Prospectus

Developing a Temperature-Dependent Kinetic Model of Rhinovirus Infection
(Technical Topic)

Societal Construction of Technology and the Dominance of Oral Poliovirus Vaccine in Low Income Areas
(STS Topic)

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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Introduction

Enterovirus is a genus that can cause a variety of symptoms including paralysis, dilated cardiomyopathy, gastrointestinal distress and respiratory infection and includes poliovirus, coxsackievirus, echovirus and rhinovirus (Mohamud & Luo, 2019). Large outbreaks of poorly understood enteroviruses, such as Enterovirus A71 and Echovirus 13, 18 and 30, which cause Hand, Foot and Mouth Disease and viral meningitis respectively, have been recorded in the past decade (Center for Disease Control [CDC], 2020b). Not accounting for poliovirus, which has been controlled by vaccination campaigns, it is estimated that 10-15 million people have some enterovirus infection every year (CDC, 2020b). Currently, poliovirus is the only enterovirus with an FDA approved vaccine while treatment for other enteroviruses consists only of symptom management and does not prevent infection or transmission (U.S. Food and Drug Administration, 2020). Development of potential therapies is slow and costly, partly due to a lack of current modeling technology

Technology to kinetically model enteroviruses is necessary to allow for rapid research and development of potentially life saving therapeutics and vaccines. Without the ability to computationally model enterovirus, researchers must use experiments in mice or cultured cells to investigate infection mechanisms, which are time consuming and difficult. Slow research of viral outbreaks can lead to additional illness and death. A solution to this technical problem is the development of a mechanistically detailed and temperature-dependent kinetic model of enterovirus. However, a technical solution alone is insufficient to fully resolve the issue of providing better treatment for viral disease because it does not address the social aspects, such as accessibility and practicality of treatments, that are affected by the development of vaccines and therapies for viral infection.

In the early twentieth century, prior to the development of the poliovirus vaccine, thousands of people perished each summer from poliomyelitis (Ochmann & Roser, 2017). Two versions of the poliovirus vaccine were developed in the middle of the century: the oral poliovirus vaccine (OPV) and the intravenous poliovirus vaccine (IPV) (The College of Physicians of Philadelphia, n.d.). OPV is most commonly used in nations where poliovirus outbreaks are still prevalent. The oral vaccine has greater efficacy, but also carries more potential health risks than the IPV, meaning neither is an objectively better technology (CDC, 2020a). The current understanding of the dominance of OPV does not take into account how the relevant social groups shaped the technology. By ignoring how social factors affect adoption of vaccines, we will not understand how to better design vaccines to meet users needs. Using Societal Construction of Technology (SCOT), I will analyze how the needs of the relevant user groups led one vaccine to dominate over the other in its respective community. The deficiencies in treatment of enterovirus represent a socio-technical problem that requires a solution that is both technical and social in character to address the lack of current methods to develop vaccines and to understand the impacts social factors have on a community's ability to adopt these vaccines. In the following sections I describe a technical project that will develop a computational modeling tool to better understand enterovirus. I also will lay out a STS research project that analyzes the domination of the OPV using the STS framework of SCOT.

Technical Problem

Human Rhinovirus (HRV), a member of the enterovirus genus, is associated with upper respiratory tract infection, sinus infection and bronchitis (Garmaroudi et al., 2015; Jacobs et al., 2013). HRV is a significant risk to public health and caused over 700 hospitalizations in 2015,

impacting the health of immunocompromised individuals, the eldery, infants, and patients with chronic respiratory diseases (Hung et al., 2017).

Viral kinetic modeling has become an essential tool for researching viruses like HRV. Viral models allow us to quickly and accurately research and develop better treatments for HRV, which can lead to a decrease in illness and death due to HRV infection. Current viral modeling separates the viral life cycle into three modules: delivery, replication and encapsidation (Figure 1). Delivery is how the virus binds to and enters a host cell. Replication is how the virus creates copies of its genomic information. Encapsidation is when viral proteins come together with the viral genome to create new infectious virions.

Detailed structural models exist for viruses like Poliovirus, HIV, Arbovirus, and Influenza A (Gale, 2019; Krakauer & Komarova, 2003; Sidorenko & Reichl, 2004). However, these models lack certain modules of the life cycle or do not take into account the effect of an immune response on viral kinetics. Thermodynamics and temperature-dependence were missing from some of these models, limiting their accuracy when temperatures vary from normal physiological temperature, for example in the nasal pathway (Foxman et al., 2015; Raran-Kurussi et al., 2013).

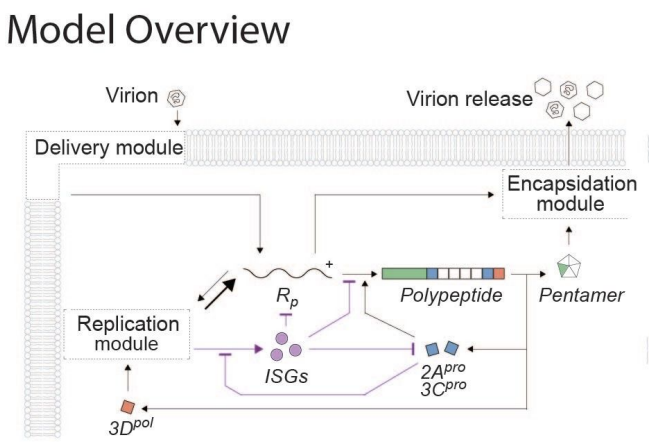

Figure 1: Overview of the model architecture. Three main modules are represented: Delivery, Replication, and Encapsidation. The positive sense RNA (R_p) is replicated, triggering an innate immune response (ISGs). RNA is translated as a single polyprotein that is then cleaved yielding proteases 2A and 3C, polymerase 3D and capsid proteins which form pentamers. RNA is packaged inside of complete capsids and mature virions are released.

While past iterations of our model shown in Figure 1 exist for other enteroviruses, like CVB3 and Poliovirus, these iterations are lacking in some aspects (Lopacinski, 2020). Neither of them represent the same heterogeneity as HRV, and so are less generalizable. This means that in the event of a new outbreak of enterovirus, it would take more time to adapt the model to a new virus. Moreover, in the previous enterovirus models, multiple parameters related to encapsidation were grouped into a single kinetic parameter because there was not sufficient data. Therefore, the previous model estimates the encapsidation process and oversimplifies this complicated mechanism, decreasing the accuracy of its predictions. Failure to develop an easily adaptable and complete kinetic model of enterovirus means we will be less prepared to study and treat future outbreaks. Our model of HRV will provide an enhanced tool for researching enterovirus infections by improving upon the insufficiencies of the previous model.

We will develop a complete kinetic model of HRV infection that is temperature-dependent and has mechanistically detailed encapsidation parameters. This model incorporates the entire viral lifecycle and the immune response during infection. Our model will be quickly adaptable to new strains of HRV or other enteroviruses, and will allow for more rapid and accurate study of viral mechanisms. Model optimization and estimations taken from similar reactions will be used to fill in the gaps in our knowledge of parameters. This will allow for the creation of a mechanistic model of encapsidation that reflects the detail of the rest of the model. Thermodynamics will be used to create temperature-dependent functions for the model parameters. Our MATLAB code will use systems of differential equations to track virus

concentrations in the cell. Finally, we will analyze data from current literature to verify the accuracy of the current model and show that our model accomplishes the above goals. By improving the available tools to study enteroviruses, better treatment for enterovirus infection can be quickly developed.

STS Problem

The early 19th century brought increasingly devastating outbreaks of poliomyelitis, a disease characterized by sometimes permanent flaccid paralysis (Baicus, 2012). During this time, poliovirus outbreaks occurred every summer, causing terror and resulting in thousands of deaths. In 1952, cases in the US peaked with nearly 60,000 cases and 3,000 deaths (Ochmann & Roser, 2017). These figures do not account for those who survived with permanent disabilities.

The first vaccine for poliovirus was a killed-virus vaccine developed by Dr. Jonas Salk in 1955. This vaccine, called the intravenous polio vaccine (IPV), was administered by a shot. It succeeded in decreasing cases from 10 out of 100,000 people to 0.1 out of 100,000 people and was 90% effective (Baicus, 2012). However, many scientists believed that the only way to develop a 100% effective vaccine that imparts long term immunity was to use a live attenuated vaccine. In 1960, this led Dr. Albert Sabin to develop a new vaccine that could infect the mucous membranes of the stomach and replicate (something a dead virus cannot do). This also meant that the vaccine could be taken orally and was named the oral polio vaccine (OPV) (Ciapponi, et al., 2019). OPV quickly became the preferred vaccine in developing countries, however today only IPV is recommended for use in the US (Global Polio Eradication Initiative [GPEI], n.d.b; CDC, 2020a). OPV, being a live virus, can mutate and lead to symptomatic poliomyelitis in rare cases, meaning that while it is more effective, there is greater risk in comparison to IPV. Both OPV and IPV induce antibody formation in the blood which helps the body fight off an

infection, however, only OPV builds immunity in the mucus lining of the gastrointestinal tract, which prevents infections in the first place.

Because of these biological facts, the dominance of each vaccine in its given market has been understood through the context of their various biological merits (GPEI, n.d.a). However, this does not take into account the social factors that lead to the relevant groups adopting the specific vaccine that best met their needs. It also ignores how the needs of the relevant social groups were taken into account by designers to reach the current version of the OPV. By analyzing how the ideas and needs of low income communities made OPV the more appealing vaccine, we can understand how OPV is socially constructed. Using the Science, Technology and Society framework of Social Construction of Technology I will analyze how OPV dominated in markets where its practicality, accessibility, and affordability interacted with social factors to make it more appealing than IPV. Additionally, I will show how scientists took into account the ideas held by the users and by public health officials to improve upon subsequent iterations of the OPV. In this framework social factors lead separate relevant groups to adopt the technology that best meets their needs (Pinch & Bijker, 1984). These relevant groups can be institutions, organizations, or unorganized groups of individuals, and are not restricted to users. SCOT also encompasses the idea of interpretive flexibility, which explains that artifacts like vaccines are culturally and socially constructed. I will analyze documents from the World Health Organization and the Global Polio Eradication Initiative to identify how needs of the relevant community lead them to adopt one vaccine over the other. This will reveal how neither vaccine was an objectively better technology, but rather met various groups' needs and wants better. A better understanding of this relationship between the biological aspects of vaccines and the social needs of people who use them will help to develop superior treatment of enterovirus.

Conclusion

The social and technical research projects outlined here will help address the socio-technical issue of improving treatment of enterovirus disease. The technical report will deliver a new design for a detailed and temperature-dependent kinetic model of HRV infection. The addition of HRV's heterogeneous delivery modules to the enterovirus model's repertoire will make it more adaptable. This model will allow for rapid and accurate investigation of future strains of HRV or enterovirus outbreaks, possibly leading to rapid development of vaccines or therapeutics.

The STS research paper will use the SCOT framework to analyze how varying social needs led OPV to dominate different markets than IPV. This analysis will provide better insight into how social structures interact with the accessibility and practicality of vaccines, leading to adoption of one version over the other. The results of the technical report will help to resolve the broad socio-technical issue of improving treatment for enterovirus diseases by creating a tool to understand enterovirus mechanisms and research treatment options. The research of the STS paper will help to understand the correlation between which factors of vaccine design are desirable under which social factors.

Word Count: 1955

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