Simulating Nutrient Preferences to Inform Co-culture Design for Probiotic Manufacturing

(Technical Paper)

The Effect of Racial Discrimination on the Underrepresentation of Minority Groups in Clinical Trials

(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

Introduction

Every treatment or medication that is being used by patients has gone through an extensive development process. The process of drug development starts from an idea conceptualized in a research and development group, and it is followed by the research of that drug or treatment. The drug or treatment then enters the preclinical research phase where it will undergo laboratory and animal testing to provide an initial assessment of safety. After passing the preclinical phase, a series of clinical trials will be performed on human subjects to test the efficacy of that drug or treatment (Kaitin, 2010). Once the drug passes the clinical trial phase, the drug or treatment will be approved by the FDA in order for it to be manufactured and eventually given to patients.

The proposed technical project addresses the manufacturing and post-clinical trial phase of the drug development, more specifically of probiotics. Currently, a major limitation in the development of probiotics is the ability to scale up probiotic cultures so that they can be manufactured more extensively (Fenster et al., 2019). The primary aim of the project is to make the treatment of malnutrition more cost-effective by using metabolic network models to find optimal probiotic combinations to increase production.

The proposed STS project focuses on the societal implications involved in the clinical trial phase. Clinical trials are a critical step in drug development because the results can determine whether or not a drug or treatment is effective. A major problem in the clinical trial phase is the low patient enrollment rate, more specifically underrepresented patient populations, which can negatively impact the statistical validity of that trial (Unger, Cook, Tai, & Bleyer, 2016). The STS project aims to explore the social factors that contribute to the

underrepresentation of certain social groups in clinical trials. Both projects aim to address issues around the drug development process.

Technical Topic

In 2018, 21.9% of children under the age of 5 were two standard deviations below the median height, and an additional 7.3% of children were two standard deviations below the median weight for their age ("UNICEF - Definitions," n.d.). These afflictions are the result of poor nutrition, beginning in utero and continuing into early childhood (United Nations Children's Fund (UNICEF), World Health Organization, & The World Bank, 2019). Malnutrition is considered a pressing global health concern, a contributing factor for almost half of all childhood deaths, and an agent in developmental impediments (Walson & Berkley, 2018). Gut dysfunction and altered gut microbiota have been linked to clinical outcomes of infantile malnutrition (Subramanian et al., 2014). Thus, nutritional rehabilitation therapies are needed to help restore a healthy gut microbiome.

Current therapies that involve the administration of probiotics which are most often composed of only a single bacterial species that is grown in a bioreactor and freeze-dried before it is delivered to a human, have proven to be ineffective for sustainable growth (Fenster et al., 2019). A promising new strategy is the transfer of multi-species probiotics that consist of live gut microbes that can restore the gut microbiome. Although these multi-species probiotics show great promise, they have not yet been scalable for large scale administration due to the complexity of the metabolic interactions associated with co-culturing multiple bacterial strains. To become feasible for large-scale administration, new strategies must be employed to increase manufacturing yield of these human gut bacteria (O'Toole, Marchesi, & Hill, 2017). The technical project aims to predict optimal combinations of strains of gut microbes, leveraging

metabolic data to understand how strains interact. Funding for the project is provided by a Bill & Melinda Gates Foundation grant, and the work will be documented in a journal article, with the intention to submit a manuscript about early findings to journals in January 2020.

To achieve this, Caroline Bereuter, Sami Clayton and I plan on developing a computational pipeline that can be applied to various probiotic strains to develop metabolic models, and then use these models to determine optimal strain combinations. The timeline for the generation of the computational framework is illustrated by Figure 1. The pipeline starts with the generation of genome-scale metabolic network models for gut microbes. This will involve finding genome annotations for relevant microbes and then searching those genomes for homologous proteins with known enzymatic activity. (Biggs, Medlock, Kolling, & Papin, 2015). After the generation of metabolic network models for different strains of probiotics, metabolomics and biomass data will then be incorporated to automatically refine the models

The data will be generated from experimental analysis of 10 different probiotic strains from human gut-derived microbes to determine nutrient preferences, and is currently being collected by the technical advisor. Following creation and refinement of the metabolic models, nutrient preferences and secreted products will be simulated. These computational predictions of nutrient

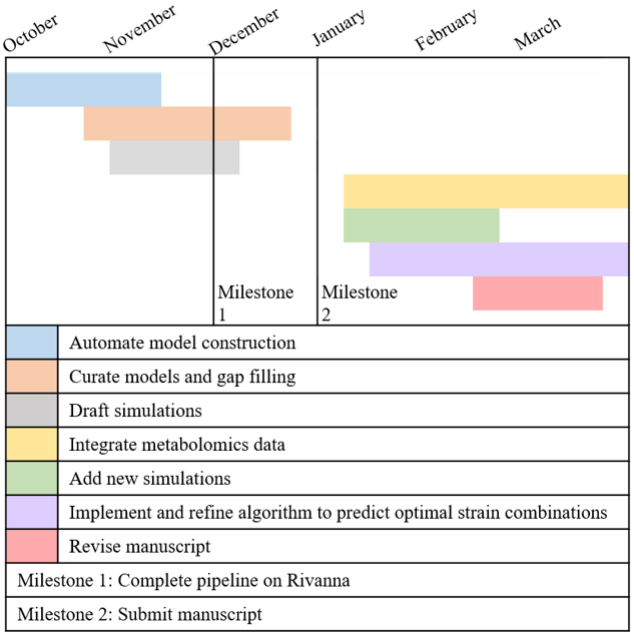

Figure 1: Timeline of Capstone Project: The timeline depicts the schedule for completion of the creation of the models, simulations, integration of metabolomics data, and generation of predictions (Created by Bereuter, Clayton, & Lin, 2019)

preferences and metabolites will be integrated into a machine learning- based process to predict optimal species combinations.

We will be using a novel algorithm, Growth Optimization by Packing Metabolomes (GO-PacM), to predict optimal co-cultures. GO-PacM treats each bin as a batch fermenter and each item as a probiotic strain. Instead of filling a volume like a traditional bin-packing problem, GO-PacM will maximize biomass by efficiently packing the "metabolic space" with co-cultures of probiotic strains using metabolomics and biomass data. When GO-PacM is solved, the solution will include the maximum cross-feeding potential of multiple probiotic strains in culture. To validate the optimized combinations, microbes will be grown in both optimal and random combinations and biomass yield evaluated to measure improvements with the predictions.

STS Topic

Clinical trials are essential for the advancement of biomedical research and developing new treatments for diseases. In addition, clinical trials are important for discovering new ways to detect, diagnose, and reduce the risk of disease. In general, conducting clinical trials informs researchers what does and doesn't work in people. Currently, one of the biggest barriers in the advancement of medical research is the low adult patient participation in clinical trials. For example, only about 5% of adult cancer patients are involved in cancer clinical trials, and according to the author of the book *Emperor of all Maladies*, Siddhartha Mukherjee, it is not a high enough number for cancer research to move forward (Brody, 2015; Unger et al., 2016).

In addition, certain ethnic and social groups are strongly underrepresented in clinical trials. Low participation and or representation of groups such as African Americans or Hispanics, can negatively impact the statistical validity of the study for a population that would receive that treatment or drug (Davis, Arnold, Mills, & Miele, 2019). The lack of participation by minority groups in clinical trials makes it even more critical to understand what different factors or

barriers influenced the underrepresentation of minorities in clinical trials so that solutions can be developed to increase representation of minority groups in trials (George, Duran, & Norris, 2014; Russo, Stout, House, & Santana, 2019). To illustrate this issue, according to a journal article by Propublica, a new drug was approved by the FDA to treat multiple myeloma, one of the deadliest blood cancers, after conducting a clinical trial where participants who took the medication could go 6 months without their cancer spreading (Caroline Chen, 2018). However, out of the 722 patients in the trial, only 13 or 1.8% were African American and out of the patient population that are diagnosed with multiple melanoma, 20% are African American. The racial disparity in the trial makes it difficult to assess the effectiveness of the drug in African American patients. Other minority groups are also underrepresented in clinical trials. One report estimated that Hispanics made up only 7.6% and 3% of clinical trial participants conducted by the NIH and industry-sponsored trials, respectively (Fisher & Kalbaugh, 2011). Another study reported that only 17% of participants in clinical trials conducted by the FDA were racial/ethnic minorities, despite the fact that they constitute at least 30% of the population (Evelyn et al., 2001).

One contributing factor to the underrepresentation of certain minority groups, such as African Americans and Native Americans, in clinical trials is the general mistrust among these groups toward the medical research establishment. The mistrust among these minority groups can be traced back to a history of racial discrimination and mistreatment by the health care industry and the field of medical research towards these groups (George et al., 2014). Cases such as the Tuskegee syphilis study, where a cohort of African American men were left untreated for many years in order to determine how the disease progressed, is one of the many examples of how minorities were mistreated in clinical research (Hussain-Gambles et al., 2004). The social construction of technology (SCOT) framework will be used in order to evaluate how the general

mistrust of medical research institutions among minority groups developed throughout history. SCOT is a theory which states that human actions shape the development and perception of technology. SCOT has been criticized to be very focused on how technologies arise but ignores the consequences after the fact. Specifically, I will be looking into how social constructs of clinical trials are established through the mistreatment of vulnerable subjects in clinical trials, in particular racial and ethnic minority groups. I will also analyze how these constructs have shaped the way clinical research institutions handle the recruitment and treatment of these groups in order to further illustrate how it is a contributing factor for the underrepresentation of minority groups in clinical trials.

In addition, actor network theory (ANT) will be applied in order to identify specific actors that are involved in the underrepresentation among minority groups in clinical trials. Actor network theory is a framework that identifies certain actors that are involved with a particular technology and creates connections between these actors in order to describe how a technology evolves within a certain social context (Callon, 2001). A major critique on the ANT is that it implies that all actors have equal importance and also does not account for pre-existing structures such as powers (Doolin & Lowe, 2002). The major actors that influence the underrepresentation of minorities in clinical trials is the lack of clinical trial awareness or medical education, distance from medical centers, and patient physician relationships. ANT will be used to assess the role of all of these actors in the underrepresentation of minorities in clinical trials and provide a network that will be used to assess the relationships between these actors. The analysis will help determine the effects of certain barriers involved with the recruitment of minority groups so that solutions can be developed to address these factors in order to improve the clinical trial process and provide results that better represent patient populations.

Research Question and Methods

The primary research question for the STS project is to determine why there is underrepresentation of certain minority groups and what social, political, and cultural forces contribute to their underrepresentation in clinical trials. Throughout the Spring 2020 semester, I plan to use documentary research methods in order to conduct the analysis for the proposed research project. More specifically, an extensive literature search through databases such as PubMed and Web of Science will be carried out to identify relevant articles. I will also be looking through journals, such as the American Journal of Clinical Research, the American Journal of Public Health, and the Journal of General Internal Medicine. The goal of the literature review will be to identify the barriers to the low participation of minorities in clinical trials and provide evidence for how these barriers play a role in their underrepresentation in clinical research. In addition, historical case studies will be used to evaluate how previous cases of mistreatment and victimization of minority groups in clinical research shaped their perceptions on medical research institutions and how these cases have influenced the way these institutions recruit and treat minorities. Network analysis will also be used to identify and connect different actors involved in the underrepresentation of minority groups in clinical trials. The creation of actor networks will allow for a better understanding of how certain barriers influence each other and the limited participation of minorities in clinical trials.

Conclusion

Successful completion of the technical project will serve as a way to predict the optimal combinations and nutrient preferences of any bacterial strains to be used in the development of probiotics. The optimal combinations of bacterial strains, generated from this computational framework, can be co-cultured in order to improve biomass yield. The proposed computational framework will also serve to lower costs by reducing nutrients required per batch and improve

scalability by utilizing a more robust combination of strains. This more efficient process of manufacturing with gut microbial strains will help to make live biotherapeutic strategies more accessible to those in need. If the implementation of the computational framework is successful, a peer-reviewed manuscript will be submitted for this work.

Research into the identification of different factors and barriers, using the social construction of technology and actor network frameworks as lenses, will help explain the reasons behind the underrepresentation of minorities in clinical trials. The analysis of barriers leading to the underrepresentation of minorities in clinical trials will help in the development of strategies and solutions that aim to increase the enrollment of patients from these groups. Incorporation of minorities in clinical trials will offer a more realistic representation of the patient population that will receive the drug or treatment and ultimately provide results that will serve as better indicators for how minority groups will respond to a new medicine or treatment.

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