Development of a Continuous Sampling System for *In Situ* Monitoring of Anaerobic Coculture
(Technical Paper)

Assessing the United States' Healthcare System through an Actor Network Theory Framework
(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

With a biotechnology market of approximately $120 billion, the United States (U.S.) is one of the world leaders in health technology development ("Top 4 Countries," 2020). However, the overall quality of the US healthcare system lags behind many other developed countries. The U.S. spends an average of $8,047 per citizen on public health, a number that is substantially higher than any other country. Despite this large cost, the average life expectancy of a U.S. citizen is relatively low, at 78.7 years (Byrnes, 2019). By identifying flaws in the current U.S. healthcare system and analyzing the more successful healthcare systems, such as Canada, this paper aims to reduce the cost of healthcare for the U.S. citizens while potentially improving the quality of healthcare and life as well.

In addition to macroscopic issues with the overall healthcare system in the U.S., there are also ways to improve the U.S. healthcare system through solving microscopic issues. Specifically, the technical work of this paper aims to improve technology for detecting susceptibility to nosocomial *Clostridiodes difficile* Infection (CDI) and sensitivity to recurring infection. *Clostridiodes difficile* (*C. difficile*) is a toxic gut bacterium that can cause various symptoms from diarrhea to fatal colon inflammation ("C. difficile infection," 2020). One of the most common ways U.S. citizens get CDI is after hospital antibiotic treatments. By interrupting a healthy microbiome via antibiotic disruption, many of the beneficial bacteria in the gut are killed, significantly reducing the diversity of the microbiome and negatively impacting the susceptibility of the human host to infection by pathogenic bacteria such as *C. difficile*. Thus, there is a substantial need to develop tools that can rapidly quantify the patients' susceptibility to pathogenic bacteria following antibiotic treatment in the clinical setting. A rapid point-of-source testing method would both improve patient outcomes both medically and financially, as current microbiota testing can only be performed in specialized laboratories (Miezeiewski et al, 2014).

By developing a technology that can rapidly detect CDI in the clinical setting, the technical work hopes to improve the outcomes of numerous antibiotic-treated patients in the future, improving the overall healthcare of the U.S.

Technical

Each year, there are over half a million CDI cases in the United States and around 29,000 fatalities resulting from CDI within one month of initial diagnoses (Mada, 2020). CDI costs the United States' Healthcare system approximately $6.3 billion dollars annually along with an additional 2.4 million inpatient hospital days ("Reducnig C. Diff Infections," 2020). For patients, this infection typically causes watery diarrhea three or more times a day along with mild abdominal cramps and tenderness. In severe cases CDI can cause aggressive intestinal inflammation, colon enlargement, and sepsis (Clinic Staff, 2020).

Although this infection affects so many people each year, there is minimal preventative and diagnoses technology. Currently, CDI is detected through stool sample analysis via several different analysis technologies, including polymerase chain reaction (PCR), glutamate dehydrogenase test, enzyme immunoassay test, or cell cytotoxicity assays. These tests can be very costly to patients, as they can only be performed in specialized laboratories, increasing both the cost of care to patients and length of inpatient stay (Staff, 2020). Additionally, little technology exists to be able to quantify and assess a patient's susceptibility to CDI following antibiotic treatments. The most common method to assess host microbiome susceptibility to CDI is through metagenomic analysis, which is the study of genomic content from a mixture of microorganisms (Ajami et al, 2016). Microbiota susceptibility to CDI is analyzed using 16s RNA gene amplification via PCR, assessing the biodiversity of the gut microbiome. Again, these tests can only be performed in specialized laboratories and are expensive for patients. Thus, in order

to reduce the effect of CDI on the United States' population, there is a need for a point-of-care testing technology, reducing the amount of time before patients receive results while decreasing the overall testing cost simultaneously.

The technology being investigated as a viable point-of-care technology is single-cell impedance cytometry. Single-cell impedance cytometry is a high-throughput research tool used to assess samples of cells in a quick, label-free manner. By flowing the sample through an alternating electric field, information such as cell size and conductive properties can be assessed by the return signal's delay and magnitude. With some design improvements, this technology can be beneficial to CDI susceptibility assessment in a clinical setting (Petchaku et al, 2017). When *C. difficile* is germinated, it changes from a dormant spore to a vegetative, rod-shaped bacterium that is larger in size than the spore; the electrical differences in these two forms of *C. difficile* have already been successfully detected by the Swami laboratory at the University of Virginia. By analyzing *C. difficile* cocultured with stool supernatant with impedance cytometry, the Swami laboratory research team has been able to detect significant differences in spore germination rates as early as 4 hours post-inoculation, supporting the idea that impedance cytometry can potentially be applied in the clinical setting as a rapid diagnostic technology for assessing microbiota susceptibility to *C. difficile* colonization (Moore et al, 2020).

In the current sampling set-up, the *C. difficile* cultures of interest are exposed to atmospheric air during data acquisition. This is problematic because *C. difficile* is an obligate anaerobe quickly dying in the presence of oxygen. Resultingly, the Swami laboratory can only acquire *C. difficile* sample data of a culture of interest at one time point before the sample dies. This sampling system has provided evidence that this technology can detect *C. difficile* germination; however, in order to more thoroughly assess *C. difficile* germination and growth

kinetics with impedance cytometry, an anaerobic sampling system must be designed and incorporated into the current system. Thus, the goal of the technical project is to design a continuous sampling system for in situ monitoring of anaerobic coculture to better understand *C. difficile* growth kinetics and germination patterns.

To complete this project, the team first developed prototypes and selected the prototype that would work the best and be actually feasible to create. After identification of necessary functions of the system and selecting the best prototype design, flow resistance testing was conducted on the impedance cytometer. This is essential to determine the pressure range necessary for the upstream flow regulator to produce in order to successfully take impedance cytometry samples. The next step is to start ordering all the components necessary to assemble to device. After assembling the device, preliminary tests will be conducted to ensure that the system can produce consistent flow rates at the necessary pressure magnitudes. Finally, after assembly and basic preliminary testing, the anaerobic coculture device will be implemented into the current impedance cytometer system; to test the efficacy of this new system, tests on *C. difficile* samples cocultured with known metabolic supernatant profiles will be conducted, and growth rates and germination data will be compared to known trends to confirm to validity of this sampling method. By successfully accomplishing this design project, the growth and germination kinetics of *C. difficile* will be better understood, and impedance cytometry will be one step closer to a technology that is feasible for clinical point-of-care microbiota testing to CDI.

STS Topic

The United States' spends more on healthcare than any other country in the world by a significant quantity. In 2018, the US spent 16.9 percent of its GDP on healthcare, almost twice as much as the average developed country. To put this into perspective, the next highest healthcare

spender was Switzerland, spending 12.2 percent of its GDP on healthcare. Even though the US spends the most on healthcare, it has one of the lowest average life expectancies of OECD countries at 78.6 years. Using Switzerland as a comparison again, their life expectancy is 83.6 years, significantly higher than the US (Tikkanen et al, 2020). In order to lower the cost of US healthcare while increasing life expectancy as well, problems within the current system must first be identified. Although underlying healthcare issues can be a result of an entire network of problems and flaws, it is necessary first identify the main players of the US healthcare system and assess both failures and successes stemming from each component. After identifying the major issues with the current system in the US, leading healthcare systems, such as those in Canada and Germany, will be analyzed as well to assess what works well for them. Resultingly, suggestions will be made on what concepts from other superior healthcare systems can be feasibly incorporated into the current system.

The United States' healthcare system can be broadly viewed as having four major stakeholders. The first is the purchasers, who supply the funds for healthcare. This includes individuals consuming healthcare, companies that pay for employee insurance, and the government that subsidizes public programs like Medicare and Medicaid. At a deeper level, essentially most individuals of the US can be considered in the purchase category. Consumers finance businesses through purchases of products, and they support government programs by paying taxes; however, the thesis will focus on businesses and governments, as they are the most important organized purchasers of healthcare in the nation.

Another key stakeholder is the insurers. At a most basic view, these companies receive money from purchasers and pay providers for care. The traditional roles of insurance providers are to obtain money from purchasers, absorb the medical cost risks of the purchasers, and then

pay providers when insured purchasers need medical care. The government can be considered both an insurer and purchaser with its programs; additionally, business that self-insure their workers can also be considered both purchasers and insurers.

Another important stakeholder in the US healthcare system is the providers. This is a broad category, including but not limited to: hospitals, clinics, physicians, nurses, nurse practitioners, pharmacists, nursing homes, or any other entity that actually provides direct care. In the thesis, the providers category may be differentiated further into healthcare professionals and healthcare locations.

The final key actor in the US healthcare system is the suppliers. These include pharmaceutical companies, medical supply businesses, computer industries. Together, the suppliers provide equipment, medications, health records, and other supplies necessary for providers to treat patients.

In order to analyze how the United States' healthcare system can improve, an Actor-Network Theory (ANT) approach will be utilized, which was founded by French sociologist Bruno Latour and his team in the 1980s. The main feature of ANT analysis is, "…its focus on inanimate entities and their effect on social processes" (Cresswell et al, 2010). ANT uniquely allows inanimate objects (like technology) to affect and play key roles in a network of interest. Actors can be both human and non-human, and are generally defined as "entities that do things." A network is defined as a group of unspecified relationships among entities of which the nature itself is undetermined. Networks are not reliable and can become unstable and change as a result of a variety of reasons, including entry of new actors, desertion of existing actors, and changes in alliances (Seabrook, 2020). Actors of a network, like the US healthcare system, communicate through intermediaries. "Intermediaries" is another broad term to describe how actors are able to

translate their intentions onto other actors. Translations involve all the techniques through which an actor recognizes other actors and arranges them in relation to each other. Thus, each actor has their own view (assuming a human actor) of the distribution of their network and how the actors are arranged in relation to each other (Seabrook, 2020). One of the biggest critiques of the ANT perspective is that research is entirely descriptive and fails to provide adequate explanations for social processes, since ANT requires judgement calls from the researcher to determine the network and important actors ("Criticism of Actor-Network Theory," 2010). This thesis will work to minimize this critique by basing defined actors and perceived networks on evidence from multiple sources. Additionally, each claim about the network and suggested changes will be evidence-based in an attempt to successfully utilize ANT to provide realistic suggestions to the US healthcare system. Overall, analyzing the US healthcare system through the ANT framework is critical if change is actually to occur in the current system. Successful application of the framework to the US healthcare system will aim to both reduce cost of healthcare in the United States' while also improving the overall life expectancy of the US population.

Methodologies

Research Question: How can the US healthcare system change to lower the cost to patients and improve on life expectancy?

To answer my research question, I will use ANT and case studies on the countries with some of the most successful healthcare systems. By using ANT, I will depict the US healthcare system and describe the power that each key actor currently has along with network relationships that could be damaging the US healthcare system. I will then perform case studies utilizing the ANT framework on the most successful healthcare systems, like Germany and Canada (Radu, 2020). Although countries like Canada may utilize healthcare practices that may be deemed as

too radical to be realistically applied to the US system, such as universal healthcare, I will remain cognizant about practicality and focus my works on identifying key components that actually have a chance of being implemented into the US healthcare system.

I will be collecting a wide variety of sources for this thesis. While assessing the current US healthcare system through ANT, I am gathering sources composed of authors and perspectives from each of the key actors identified along with outside sources, such as research scientists and credible news authors. When assessing the healthcare systems of other countries and discovering what works well with them, I will gather sources from researchers from these countries along with United States authors who have reviewed other healthcare systems. Throughout the entire research process, key words such as healthcare cost, healthcare benefits, healthcare flaws, and healthcare stakeholders will be used. Both benefits and issues will be identified in the US along with other countries to optimize results of the analysis, as it is equally important to identify both success and failures of each healthcare system being analyzed. By utilizing ANT to identify the major network of the US healthcare system and other countries being analyzed, I hope to be able to not only identify what is wrong with the current US healthcare system, but to be able to provide feasible suggestions for solutions. Resultingly, by improving the individual system components of the US healthcare system, the resulting effect of utilizing the suggestions will be to lower the cost of healthcare in the United States while additionally improving the life expectancy of US citizens.

Conclusion

In summary, successful completion of the technical project will consist of an anaerobic coculture system, which will be able to be incorporated into the impedance cytometer system for in situ monitoring of *C. difficile* growth kinetics and germination patterns. This will allow

impedance cytometry to be one step closer to being a viable point-of-care CDI susceptibility technology, which would resultingly reduce the incidence of the infection and save substantial patient money and time.

Successful completion of the STS research would provide realistic suggestions for the improvement of the current US healthcare system. By identifying problems with the system at the macro level and comparing the current system to more successful systems, I hope that the suggestions, if implemented, will reduce the overall cost of healthcare in the US while also improving the life expectancy in the US.

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