, technology leads to changes that enforce a political order. The implication of Winner's work is that technology can change society, contrasting Pinch and Bijker's idea of interpretive flexibility, whereby technologies in the early stages of their development have a broad scope of possible uses, forms, and meaning. In Pinch and Bijker's perspective, societal groups have an immense impact on the final result of the technology as they are the ones that discuss the needs, values, and motives they want the technology to satisfy, not the other way around. I chose to use Winner's article because I believe some functions of technology are inherently societal, due to its design or its literal function. For example, social media is meant to bring people together, no matter the distance. However, that may become political if controversial groups of people are brought together and allowed to organize. It'll be interesting to gather and analyze data on this subject through these two contrasting, but related frameworks.

Research Question and Methods

I will be researching the following question: How are social media and other digital technologies threatening our democracy? This topic is important to explore because several high-level incidents have contributed to the breakdown of democracy in the U.S. and around the world. Furthermore, tech companies like Facebook are still largely unregulated. Nevertheless, evidence is pouring in that these technologies are damaging society in unexpected ways. Therefore, we must first understand the ways in which technology damages society so that they can be mitigated and prevented from happening. Additionally, determining what party is in charge of implementing a solution is vital. I will use the methods of interviewing, bibliographic analysis, and historical analysis to collect and analyze data. I plan on interviewing Siva Vaidhyanathan, a UVA media studies professor who is vocal about Facebook's damaging effects on democracy. Secondly, I plan on interviewing Christopher Ali, a media studies professor at UVA, for his research interests in politics of rural communities where internet access is scarce. Lastly, I plan on interviewing David Waldner, a UVA political science professor, to understand how democracies break down. Example interview questions are located in Appendix A. For the bibliography analysis, I will categorize the bibliography of relevant papers into the sector they come from: government, academia, or private sector. Papers I will be using for this analysis all have been cited over 150 times, meaning they are especially impactful on the subject of democracy and social media. These sources include "Social Media and Local Government: Citizenship, Consumption and Democracy", "Using social media dialogically: Public relations role in reviving democracy", "From Liberation to Turmoil: Social Media And Democracy", and "Populism 2.0: Social Media Activism, the Generic Internet user and Interactive Direct Democracy". Doing so will be important to understanding which sector is focusing most on the

issue and where more work needs to be done. Lastly, I plan on conducting a historical analysis by making a timeline of Presidential tweets made by the most recent U.S. Presidents during their presidency: Joe Biden, Donald Trump, and Barack Obama. From each tweet, I plan on counting how many times "social media" or something related is referenced along with social groups and their values or needs regarding the technology. I hope that this will illustrate the evolution of social media through its period of interpretive flexibility whereby different social groups are vying for their needs to be met. I also hope to categorize tweets based on whether or not they're centralized or decentralized, egalitarian or inegalitarian, repressive or liberating. By doing so, I'll be able to better understand the inherent political message that each tweet carries with it during each presidency.

Conclusion

The world desperately needs more vaccines, especially in poor and rural areas. Manufacturing the BEVS COVID-19 vaccine will deliver more doses of vaccines to save lives, boost economies, and reduce global unrest caused by this pandemic. In addition, the manufacturing process is easily established in poorer nations, allowing them to fight against the pandemic and protect themselves against future ones. Up until recently, tech companies like Facebook, Apple, and Google were perceived as the pinnacle of innovation in the United States. Nevertheless, that same innovation has torn societies apart and threatens democracy. Because digital technology is relatively new and unregulated, we must further explore how these technologies can harm us, what actions to take, and who is responsible. From exploring this STS topic, I expect to conclude that tech companies require more accountability for their technologies and I believe governmental regulation is a way to achieve this.

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Appendix A

Sample Questions for Interviews

1. How concerned are you for our democracy? Why?
2. What do you think is the biggest threat to our democracy today? Why?
3. Do you think social media is a threat to our democracy? In what ways?
4. When were times in history where political divide was stark? In your eyes, how were those times different than now? How did those events reconciliate?
5. Why do you think we are so divided politically today? Do you believe tech companies are mostly responsible for sowing deep political divides? Why or why not?

6. What do you think the future of news will look like in America? We went from having three major television networks to having YouTube, which curates videos to every person. How do you think that will affect political discourse in the future?