Mathematical Modeling and Control of Disease Spread in Healthcare Settings

Research Project Summary (Please provide an overview of your project -- this will be shared with students as a project description; maximum 500 words):

Mathematical modeling is a useful technique to describe dynamics happening within events and allows one to address questions and test hypotheses that may not be feasible to study in reality. This work uses mathematical modeling and analysis techniques to quantify the role that environmental pathways play in the transmission of disease in healthcare settings. *Clostridioides difficile* (*C. difficile*) is one of the most frequently identified healthcare-acquired infections in United States hospitals. Colonized patients, both symptomatic and asymptomatic, shed *C. difficile* endospores that can survive for long periods on surfaces outside the host and are resistant to many commonly-used disinfectants. Transmission pathways can include contact with endospores on fomites, objects likely to carry infection. This project investigates the relative contribution of two environmental pathways to *C. difficile* transmission in healthcare settings. Due to the small hospital ward size, patient and pathogen populations are simulated stochastically and compared with the average behavior described by a system of ordinary differential equations. Students will simulate mathematical models and use the results to examine the role surfaces with varying touch frequencies contribute to patient colonization. Further, students will work to develop control strategies and determine their effectiveness in mitigating the spread of *C. difficile* in healthcare settings.
**Introduction and Background**

Mathematical modeling allows one to describe dynamics happening in the real world by translating the knowledge and beliefs of interactions into the language of mathematics. For this reason, mathematical modeling is a useful technique used to describe natural occurrences and allows one to address questions and test hypotheses that may be not be feasible to study in reality.

Modeling interacting systems of the real world requires compromise. In order to avoid complicated systems, mathematical modelers must first identify the most important components in the system to include in the model, excluding everything else. Even with these simplifying assumptions, mathematical models can be used to develop scientific understanding, test the effect of changes in a system, and aid in decision making. This work uses mathematical models to better understand the dynamics occurring in the transmission of *Clostridioides difficile* (*C. difficile*) in healthcare settings, specifically the roles that touch surfaces play in the spread of the disease, and aims to make determinations about how to control disease spread. Specifically, optimal control theory will be used to determine the optimal cleaning rates to reduce disease spread while balancing associated costs for hospital wards.

In current models of infections originating in a hospital, transmission is often assumed to be a result of direct contact between hosts. However, many pathogens are able to infect hosts indirectly through the environment. To properly understand and prevent transmission of such pathogens, environmental reservoirs must be incorporated into modeling disease dynamics. My collaborators and I have developed a model of *C. difficile*, a gram-positive, endospore-forming bacterium, as a case study to develop and analyze models mechanistically addressing environmental transmission and to investigate the implications in disease dynamics, control, and surveillance.

*C. difficile* is the leading cause of infectious diarrhea and one of the most common healthcare-associated infections in United States hospitals. It causes 223,900 cases in hospitalized patients and 12,800 deaths annually, and the corresponding attributable healthcare costs is about one billion dollars each year. *C. difficile* is typically contracted after antibiotic use, when the healthy gut microbiota that prevents colonization is compromised. Colonized patients, both symptomatic and asymptomatic, shed *C. difficile* spores. These endospores can survive long periods outside the host and are resistant to disinfectants commonly used in healthcare settings. Transmission pathways can include contact with environmental reservoirs of endospores on fomites (objects likely to carry infection). Examples of fomites in a hospital room include bed rails, supply carts, IV pumps, and curtains classified as “high-touch frequency” objects, while thermostats, sinks, paper towel dispensers, and trash cans are classified as “low-touch frequency” objects. In our model, we assume high-touch frequency fomites are cleaned daily while low-touch frequency objects are cleaned only upon patient discharge or death.

Environmental control strategies include terminal cleaning and regular disinfection of isolation rooms or all rooms, and generally involve disinfectant substitutions, enhanced cleaning and disinfection practices, and recently, the use of automated disinfection technology. The CDC recommends daily cleaning of the immediate vicinity around an infected patient and disinfecting of an infected patient’s entire room upon discharge with a chlorine-derived disinfectant, the most effective chemical against *C. difficile*. Compliance with these guidelines is often sub-optimal and chlorine-derived cleaners are only used when necessary since they can damage and harm equipment. There is no “standard” cleaning procedure that optimally reduces the number of *C. difficile* spores to reduce future contamination.
Proposed Research Plan

Since *C. difficile* spores can survive for long periods on fomites not adequately cleaned or disinfected and are correlated with infection rates in healthcare settings, fomites can be a continuous source of transmission. This raises the question of what type of fomite in a healthcare setting contributes more to the transmission of *C. difficile* infection, fomites that are handled more frequently and tend to be cleaned and disinfected more often, or those that are handled less frequently and tend to be cleaned and disinfected less often. In most mathematical models of healthcare associated infections, transmission is assumed to be direct, that is, through physical contact between susceptible and infectious individuals. Several studies have formulated agent-based (ABM), stochastic differential equation (SDE), and ordinary differential equation (ODE) models to incorporate environmental pathways in the transmission of healthcare associated infections, but have not considered explicitly including the bacterial spore population.

Building off of a compartmental model by Lanzas and colleagues [23], our model of *C. difficile* transmission has four population classes: resistant patients who have not recently had an antibiotic; susceptible patients who have recently had an antibiotic; asymptomatic colonized patients who have been colonized by *C. difficile* bacteria; and symptomatic diseased patients; as well as two environmental compartments: high-touch and low-touch frequency fomites, measured in spores per square centimeter. The movement among these classes is expressed mathematically by a system of ODEs. Since hospital wards have small populations, the ODE model is also simulated stochastically using the Gillespie algorithm. The Gillespie algorithm uses a Monte Carlo procedure to numerically simulate the time evolution of a system. Within the simulation, we can track the distinct colonization events attributed to the high- and low-touch fomites in order to quantify the contribution of each to symptomatic cases.

The stochastic simulation shows that, on average, approximately 77% of new colonizations are caused by a contact with a high-touch frequency fomite, despite the extra daily cleaning high-touch frequency fomites receive. The remaining 23% of new colonizations are caused by a contact with a low-touch frequency fomite. Using this knowledge, we can guide healthcare facilities in methods to reduce *C. difficile* spread. Our published paper [46] focuses on the results from decreased spores on fomites, increased efficacy of cleaning and disinfecting, and changes in patient interaction. The results can be related to manageable adjustments in a healthcare setting.

While we have identified feasible management strategies to prevent disease transmission, the focus must now be turned to the development of an optimal cleaning strategy. That is, at what level should patient rooms be cleaned (both daily and terminally) while reducing associated costs of cleaning (in terms of time and money). Optimal control theory is a branch of mathematical optimization that focuses on finding a control for a dynamical system over a period of time so that a cost objective functional is minimized (or maximized). Using differential equations describing the paths of the control variables, the cost function measuring associated time and monetary constraints can be minimized. That is, an optimal strategy to reduce the number of colonized patients may be determined while minimizing cleaning and the costs associated with this cleaning. Various hospital scenarios will be considered, such as times of increased colonizations and times of outbreak, to see how these scenarios modify the optimal cleaning strategy.

To simulate the model and apply optimal control theory, students will use MATLAB, which has built-in solvers for systems of differential equations, to consider possible patient and environmental class trajectories. Even without prior programming experience, students can learn the necessary tools in MATLAB through example codes. Students will learn the necessary optimal
control theory by conducting reasonable textbook examples and then applying the skills learned to the existing mathematical model. At the conclusion of the Program, students should have results that could be implemented in a hospital ward.

**Mentorship Plan**

Students will meet with Dr. Sulyok at least three times per a week, in addition to attending the SURE seminars and weekly Math Research Seminars. During the Math Research Seminars, students will present their current progress on their research to other students and faculty working on mathematics research over the summer. This will afford students practice presenting their research and provides an opportunity for students to get feedback from other mathematicians not directly involved with their research project.

Students will be expected to keep a research journal and write a final paper by the conclusion of the Program. The schedule below provides details and timelines for the students and will help keep them accountable and organized while completing their work. Dr. Sulyok would expect that students involved with this project present at local, regional, and/or national mathematics conferences and would encourage them to continue this research throughout the academic year.

Student responsibilities will include understanding the necessary biological background for the application of the mathematical model, programming both the model and optimal control theory application, and writing their final results in a way that the research could be later submitted for publication. Dr. Sulyok’s focus will be guiding the research by creating a structured program. Some ways to guide the research will include:

- Establishing small goals for students to accomplish before each meeting so that they always know what tasks to work on.
- Encouraging students to keep a time log and journal where they demonstrate what they have been working on, for how long, what worked well, what did not work well, and what they learned from it. Using information from this time log, Dr. Sulyok will help students become more productive researchers.
- Meeting at least three times per week to check in with students to determine progress or roadblocks.
- Aiding students in reading academic articles and synthesizing important methods and results that may be applicable in their research project.
- Developing a research program that will help students succeed in their future careers – whether that is discussing graduate school, how this research applies in government or industry, writing CVs and/or resumes, developing presentation skills, etc.

Participating in undergraduate research is an opportunity for students to learn skills to help them become a life-long learner. There will be a stressed importance of time-management and independent work. The program will begin with background papers provided by Dr. Sulyok, but from there, students will be expected to find papers to further their research. In every meeting, students will be required to present an update on the work they have completed since the last meeting so that they may practice explaining methods, findings, and processes. Instead of the meeting being led by Dr. Sulyok, students will drive the meeting to encourage them to be responsible for their research.
Proposed Timeline

**Week 1:** Read background materials which introduce the project (mathematically and biologically) provided by Dr. Sulyok. Do a literature review for the current research in mathematical modeling of *C. difficile*. Complete a typed one to three paragraph synopsis of what might be useful from the articles. Work on textbook optimal control theory problems.

**Week 2:** Continue reading (and rereading) background papers. Write a summary of the relevant information from each paper and begin reviewing any existing code that can be modified for use in the project. Continue to learn optimal control theory. At this point, students should have a working title page and the LaTeX template set up.

**Week 3:** Start brainstorming ideas for what parameters and variables could be controlled in the existing model. Make a concept map of the ideas for the final paper and how they interconnect.

**Week 4:** Write a (rough) abstract about the summer plan and begin the process of achieving that goal (through coding and a continued literature review, if necessary). Keep track of coding in a research journal. Include foundation materials in the final paper.

**Week 5:** Continue to work on coding and analyzing outputs. Record what these mathematical results imply about the system being studied. Include initial results in the final paper.

**Week 6:** Use the relevant results to begin writing a formal paper detailing the work that has been completed. Write a draft of the introduction. This will incorporate material from the paragraphs written during the literature search. Continue adding supporting materials. Start working on any figures to be included in the paper.

**Week 7:** Think about what results should be included in the final report. Begin finalizing results and continue to add supporting materials. Draft a conclusion. Insert figures. If possible, write a fifteen minute talk with slides, and use the talk to improve the organization, figures, and exposition of the paper.

**Week 8:** Edit the paper and continue to add any sections or information that may be missing. Do an overall editing pass to complete the first draft. Continue to add further results if needed.

**Week 9:** Finalize and summarize results. Attend and present at MAA MathFest. Get feedback from others not involved with the project.

**Week 10:** Finalize paper and presentation. Edit the second draft. Possibly submit to a journal.
References


Control and Prevention, 2008.

**Budget**

The only possible funding requirement would come from the need for students to have MATLAB access on their personal computers. We should be able to connect to the MATLAB license already obtained by Lewis University remotely using a student VPN. I am requesting no funds for supplies.

I would be happy to have two SURE students for this project.
Description of any additional funding you will be using for your proposed research (Doherty Grant, Lasallian Research Grant, External Research Grant, etc.) and how it will be used in this project.

I have no additional funding for this research.

Criteria for student applicants (Please report minimum criteria you will expect from student applicants, such as coursework that must be completed prior to starting work on this project):

Interested students need the mathematical maturity to analyze and/or develop mathematical models, so students should have at least completed Calculus II. Differential equations and/or mathematical modeling experience would be an added bonus, but is not necessary for success in this project.

This project involves programming. It would be ideal for students to be comfortable with their ability to read and implement code, and possibly learn a new programming language (with example codes provided). Much of the work will involve understanding and modifying existing code, and there will be less of an emphasis on writing code from scratch unless the students desire to. Therefore, a student with little to no coding experience could succeed as long as they are willing to put in the effort.
As a faculty mentor, you will be required to participate as a leader for one of the weekly student seminars. This will be a 60-minute presentation at 9:00 am. Please indicate topics of interest from the themes listed below, or suggest an additional topic, that you might enjoy presenting.

___ Ethics in Research
___ Literature Search and Library Resources
___ Scientific Method and Problem-Solving Skills

Presentation Skills
___ Data Analysis and Data Management
___ Technical Writing

Resume Writing and Marketing

Preparing for Graduate School

Interview Skills

Mock Presentation Supervisor (Practice for Symposium)

Other (Please Describe): Workshop on how to use LaTeX (typesetting) and Beamer (presentations)
The James Girard Summer Undergraduate Research Program (SURE) is designed to support the execution of this proposed project by the faculty mentor and a single undergraduate student. After review of faculty proposals, selected projects will be advertised to Lewis University students, and all interested undergraduates will then be required to apply into the program, denoting the project for which they would like to be considered. Student applications will be reviewed for completeness by the program director and then forwarded to the appropriate faculty mentor for final selection of a candidate. Faculty may submit up to 2 projects for funding through the program. Although faculty mentors may also mentor additional students in the summer not funded through the program, the weekly program events and presentations will be exclusive for students in the program.

By submitting this application, you are agreeing to the following responsibilities of a SURE Faculty Mentor:

- Working closely with your student to ensure a worthwhile educational experience. Regular interactions with your student are an expectation (a minimum of once a week, but more frequently is encouraged). Interaction with other mentors and students is strongly encouraged
- Participating in the welcome and orientation day
- Leading at least one of the weekly workshops for the entire group of participants
- Writing at least one blog related to your area of expertise for the program website
- Participating in the Summer Research Symposium

This application will be reviewed by a faculty panel for acceptance into the program; determination of selected projects will be communicated after review. Project descriptions will then be made available to Lewis University undergraduate students, who can apply to the program and specific projects online via our website. Student applicants will be matched with mentors using a selection process where mentors rank interested students based on their applications and students rank projects based on their interests.

Any questions and all completed applications should be sent to Brittany Stephenson (SURE Director) at bstephenson@lewisu.edu.