Undergraduate Thesis Prospectus

Developing a Temperature Dependent Kinetic Model of Rhinovirus Infection

(technical research project in Biomedical Engineering)

Distrust of Pharmaceutical Companies in the U.S.

(sociotechnical research project)

by

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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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General Research Problem

How can public health for citizens of the United States be improved?

More than ever, in the wake of the Covid-19 global pandemic, it is useful to consider the interactions between technology and society with respect to public health. Infectious diseases had a prevalence of 71.4 per 10,000 people in the United States from 2009 to 2017 (Davgasuren et al., 2019). This prevalence can be assumed to have increased based on the recent emergence of the new Covid-19 virus. Thus, there is need for more effective therapeutics against infectious diseases to prevent the possibility of more infections. Technology can better inform knowledge about disease pathology which offers the potential for improved treatment development. Through the development of computational models, pathogen behavior *in vivo* can be simulated to allow for an increased understanding of infection of the body. Public health can also be improved by changing the nature of the interactions between the public and the healthcare system. For instance, in a study of 961 adults in the U.S., it was found that distrust was as high as 80% of all respondents to a survey designed to measure distrust of the healthcare system (Armstrong et al., 2006). Currently, public trust is very low which could pose significant risks for the health of the general population. Better understanding the cause of the distrust will enable a refinement of the relationships between the public and participants within the public health sector. Thus, both advancements in technology and reform within society play a crucial role in improving public health in the U. S.

Developing a Temperature Dependent Kinetic Model of Rhinovirus Infection

How can computational modeling of rhinovirus inform knowledge of enterovirus behavior?

Dr. Kevin Janes, faculty of the Department of Biomedical Engineering, will advise my teammate Page Murray and I on this technical project. It involves using rhinovirus, a member of the enterovirus genus, as a model to gain insight into the mechanisms of the viral genus as a whole to better inform treatment for these illnesses. Rhinovirus is associated with upper respiratory tract infections, sinus infections, and ear infections, all of which can be indicators of the common cold and bronchitis (Garmaroudi et al., 2015; Jacobs et al., 2013). It is responsible for over half of cold-like illnesses annually. While the common cold is ordinarily a relatively mild disease, it can pose a significant risk to vulnerable populations like the elderly or patients suffering from chronic respiratory diseases like asthma. Additionally, rhinovirus represents a significant economic burden. A survey of 4,051 U.S. households revealed that approximately $40 billion is spent annually on respiratory tract infections caused by rhinovirus. This includes the direct costs of medical visits and the indirect costs associated with time off from work or school (Jacobs et al., 2013). Enterovirus' as a whole, including coxsackievirus and echovirus which can potentially cause heart inflammation and upper respiratory tract infections respectively, pose a wider range of health risks and an even larger economic strain (Mohamud and Luo, 2019). Therefore, developing a kinetic model of rhinovirus infection will lead to an improved understanding of not only rhinovirus, but enterovirus' as a whole, which is necessary for the development of effective therapeutics for such illnesses. Currently, the majority of treatments for enterovirus', like rhinovirus, are concerned with symptom management. In the case of rhinovirus, antiviral development has been complicated by concerns surrounding drug toxicities and difficulties achieving desirable results *in vivo* (Jacobs et al., 2013). Vaccine development has proven difficult because of the multiple serotypes (minor and major) and species (A, B, and C) of virus which inherently produce a lot of variability making it difficult to

identify a reliable target for treatment (Jacobs et al., 2013; Colonno et al., 1988; Hung et al., 2017). Therefore, an improved treatment for rhinovirus, among other enterovirus', is necessary.

Currently, a model for coxsackievirus B3 and poliovirus, both of which are members of the enterovirus genus, exists. The model details the different components of the viral lifecycle including delivery, replication, and encapsidation. Outputs include information about the number of virions, the elicited immune response, and the amount of double stranded ribonucleic acid (RNA) which is indicative of viral replication (Lopacinski, 2020). However, the current models have a few shortcomings. For instance, the current encapsidation module clumps parameters into a single kinetic value. Therefore, this oversimplifies the viral mechanisms, failing to represent the process as accurately as possible. Moreover, the current models ignore any temperature dependence of the kinetic parameters merely assuming constant values.

The proposed new model will be created using MATLAB as a mass action compartment model. It will include a delivery, a replication, and an encapsidation module, as the models before have. Therefore, the model aims to clearly define the kinetic parameters specific to rhinovirus involved in each of these modules. This model will be unique in that the encapsidation module will ungroup parameters offering a more precise look at this stage of the process. This will involve a literature search to determine which parameters have been derived, and which remain unknown. For unknown parameters, optimization methods will be used to determine approximate values. The model also aims to incorporate temperature dependent kinetics. Rhinovirus has been found to have better viral propagation at 30℃ than 37℃, the latter of which is body temperature (Raran-Kurussi, 2013). This behavior is counterintuitive because at higher temperatures, kinetic parameters are increased which would suggest an increase in viral propagation. Therefore, the incorporation of temperature dependence is key to a more accurate

understanding of rhinovirus behavior. Upon completion of this project, a computational model that predicts rhinoviral kinetic behavior will exist. This model will be useful to inform treatment development, not only for rhinovirus, but for enterovirus' as a whole.

Distrust of Pharmaceutical Companies in the U.S.

How are big pharmaceutical companies attempting to regain trust in the eyes of the public?

Pharmaceutical companies develop and sell life-saving medications, so it is of utmost importance that they have consumers' trust. However, the public harbors a variety of fears related to the safety and commercialization of such products (Brown and Calnan, 2012). There is widespread concern that the intense marketing effort made by pharmaceutical companies is motivated by the desire for profit rather than serving patients' interests (Mulinari, 2016; Brown and Calnan, 2012). Likewise, there is concern that marketing techniques may distort scientific findings, over estimating efficacy and underestimating negative side effect. Therefore, the reputation of "big pharma" is suffering. This skepticism is particularly dangerous because it can encourage behaviors that may damage current public health, like refusal to vaccinate children. Moreover, it threatens medical innovation, which poses a risk to the future of public health (Pahus, 2020).

Participants involved include the big pharmaceutical companies themselves, who create the products used by the public for disease relief and prevention. They claim to be dedicated to serving patients and making medicines affordable (Pfizer, 2020). Closely related, is the Food and Drug Administration (FDA), which imposes strict guidelines related to product safety but cannot legally control drug prices (FDA, 2019). The American Medical Association (AMA), which is an organization for doctors in the United States, is an important stakeholder as doctors are involved

in the prescription and administration of many pharmaceutical products. The AMA supports the assurance of affordable drugs, increasing competition within the pharmaceutical industry, and greater transparency on the end of the pharmaceutical companies (AMA, 2015). On a related note, advocacies, such as Patients for Affordable Drugs, make efforts to lower the cost of prescription drugs by sharing patient stories (May, 2020). Lastly, consumers of pharmaceutical products distrust the marketed safety of such products and the incentives of the companies (ICWA, n.d.).

Researchers have investigated marketing practices in the pharmaceutical industry. Pharmaceutical companies spend roughly one-third of their revenue on marketing products (Mulinari, 2016). A huge concern is the price of prescription drugs being unreasonably high due to intense marketing efforts, which are often direct-to-consumer advertisements. A study conducted by Aikin et al. (2004) found that in 2002, nearly 81% of respondents had seen a direct-to-consumer pharmaceutical ad, which speaks to their prevalence. Moreover, research by Filipova (2020) found that direct-to-consumer advertising could mislead patients and worsened patients' relationships with their physician. This contributes to an understanding of public doubt of the true incentives of pharmaceutical companies which arises from marketing efforts. This same doubt is implied to be related to how anti-vaccine movements gain support. A study by Ortiz-Sánchez et al. (2020) found that anti-vaxxers disseminate information on social media, like Twitter, related to distrust in pharmaceutical companies to gain support. This distrust is largely motivated by the belief that pharmaceutical companies are motivated to distribute vaccines because of the large profits they receive, while the health benefits may still be unclear (Ortiz-Sánchez et al., 2020). This relates to the concept proposed by Merton (1957) of manifest versus latent function. It seems that consumers are suspicious of the pharmaceutical industries manifest

function of providing medical solutions to treat and/or prevent illnesses affecting the general public. Instead, it is believed that the pharmaceutical companies' marketing of products may support a latent function of economic gain. This discrepancy between manifest and latent function seems to be the cause of the public distrust of pharmaceutical companies.

It has been claimed that competence, benevolence, and integrity are the most important factors to a perception of trustworthiness (Mayer et al., 1995). A study by Fouli and Hart (2018) found that discursive strategies, like explicit expression of beliefs that portray a dedication to business ethics and expressions indicative of an empathetic attitude, increase public perception of company trustworthiness. This would suggest that in constructing company webpages and making public statements, pharmaceutical companies should use phrasing that increases perceptions of integrity and benevolence as this is predicted to boost their reputation. However, it must be remembered that the public will not accept company claims naively. This suggests that pharmaceutical companies must find a genuine way to rebuild their public perception (Fuoli and Hart, 2018).

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