Two Applications of Mathematical Modeling: Control Mechanisms of Heart Rate Variability and Contribution of Environmental Pathways in Disease Transmission

Lindsey Fox
University of Tennessee, lfox7@vols.utk.edu

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Two Applications of Mathematical Modeling: Control Mechanisms of Heart Rate Variability and Contribution of Environmental Pathways in Disease Transmission

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Lindsey Rhea Fox
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Abstract

Mathematical modeling has been proven to be an extremely useful tool in describing natural phenomena. It allows one to address questions and test hypotheses that may be unfeasible or unethical to study in reality. This work seeks to use mathematical models to describe and study two phenomena, one relating to physiology and the other to the spread of infectious diseases.

The first modeling study explores the physiological control mechanisms governing heart rate variability. Correlation between loss of heart rate variability and physiological states of stress has been well documented in clinical practice and experimental studies, however, this correlation has not been fully linked to underlying physiological mechanisms. This study combines two previous mathematical models of neuroendocrine control of heart rate and circulation to explain the source of heart rate variability in a resting, healthy state. Respiration is also incorporated into the system of ordinary differential equations as a disturbance to the system to characterize the role of respiration in heart rate variability.

The second modeling study investigates the contribution of environmental pathways to Clostridioides difficile transmission in a healthcare setting. C. diff is the leading cause of nosocomial, infectious diarrhea in United States hospitals and is contracted after antibiotic use. Colonized patients shed spores that survive for long periods of time on surfaces outside the host. This study adds environmental reservoirs to a previous mathematical model and focuses on the contribution of high-touch and low-touch frequency fomites to the transmission dynamics of the bacteria within a hospital. Due to a small hospital size, patient and pathogen populations are simulated stochastically and compared with the average population behavior described by a system of ordinary differential equations.
Table of Contents

1 A Model to Explore Control Mechanisms of Heart Rate Variability 1
  1.1 Introduction .................................................. 1
  1.2 Background ................................................... 2
    1.2.1 Heart Rate Variability ..................................... 2
    1.2.2 Neuroendocrine System and Circulation ..................... 3
  1.3 Previous Mathematical Models .................................. 5
    1.3.1 Li et al. (2014) ........................................... 5
    1.3.2 Randall et al. (2019) .................................... 6
  1.4 Data .......................................................... 6
  1.5 Model Formulation ............................................. 9
    1.5.1 Description of HRV Model .................................. 9
    1.5.2 Parameterization of HRV Model ............................ 26
    1.5.3 HRV Model ................................................ 32
    1.5.4 Metrics of HRV .......................................... 33
  1.6 Results ....................................................... 34
  1.7 Discussion .................................................... 38

2 The Contribution of Environmental Pathways to Clostridioides difficile Transmission 40
  2.1 Introduction .................................................. 40
  2.2 Background ................................................... 41
    2.2.1 Natural History of C. diff Infection ..................... 41
    2.2.2 Environmental Pathways of C. diff Transmission .......... 43
  2.3 Previous Mathematical Models .................................. 46
    2.3.1 Models Incorporating Environmental Pathways .......... 46
    2.3.2 Lanzas et al. (2011) .................................... 48
  2.4 Model Formulation ............................................. 49
2.4.1 Description of C. diff Model ........................................ 49
2.4.2 Parameterization of C. diff Model ............................... 51
2.4.3 C. diff Model ...................................................... 56
2.4.4 Predicted Metrics of C. diff Model .............................. 59
2.5 Stochastic Simulations .................................................. 62
  2.5.1 Gillespie Stochastic Simulation Algorithm .................... 62
  2.5.2 Stochastic Simulations of C. diff Model ....................... 65
2.6 Results ........................................................................ 67
2.7 Discussion ................................................................... 70

Bibliography ..................................................................... 73

Appendices ....................................................................... 84
  A Tables ......................................................................... 85
    A.1 Chapter 1 Tables ..................................................... 85
    A.2 Chapter 2 Tables ..................................................... 93
  B Figures ....................................................................... 107
    B.1 Chapter 1 Figures ................................................... 107
    B.2 Chapter 2 Figures ................................................... 126

Vita ................................................................................. 139
List of Tables

1  HRV Model: Variables ......................................................... 85
2  HRV Model: Auxiliary Variables ........................................... 86
3  HRV Model: Parameters ..................................................... 87
4  HRV Model: Results .......................................................... 91
5  C. diff Model: Classes ....................................................... 93
6  C. diff Model: Parameters .................................................. 94
7  C. diff Model: Shedding Parameters .................................... 96
8  C. diff Model: GSSA Events ............................................... 97
9  C. diff Model: Scenarios .................................................... 99
10 C. diff Model: Results from Scenario #0 .............................. 100
11 C. diff Model: Results from Scenario #1 .............................. 101
12 C. diff Model: Results from Scenario #2 .............................. 102
13 C. diff Model: Results from Scenario #3 .............................. 103
14 C. diff Model: Results from Scenario #4 .............................. 104
15 C. diff Model: Ranges of Middle 95% of Trajectories ............... 105
16 C. diff Model: Variances of Trajectories .............................. 106
List of Figures

1. HRV Model: PQRST Wave on ECG ................................. 107
2. HRV Model: RR Interval Example #1 ............................. 108
3. HRV Model: RR Interval Example #2 ............................. 109
4. HRV Model: Circulation ........................................... 110
5. HRV Model: Patient Data .......................................... 111
6. HRV Model: Schematic ............................................. 112
7. HRV Model: Type III Functional Response ....................... 113
8. HRV Model: Activation Level of PSNS and SNS ................. 114
9. HRV Model: Four Compartments of Circulation ................... 115
10. HRV Model: Model Output ........................................ 116
11. HRV Model: Model Output ........................................ 117
12. HRV Model: Model Output for Varied $q_w$ ....................... 118
13. HRV Model: Model Output for Varied $q_{bp}$ .................... 119
14. HRV Model: Model Output for Varied $q_{bs}$ .................... 120
15. HRV Model: Model Output for Varied $q_{rp}$ .................... 121
16. HRV Model: Model Output for Varied $H_{bp}$ .................... 122
17. HRV Model: Model Output for Varied $H_{bs}$ .................... 123
18. HRV Model: Model Output for Varied $H_{rp}$ .................... 124
19. HRV Model: Model Output for Varied $B$ ....................... 125
20. C. diff Model: Lanzas et al. Model Schematic .................... 126
21. C. diff Model: Schematic ........................................ 127
22. C. diff Model: Type II Functional Response ..................... 128
23. C. diff Model: ODE Solution of Scenario #0 .................... 129
24. C. diff Model: GSSA Trajectories of Scenario #0 ................. 130
25. C. diff Model: Middle 95% of GSSA Trajectories of Scenario #0 131
26. C. diff Model: Resistant and Susceptible Time Courses of Scenario #0 132
27. C. diff Model: Asymptomatically Colonized and Diseased Time Courses of Scenario #0 133
28  \textit{C. diff} Model: High-Touch and Low-Touch Frequency Fomites Time Courses of Scenario #0 ......................................................... 134
29  \textit{C. diff} Model: Middle 95\% of GSSA Trajectories of Scenario #1 ........ 135
30  \textit{C. diff} Model: Middle 95\% of GSSA Trajectories of Scenario #2 ........ 136
31  \textit{C. diff} Model: Middle 95\% of GSSA Trajectories of Scenario #3 ........ 137
32  \textit{C. diff} Model: Middle 95\% of GSSA Trajectories of Scenario #4 ........ 138
List of Abbreviations

ABM  
agent-based model

CDC  
Centers for Disease Control and Prevention

C. diff  
Clostridioides difficile (formerly Clostridium difficile)

DBP  
diastolic blood pressure

ECG  
electrocardiogram

FDA  
Food and Drug Administration

GSSA  
Gillespie Stochastic Simulation Algorithm

HRV  
heart rate variability

MAP  
mean arterial systemic blood pressure

MCMC  
Markov Chain Monte Carlo

MRSA  
methicillin-resistant Staphylococcus aureus

ODE  
ordinary differential equation

PSNS  
parasympathetic nervous system

RSA  
respiratory sinus arrhythmia

SA node  
sinoatrial node

SBP  
systolic blood pressure

SDE  
stochastic differential equation

SNS  
sympathetic nervous system

VRE  
vancomycin-resistant enterococci
Chapter 1

A Model to Explore Control
Mechanisms of Heart Rate Variability

1.1 Introduction

Many physiological phenomena have been correlated to specific states of health. However, potential mechanisms underlying these phenomena may be difficult to study without invasive procedures. Mathematical models provide a framework to investigate complex physiological mechanisms driving phenomena, study dynamics of varying states of health, and design and evaluate efficacy of treatments and therapies. The aim of this study is to formulate a mathematical model to explore the physiological control mechanisms governing heart rate variability.

Heart rate variability (abbreviated HRV) is defined as the variation in the duration of RR intervals on an electrocardiogram (ECG). Correlation between loss of HRV and physiological states of stress, such as heart disease, diabetes, depression, and obesity, has been well documented in clinical practice and experimental studies since the 1960s, and is quickly becoming a noninvasive, diagnostic metric of health. Previous studies of HRV focused on the statistical analysis of patient time series data. However, this correlation has not been fully linked to underlying physiological mechanisms.

This study combines two previous mathematical models to explain the source of HRV in a resting, healthy state. The first previous model describes neuroendocrine control of heart rate through the Baroreflex Mechanism and Respiratory Sinus Arrhythmia (RSA). The second previous model describes circulation via fundamental physics principles. Respiration
is incorporated into the system of ordinary differential equations (ODEs), via respiration-derived thoracic pressure, as a disturbance to the homeostatic system to characterize the role of respiration in heart rate variability.

The effect of several parameters on model dynamics, the mean of heart rate, and the variance of the RR intervals of heart rate was explored. The parameters explored included parameters whose values were not available in literature, could not be calculated from patient data, and appear to have a significant effect on model dynamics. Results show that there appears to be a trade-off occurring for most parameters associated with the Baroreflex Mechanism. HRV is higher in scenarios that do not produce extreme heart rate and blood pressure values. For the parameters associated with RSA, a direct correlation between the parameter values and HRV indicates that RSA contributes to higher HRV.

This project is joint work with Dr. Mette Olufsen of North Carolina State University, her student Mr. Ben Randall, and Dr. Judy Day of the University of Tennessee, Knoxville.

1.2 Background

1.2.1 Heart Rate Variability

HRV is defined as the variation in the time interval between heartbeats, specifically the variation in the duration of RR intervals on an ECG signal [45]. As explained in [2], an ECG machine detects the the electrical activity of the heart and produces a graphical representation of the signal, measured in millivolts (mV). The basic pattern of a heart beat seen on an ECG signal is made up of three parts: a P wave, a QRS wave complex, and a T wave. The sinoatrial node (SA node), located at the top of the right atrium of the heart, is the pacemaker of the heart and spontaneously produces an electrical impulse that travels through the atria to the ventricles, causing the heart to contract and pump blood. The P wave represents the depolarization of the atria, the QRS wave complex represents the depolarization of the ventricles, and the T wave represents the repolarization of the ventricles. Repolarization of the atria is obscured by the QRS wave complex. The R wave represents the depolarization of the main mass of the ventricles, when the heart pumps out most of the blood, and is therefore the largest wave on an ECG signal. The RR interval is the time interval between R waves. Figure 1 shows the PQRST pattern on an ECG signal. Variation in the RR interval changes the heart rate, measured in beats per minute (bpm), over time. Figures 2 and 3 show two example ECG signals and corresponding heart rate signals. Heart rate at a particular time is typically calculated from an ECG signal by dividing 60 by the duration between two identical points of consecutive PQRST patterns, such as the duration
of the RR interval. In Figure 2 there are five heart beats (PQRST patterns) in six seconds on the ECG signal, resulting in an average heart rate of 50 bpm. The variance in the RR intervals is 0.0167 square seconds. The heart rate at time 1.28 seconds, at the end of the first RR interval, is $60/1.28 = 46.875$ bpm. The heart rate at time 2.36 seconds, at the end of the second RR interval, is $60/1.08 = 55.556$ bpm. The heart rate at the end of the remaining RR intervals is similarly calculated, resulting in the heart rate signal of bpm over time. In Figure 3 there are nine heart beats in six seconds on the ECG signal, resulting in an average heart rate of 90 bpm. The variance in the RR intervals is 0.0006 square seconds. As RR intervals approach constant duration, and HRV decreases, the heart rate signal approaches a horizontal line. Figure 3 has lower HRV than Figure 2, using variance in the RR intervals as a metric for HRV.

Correlation between loss of HRV and physiological states of stress (exercise, disease, etc.) has been well documented in clinical practice and experimental studies [45]. The first study acknowledging the clinical importance of HRV found that changes in interbeat intervals preceded fetal distress, well before changes in pulse [38]. An analysis by [49] observed a decrease in HRV before clinical signs of neonatal sepsis. A study by [65] used HRV analysis to predict neonatal sepsis before clinical signs. The first investigation to link a decrease in HRV with death after a heart attack was by [94]. Studies by [46, 48, 96] also linked reduced HRV with death after a heart attack. Analyses by [14, 71, 72] linked reduced HRV with congestive heart failure. A study by [86] observed that decreased HRV was associated with cardiovascular disease and all cause mortality. An investigation by [60] found that HRV was the single most important predictor of serious ventricular arrhythmias or sudden death. In [34], hypertension was linked to reduced HRV. In [13], it was observed that decreased HRV was correlated with depression and death after a heart attack. Studies by [28, 31] found correlation between depression, anxiety, and panic disorders and reduced HRV. Further analyses by [88, 83, 7, 43] have associated low HRV with age, hyperglycemia and diabetes, insomnia, and obesity, respectively. Also, [43] observed an increase in HRV with weight loss. A study by [20] observed high HRV in physically active people. Even though there have been numerous studies since the 1960s linking low HRV with physiological states of stress, this correlation has not been fully linked to underlying physiological mechanisms.

1.2.2 Neuroendocrine System and Circulation

According to [33], the nervous system is comprised of the central nervous system, which contains the brain and spinal cord, and the peripheral nervous system, which contain all neurons outside the brain and spinal cord. The peripheral nervous system senses changes in
the environment (external or internal to the body) and sends afferent signals to the central nervous system. The central nervous system decides the appropriate response and sends efferent signals back to the peripheral nervous system to execute the response. The peripheral nervous system is comprised of the somatic nervous system, which controls voluntary actions of the body, and the autonomic nervous system, which controls involuntary actions of the body. The autonomic nervous system is comprised of the parasympathetic nervous system (PSNS), which controls “rest-and-digest” responses, and the sympathetic nervous system (SNS), which controls “fight-or-flight” responses. The neuroendocrine system stimulates or inhibits the PSNS and SNS to modulate the release of hormones to maintain homeostasis. Neuroendocrine hormones are released into the blood by neurons and influence the function of cells at other locations in the body.

The Baroreflex Mechanism senses changes in blood pressure and adjusts heart rate accordingly. When blood pressure changes, baroreceptors (mechanoreceptor sensory neurons) located in the carotid sinuses stretch and experience wall strain. The baroreceptors then change their afferent signaling pattern to the cardiac center of the medulla. The medulla then produces an efferent response through the PSNS and SNS. The PSNS response includes the release of the hormone acetylcholine to the SA node, which decreases heart rate. The PSNS response acts as a brake pedal on heart rate and cannot increase heart rate. The SNS response includes the release of the hormone nor-epinephrine to the SA node, which increases heart rate. The SNS response acts as a gas pedal on heart rate and cannot decrease heart rate. When blood pressure increases, the PSNS response is stimulated with a concurrent inhibition of the SNS response, and heart rate decreases. When blood pressure decreases, the SNS response is stimulated with a concurrent inhibition of the PSNS response, and heart rate increases. Breathing causes pressure inside the thoracic cavity to change, changing the pressure on the aortic arch, where more baroreceptors are located. The Baroreflex Mechanism senses this change in pressure and adjusts heart rate through the PSNS and SNS response.

Since the PSNS response acts directly on the SA node via the vagus nerve, the PSNS response is almost instantaneous. Since the SNS response must go through the sympathetic ganglia chain parallel to the spinal column to get to the SA node, the SNS response is delayed by about three seconds. (This delay is not considered in this study.) The SA node spontaneously produces electrical impulses, causing an intrinsic heart rate of about 100 bpm. At rest, the PSNS is more active (operating at around an 80% activation level) than the SNS (operating around a 20% activation level) and dampens heart rate to 60-80 bpm. Low HRV reflects an imbalance of increased SNS activity and decreased PSNS activity.

RSA is the observed phenomenon of heart rate increasing slightly during inhalation and decreasing slightly during exhalation. Involuntary breathing is determined by the brain when
chemoreceptor neurons detect changes in the pH level of blood from changes in carbon dioxide content. Specifically, the respiratory center in the medulla stimulate the SNS (and inhibits the PSNS) to cause the diaphragm and other chest muscles to contract, which increases the volume, and thus decreases the pressure, in the thoracic cavity, forcing air to rush into the lungs and an inhalation to occur. Exhalation does not need to be stimulated since the muscles will elastically recoil, decreasing volume and increasing pressure, forcing air to rush out. This SNS signal is not transmitted to the SA node, and therefore has no effect on heart rate. However, there are transient affects on the SA node from the PSNS response due to proximity of the respiration and heart rate control centers of the medulla that causes an increase in heart rate.

Circulation functions to service the needs of body tissues, especially the delivery of oxygen. Blood flow is driven through circulation by the pump that is the heart. During diastole, the heart is relaxed and refills with blood. During systole, the ventricles contract to pump blood out of the heart. Blood flows through two loops of circulation: systemic circulation takes blood between the heart and the body to deliver oxygen to the body tissues and pulmonary circulation takes blood between the heart and the lungs to pick up oxygen. Circulation is illustrated in Figure 4.

1.3 Previous Mathematical Models

1.3.1 Li et al. (2014)

Previous studies of HRV focused on the statistical analysis of the correlation between bodily stress and the loss of HRV in patient time series data. Li et al. [57] was one of the first studies to attempt to explain the physiological mechanisms behind this correlation through mathematical modeling. They modified a model from the text [39] that describes circulation via fundamental physics principles and combined the model with exercise data from healthy subjects to explain the loss of HRV as exercise workload increased. The model described a healthy system at homeostasis. The workload signal was inputed and viewed as a disturbance to the system to analyze how the system responds to changes in workload to maintain homeostasis. Specifically, the control system was penalized for deviating from homeostasis. Li et al. forced an exaggerated heart rate signal through alternating workloads around a low, medium, and high level. They observed that during exercise, muscle tissues need extra oxygen to maintain the workload. Thus, heart rate and arterial blood pressure increases to allow more oxygen to be delivered. However, heart rate and arterial blood pressure can only increase so much before becoming dangerous. At this point, a trade-off in the
penalizing weights is made meeting between tissue oxygen demand and increasing heart rate and blood pressure. The model was able to capture the high frequency oscillations seen in the exaggerated heart rate signal but was unable to capture the low frequency oscillations. They suggested that respiration may be the missing component of their model.

1.3.2 Randall et al. (2019)

The Valsalva maneuver is a clinical test that assesses the response of the PSNS and SNS in response to changes in blood pressure. During the Valsalva maneuver, a patient forcibly exhales against an external resistance, forcing an exaggerated drop in blood pressure and heart rate. Randall et al. [75] formulated a model of the neuroendocrine response to the Valsalva maneuver that takes inputs of blood pressure and respiration and produces outputs of baroreceptor strain, PSNS and SNS tone, and heart rate. The focus of their study was to use their model to predict PSNS and SNS dysfunction, not HRV. However, this study was novel in their incorporation of respiration in their model. Describing the mechanics of breathing and gas exchange alongside circulation would make for a very complex model. Instead, Randall et al. derived a thoracic pressure signal synced with respiration and added the role of thoracic pressure in the Baroreflex Mechanism. They also included a description of RSA as a function of thoracic pressure.

This thesis seeks to use Randall et al.’s mathematical description of neuroendocrine control of heart rate, incorporating respiration, to explore physiological control mechanisms governing HRV. Li et al.’s model, excluding the exercise components, is used to make Randall et al.’s model closed loop, i.e., describe blood pressure as a function of heart rate. Also, this study does not seek to explain the loss of HRV due to a stress or to predict non-homeostatic behavior through exaggerated data. Instead, this study aims to explain the origin of HRV in a healthy, resting state.

1.4 Data

The model formulated to explore physiological control mechanisms governing HRV describes a system in homeostasis. Data from a healthy, resting person is used to determine some parameter values and initial conditions, and is compared to the model output. The respiration signal from the data is inputed and viewed as a disturbance to the system, through respiration-derived thoracic pressure, to analyze how the system responds to changes in respiration to maintain homeostasis. The data consists of five minutes of time series signals, taken at 1,000 Hz for ECG (mV) and blood pressure, measured in millimeters of mercury.
(mmHg), for the control patients of Randall et al. [75] before the Valsalva maneuver occurs and stored in LabChart [1], data analysis software for biological signals. Heart rate (bpm) is computed in LabChart from the RR intervals on the ECG signal. The data also contains the age of the control patient.

The respiration signal ($R$) is determined from the ECG signal in MATLAB [62], a numerical computing environment and proprietary programming language, using a protocol written by Ben Randall from Randall et al. [75] that combined suggestions from [67, 74, 92]. As a patient inhales, the chest expands, causing the electrodes of the ECG-lead to move farther away from the heart. As a patient exhales, the electrodes move closer to the heart. Thus the amplitude of the QRS portion of the ECG signal indicates the depth of breathing and a mechanical respiration signal can be derived from the interpolation of the amplitudes of the QRS wave complexes of the ECG signal. The P and T waves are filtered out from the QRS wave complexes to emphasize the Q and R points, the local optima, i.e., the Q and R points, are determined, and the amplitude between each R and Q point is interpolated through using PCHIP interpolation, a built-in MATLAB function that preserves monotonicity and local extrema.

Thoracic pressure ($P_{th}$) is determined from the respiration signal since the pressure inside the thoracic cavity changes with breathing. According to the text [33], average thoracic pressure is -4 mmHg, compared to atmospheric pressure, and is sub-atmospheric (negative) to maintain expansion of the lungs. During inhalation, pressure drops to around -6 mmHg due to increased volume in the thoracic cavity. During exhalation, pressure rises to around -3.5 mmHg due to decreased volume in the thoracic cavity. Also, during inhalation, the QR amplitude on the ECG is smallest since the heart is closer to the ECG-lead, and during exhalation, the QR amplitude is largest since the heart is farther away from the ECG-lead. Thus the respiration signal (QR amplitudes in mV) can be scaled to determine the thoracic pressure (in mmHg). To scale the respiration signal, the line through the points ($t_1, R_{min}$) and ($t_2, R_{max}$) is mapped to the line through the points ($t_1, 6$) and ($t_2, 3.5$), where $t_1$ and $t_2$ are arbitrary time points, $R_{min}$ and $R_{max}$ are the means of all local minimums and maximums of the respiration signal, respectively, and 3.5 and 6 are the minimum and maximum thoracic pressures (which are treated as positive here because the thoracic pressure will be subtracted in the model input). The linear mapping must satisfy Equations (1.1) and (1.2). Solving Equations (1.1) and (1.2) for $m$ and $b$ gives Equations (1.3) and (1.4), and the thoracic pressure due to respiration in Equation (1.5).
\[
6 = m \times R_{\text{min}} + b \tag{1.1}
\]
\[
3.5 = m \times R_{\text{max}} + b \tag{1.2}
\]
\[\Rightarrow \quad m = -\frac{6 - 3.5}{R_{\text{max}} - R_{\text{min}}} \tag{1.3}\]
\[b = 3.5 - m \times R_{\text{max}} \tag{1.4}\]
\[
P_{\text{th}} = m \times R + b \tag{1.5}
\]

where

\[P_{\text{th}} = \text{thoracic pressure signal } [\text{mmHg}]\]
\[R = \text{respiration signal } [\text{mV}]\]
\[R_{\text{min}} = \text{mean of local mins of } R [\text{mV}]\]
\[R_{\text{max}} = \text{mean of local maxs of } R [\text{mV}]\]
\[m = \text{ratio of } P_{\text{th}} \text{ amplitude to mean } R \text{ amplitude } [\text{mmHg} \cdot \text{mV}^{-1}]\]
\[b = \text{vertical shift } [\text{mmHg}]\]

Mean arterial systemic blood pressure (MAP) is used to determine some parameter values and initial conditions for the model and is derived from the blood pressure signal. The blood pressure data is measured in the finger and is part of arterial systemic circulation. The blood pressure signal consists of systolic (SBP) and diastolic (DBP) blood pressure. Since the model does not describe pulsatile blood flow, MAP data is needed to describe overall blood flow. MAP is defined in Equation (1.6) by [9].

\[
\text{MAP} = \frac{SBP + 2 \cdot DBP}{3} \tag{1.6}
\]

where

\[\text{MAP} = \text{mean arterial blood pressure } [\text{mmHg}]\]
\[\text{SBP} = \text{systolic blood pressure } [\text{mmHg}]\]
\[\text{DBP} = \text{diastolic blood pressure } [\text{mmHg}]\]

The data does not include venous systemic, arterial pulmonary, or venous systemic blood pressure. However, according to [33], average venous systemic blood pressure is 5-8 mmHg,
average arterial pulmonary blood pressure is 8-20 mmHg, and average venous pulmonary blood pressure is 8 mmHg.

ECG, respiration, thoracic pressure, blood pressure, and heart rate data for one patient are shown in Figure 5.

1.5 Model Formulation

1.5.1 Description of HRV Model

This work aims to gain a better understanding of the physiological mechanisms governing HRV by incorporating respiration into a combination of two previous mathematical models that describes a healthy, resting system in homeostasis. Respiration is inputed and viewed as a disturbance to the system, through respiration-derived thoracic pressure, to analyze how the system responds to changes in respiration to maintain homeostasis. The first previous model used is from Randall et al. [75] and describes neuroendocrine control of heart rate through the Baroreflex Mechanism and RSA. The second previous model used is from the text [39], used in Li et al. [57], and describes circulation via fundamental physics principles. Model variables are summarized in Table 1, auxiliary variables are summarized in Table 2, and a schematic of the model is given in Figure 6.

Baroreflex Mechanism

The Baroreflex Mechanism adjusts heart rate based on changes in pressure to maintain homeostasis. Baroreceptors are embedded in the interior walls of the carotid sinuses and aortic arch, and experience pressure both inside and outside the arteries. Since the carotid sinuses are located in the neck, carotid baroreceptors only experience arterial systemic blood pressure from inside the artery. Since the aortic arch extends out of the left side of the heart, aortic baroreceptors experience arterial systemic blood pressure from inside the artery and thoracic pressure from outside the artery. Thus, the pressure sensed by carotid baroreceptors ($P_c$) is defined as the arterial systemic blood pressure ($P_{as}$), Equation (1.7), and the pressure sensed by aortic baroreceptors ($P_a$) is defined as the difference between the arterial systemic blood pressure and the thoracic pressure, Equation (1.8).

\[
P_c = P_{as} \quad \text{(1.7)}
\]

\[
P_a = P_{as} - P_{th} \quad \text{(1.8)}
\]
where

\[ P_c = \text{pressure on carotid baroreceptors [mmHg]} \]
\[ P_a = \text{pressure on aortic baroreceptors [mmHg]} \]
\[ P_{as} = \text{blood pressure of arterial systemic circulation [mmHg]} \]
\[ P_{th} = \text{thoracic pressure signal [mmHg]} \]

Provided \( P_{as} > P_{th} \), \( P_c \) and \( P_a \) will be positive since \( P_{as} \) is positive for all time. Since \( P_{as} \) is considered low at 70 mmHg and \( P_{th} \) ranges from 3.5 to 6 mmHg on average, this is a reasonable assumption.

When blood pressure changes, large arteries, such as the carotid arteries and aorta, distend and experience wall strain. According to [5], the relationship between arterial cross-sectional area (\( A \)) and blood pressure (\( P \)) is given by Equation (1.9). Equation (1.9) is a type III functional response [37] where arterial cross-sectional area increases with blood pressure and area saturates at low and high pressures since arteries can only physically distend so far. Randall et al. [75] used a type II functional response where area saturates only at high pressures. Figure 7 illustrates the area-pressure relationship for different values of \( q \), which determines how quickly cross-sectional area increases with blood pressure. Strain (\( \epsilon \)) describes deformation of a material in terms of relative displacement. Arterial wall strain (\( \epsilon_w \)), described by Equation (1.10), is the ratio of the change in the radius of an artery when stressed to the radius of the stressed artery. Equations (1.11)-(1.13) use Equations (1.9) and (1.10) to model arterial wall strain as a function of blood pressure.
\[ A(P) = A_0 + (A_M - A_0) \frac{P^q}{(P^*)^q + P^q} \]  \hspace{1cm} (1.9)

\[ \epsilon_w = \frac{r - r_0}{r} \]  \hspace{1cm} (1.10)

\[ A(P) = \pi r^2 \implies r = \sqrt{\frac{1}{\pi} \left( A_0 + (A_M - A_0) \frac{P^q}{(P^*)^q + P^q} \right)} \]  \hspace{1cm} (1.11)

\[ A_0 = \pi r_0^2 \implies r_0 = \sqrt{\frac{1}{\pi} A_0} \]  \hspace{1cm} (1.12)

\[ \implies \epsilon_w = 1 - \frac{r_0}{r} \]  \hspace{1cm} (1.13)

\[ = 1 - \frac{\sqrt{\frac{1}{\pi} A_0}}{\sqrt{\frac{1}{\pi} \left( A_0 + (A_M - A_0) \frac{P^q}{(P^*)^q + P^q} \right)}} \]

\[ = 1 - \frac{1 + \left( \frac{P^*}{P} \right)^q}{\frac{A_M}{A_0} + \left( \frac{P^*}{P} \right)^q} \]

where

- \( A = \) arterial cross-sectional area \([cm^2]\)
- \( A_M = \) maximally stressed arterial cross-sectional area \([cm^2]\)
- \( A_0 = \) unstressed arterial cross-sectional area \([cm^2]\)
- \( P = \) blood pressure of artery \([mmHg]\)
- \( P^* = \) average blood pressure of artery \([mmHg]\)
- \( q = \) sigmoid steepness constant for arterial wall strain \([dimensionless]\)
- \( \epsilon_w = \) arterial wall strain \([dimensionless]\)
- \( r = \) stressed arterial radius \([cm]\)
- \( r_0 = \) unstressed arterial radius \([cm]\)

Thus, the relationship between pressure and arterial wall strain for the carotid arteries and aorta is modeled as Equations (1.14) and (1.15), respectively.
\[ \epsilon_{wc} = 1 - \sqrt{\frac{1 + \left(\frac{s_w}{P_c}\right) q_w}{A + \left(\frac{s_w}{P_c}\right) q_w}} \]  
(1.14)

\[ \epsilon_{wa} = 1 - \sqrt{\frac{1 + \left(\frac{s_w}{P_a}\right) q_w}{A + \left(\frac{s_w}{P_a}\right) q_w}} \]  
(1.15)

where

\( \epsilon_{wc} = \) arterial wall strain of carotid sinuses \([\text{dimensionless}]\)

\( \epsilon_{wa} = \) arterial wall strain of aortic arch \([\text{dimensionless}]\)

\( P_c = \) pressure on carotid baroreceptors \([\text{mmHg}]\)

\( P_a = \) pressure on aortic baroreceptors \([\text{mmHg}]\)

\( A = \) maximally stressed to unstressed arterial cross-sectional area ratio \([\text{dimensionless}]\)

\( q_w = \) sigmoid steepness constant for wall strain \([\text{dimensionless}]\)

\( s_w = \) sigmoid shift constant for arterial wall strain \([\text{mmHg}]\)

Since the maximally stressed cross-sectional area of an artery will be greater than the unstressed cross-sectional area, \( A > 1 \). Thus, since \( P_c, P_a, \) and \( s_w \) are positive, the quantity under the square root in Equations (1.14) and (1.15) will be less than 1. Therefore, \( \epsilon_{wc}, \epsilon_{wa} \in (0, 1) \).

Since baroreceptors are embedded in the walls of arteries, they will also experience strain as arteries distend due to changes in blood pressure. Following [59], it is assumed that baroreceptors behave viscoelastically and the surrounding arterial wall behaves elastically. Elastic materials immediately return to their original state after experiencing strain. Viscous materials return to their original state over time after experiencing strain. Viscoelastic materials display both elastic and viscous characteristics. A simple model describing a viscoelastic material is the Voigt body, a damper (viscous) and spring (elastic) in parallel that exhibits the rate of stress relaxation in response to strain. A spring, representing the surrounding arterial wall, and a Voigt body, representing the baroreceptors, in series adequately describes baroreceptor strain \( (\epsilon_b) \) as an artery experiences wall strain. Equation (1.16) describes the spring and Voigt body model for baroreceptor strain as a function of arterial wall strain, where ‘ \( \prime \) ’ denotes differentiation with respect to time.
\[ \eta_1 \epsilon'_b + \mu_1 \epsilon_b = \mu_0 \epsilon_w \] (1.16)

where

\[ \epsilon_b = \text{strain of baroreceptors \([dimensionless]\)} \]
\[ \epsilon_w = \text{arterial wall strain \([dimensionless]\)} \]
\[ \mu_0 = \text{proportionality constant of spring \([dimensionless]\)} \]
\[ \mu_1 = \text{proportionality constant of spring in Voigt body \([dimensionless]\)} \]
\[ \eta_1 = \text{proportionality constant of damper in Voigt body \([sec]\)} \]

Letting \( K_b = \mu_0 / \mu_1 \) and \( \tau_b = \eta_1 / \mu_1 \), and solving Equation (1.16) for \( \epsilon'_b \) gives Equations (1.17) and (1.18) for the change in carotid and aortic baroreceptor strain with respect to time.

\[
\epsilon'_{bc} = \frac{K_b \epsilon_{wc} - \epsilon_{bc}}{\tau_b} \quad (1.17)
\]
\[
\epsilon'_{ba} = \frac{K_b \epsilon_{wa} - \epsilon_{ba}}{\tau_b} \quad (1.18)
\]

where

\[ \epsilon_{bc} = \text{strain of carotid baroreceptors \([dimensionless]\)} \]
\[ \epsilon_{ba} = \text{strain of aortic baroreceptors \([dimensionless]\)} \]
\[ \epsilon_{wc} = \text{arterial wall strain of carotid sinuses \([dimensionless]\)} \]
\[ \epsilon_{wa} = \text{arterial wall strain of aortic arch \([dimensionless]\)} \]
\[ K_b = \text{gain constant for strain of baroreceptors \([dimensionless]\)} \]
\[ \tau_b = \text{time constant for strain of baroreceptors \([sec]\)} \]

Afferent signaling of baroreceptors to the medulla varies in response to changes in strain. According to the text [33], as an artery wall distends due to increased blood pressure, and baroreceptors experience more strain, sodium ion channels in the membrane of baroreceptors open. An influx of positively charged sodium ions causes the baroreceptors to fire action potentials to the medulla. As an artery wall contracts due to decreased blood pressure, and baroreceptors experience less strain, sodium ion channels in the membrane of baroreceptors close. With fewer positively charged ions, the threshold is not met to fire an action potential to the medulla. Some sodium ion channels are always open, so baroreceptors are constantly...
sending strain information to the medulla, but will fire action potentials at a faster rate when under strain. Little is known about how information from various baroreceptor locations is integrated in the medulla. This model, therefore, does not model the individual firing of baroreceptors. Instead the neural integration \( n \) of baroreceptor signals is assumed to be a linear combination of the signals from the carotid sinuses and the aortic arch, as described by Equation (1.19). The afferent signal from the baroreceptors is the strain experienced in distention relative to the strain experienced not in distention, the difference between the arterial wall strain and the baroreceptor strain.

\[
n = B(\epsilon_{wc} - \epsilon_{bc}) + (1 - B)(\epsilon_{wa} - \epsilon_{ba}) \tag{1.19}
\]

where

- \( n \) = afferent signal of baroreceptors [sec\(^{-1}\)]
- \( \epsilon_{wc} \) = arterial wall strain of carotid sinuses [dimensionless]
- \( \epsilon_{wa} \) = arterial wall strain of aortic arch [dimensionless]
- \( \epsilon_{bc} \) = strain of carotid baroreceptors [dimensionless]
- \( \epsilon_{ba} \) = strain of aortic baroreceptors [dimensionless]
- \( B \) = linear combination constant for afferent signal of baroreceptors [sec\(^{-1}\)]

To show that \( n > 0 \), two cases are considered for Equations (1.17) and (1.18). Parameters \( \tau_b \) and \( K_b \) are positive, \( B \in [0, 1] \), and \( \epsilon_{wc}, \epsilon_{wa} \in (0, 1) \).

Case 1: \( \epsilon'_{bi} \geq 0 \) for \( i = \{c, a\} \)

\[
\epsilon'_{bi} \geq 0 \implies K_b \epsilon_{wi} = \tau_b \epsilon'_{bi} + \epsilon_{bi} \geq \epsilon_{bi} \\
K_b < 1 \implies \epsilon_{wi} \geq \frac{1}{K_b} \epsilon_{bi} > \epsilon_{bi} \\
\implies \epsilon_{wi} - \epsilon_{bi} > 0 \\
\implies n = B(\epsilon_{wc} - \epsilon_{bc}) + (1 - B)(\epsilon_{wa} - \epsilon_{ba}) > 0
\]
Case 2: $\epsilon_{bi}' < 0$ for $i = \{c, a\}$

\[ \epsilon_{bi}' < 0 \implies K_b\epsilon_{wi} = \tau_b\epsilon_{bi}' + \epsilon_{bi} < \epsilon_{bi} \]

\[ \implies n = B(\epsilon_{wc} - \epsilon_{bc}) + (1 - B)(\epsilon_{wa} - \epsilon_{ba}) \]

\[ > B(\epsilon_{wc} - K_b\epsilon_{wc}) + (1 - B)(\epsilon_{wa} - K_b\epsilon_{wa}) \]

\[ = B(1 - K_b)\epsilon_{wc} + (1 - B)(1 - K_b)\epsilon_{wa} \]

\[ K_b < 1 \implies n > 0 \]

The afferent signals of baroreceptors are integrated in the medulla, which generates efferent signals to the SA node through the PSNS and SNS to moderate heart rate in response to changes in blood pressure. According to the text [33], when blood pressure increases, along with the afferent signal, a PSNS response is stimulated, with a concurrent inhibition of the SNS, to decrease heart rate. Similarly, when blood pressure decreases, along with the afferent signal, an SNS response is stimulated, with a concurrent inhibition of the PSNS, to increase heart rate. Thus, pressure, as well as $n$, and PSNS activity are positively correlated, and blood pressure, as well as $n$, and SNS activity are negatively correlated. The type III functional responses given in Equations (1.20) and (1.21) model the correlation between the afferent signal and the activation level of the PSNS and SNS due to the Baroreflex Mechanism ($G_{bp}$ and $G_{bs}$), respectively, which saturate at high and low signals. Randall et al. [75] used a type II functional response where activation saturates only at high signals. An activation level of 0 means that particular nervous system is completely inhibited and an activation level of 1 means that particular nervous system is completely stimulated. Figure 8 illustrates the behavior of Equations (1.20) and (1.21).

\[ G_{bp} = G_{bp_{min}} + (1 - G_{bp_{min}}) \cdot \left( \frac{n^{q_{bp}}}{s^{bp} + n^{q_{bp}}} \right) \] (1.20)

\[ G_{bs} = 1 - (1 - G_{bs_{min}}) \cdot \left( \frac{n^{q_{bs}}}{s^{bs} + n^{q_{bs}}} \right) \] (1.21)
where

\( G_{bp} = \) activation level of PSNS due to Baroreflex Mechanism \([\text{dimensionless}]\)  
\( G_{bs} = \) activation level of SNS due to Baroreflex Mechanism \([\text{dimensionless}]\)  
\( n = \) afferent signal of baroreceptors \([\text{sec}^{-1}]\)  
\( q_{bp} = \) sigmoid steepness constant for activation of PSNS due to Baroreflex Mechanism \([\text{dimensionless}]\)  
\( q_{bs} = \) sigmoid steepness constant for activation of SNS due to Baroreflex Mechanism \([\text{dimensionless}]\)  
\( s_{bp} = \) sigmoid shift constant for activation of PSNS due to Baroreflex Mechanism \([\text{sec}^{-1}]\)  
\( s_{bs} = \) sigmoid shift constant for activation of SNS due to Baroreflex Mechanism \([\text{sec}^{-1}]\)  
\( G_{bp\text{min}} = \) minimum activation level of PSNS due to Baroreflex Mechanism \([\text{dimensionless}]\)  
\( G_{bs\text{min}} = \) minimum activation level of SNS due to Baroreflex Mechanism \([\text{dimensionless}]\)

Since \( s_{bp}, s_{bs}, n > 0 \) and \( G_{bp\text{min}}, G_{bs\text{min}} \in [0, 1], G_{bp} \in [G_{bp\text{min}}, 1] \) and \( G_{bs} \in [G_{bs\text{min}}, 1] \).

Similar to the afferent signal, individual firing of neurons involved in the efferent signal is not modeled. Therefore the change in the tone, or activity, over time of PSNS and SNS due to the Baroreflex Mechanism \( (T_{bp} \text{ and } T_{bs}) \), incorporating Equations (1.20) and (1.21), is modeled by Equations (1.22) and (1.23), respectively, and describe adjustment back to homeostatic levels after being activated (stimulated or inhibited) away from homeostatic levels.

\[
T_{bp}' = \frac{K_{bp} G_{bp} - T_{bp}}{\tau_{bp}} \quad (1.22)
\]
\[
T_{bs}' = \frac{K_{bs} G_{bs} - T_{bs}}{\tau_{bs}} \quad (1.23)
\]
where

\[ T_{bp} = \text{tone of PSNS due to Baroreflex Mechanism [dimensionless]} \]
\[ T_{bs} = \text{tone of SNS due to Baroreflex Mechanism [dimensionless]} \]
\[ G_{bp} = \text{activation level of PSNS due to Baroreflex Mechanism [dimensionless]} \]
\[ G_{bs} = \text{activation level of SNS due to Baroreflex Mechanism [dimensionless]} \]
\[ K_{bp} = \text{gain constant for tone of PSNS due to Baroreflex Mechanism [dimensionless]} \]
\[ K_{bs} = \text{gain constant for tone of SNS due to Baroreflex Mechanism [dimensionless]} \]
\[ \tau_{bp} = \text{time constant for tone of PSNS due to Baroreflex Mechanism [sec]} \]
\[ \tau_{bs} = \text{time constant for tone of SNS due to Baroreflex Mechanism [sec]} \]

To find bounds on \( T_{bp} \) and \( T_{bs} \), \( G_i \in [G_{i_{\text{min}}}, 1] \) is used after integrating Equations (1.22) and (1.23) via integrating factor \( e^{\frac{1}{\tau_i} t} \), as shown in Equations (1.24)-(1.27) for \( i = \{bp, bs\} \) and \( t \in [0, \infty) \). Parameters \( K_{bp}, K_{bs}, \tau_{bp}, \) and \( \tau_{bs} \) are positive.

\[
T_i(t) = \frac{K_i}{\tau_i} e^{\frac{1}{\tau_i} t} \int_{s=0}^{s=t} G_i(s) e^{\frac{1}{\tau_i} s} ds \tag{1.24}
\]

\[
G_i \in [G_{i_{\text{min}}}, 1] \Rightarrow \frac{K_i}{\tau_i} e^{\frac{1}{\tau_i} t} \int_{s=0}^{s=t} G_{i_{\text{min}}} e^{\frac{1}{\tau_i} s} ds \leq T_i(t) \leq \frac{K_i}{\tau_i} e^{\frac{1}{\tau_i} t} \int_{s=0}^{s=t} e^{\frac{1}{\tau_i} s} ds \tag{1.25}
\]

\[
\Rightarrow \frac{K_i}{\tau_i} e^{\frac{1}{\tau_i} t} \left( G_{i_{\text{min}}} \tau_i e^{\frac{1}{\tau_i} t} - G_{i_{\text{min}}} \right) \leq T_i(t) \leq \frac{K_i}{\tau_i} e^{\frac{1}{\tau_i} t} \left( \tau_i e^{\frac{1}{\tau_i} t} - \tau_i \right) \tag{1.26}
\]

\[
e^{\frac{1}{\tau_i} t} \in (0, 1) \Rightarrow 0 < K_i G_{i_{\text{min}}} - K_i G_{i_{\text{min}}} e^{\frac{1}{\tau_i} t} \leq T_i(t) \leq K_i - K_i e^{\frac{1}{\tau_i} t} < K_i \tag{1.27}
\]

Thus, \( 0 < T_{bp} < K_{bp} \) and \( 0 < T_{bs} < K_{bs} \).

**Respiratory Sinus Arrhythmia**

RSA is the phenomena of heart rate synchronizing with involuntary respiration. When thoracic pressure increases during inhalation, the PSNS is inhibited. Thus thoracic pressure and PSNS activity are negatively correlated. Similar to Equations (1.20) and (1.21), the relationship between thoracic pressure and the activation level of the PSNS due to RSA \( (G_{rp}) \) can be described by the type III functional response in Equation (1.28). Randall et al. used a type II functional response. An activation level of 0 means the PSNS is completely inhibited and an activation level of 1 means the PSNS is completely stimulated. The behavior of Equation (1.28) is similar to the behavior of Equation (1.21) shown in Figure 8.
\[ G_{rp} = 1 - (1 - G_{rp_{min}}) \cdot \left( \frac{P_{th}^{q_{rp}}}{s_{rp} + P_{th}^{q_{rp}}} \right) \]  \hspace{1cm} (1.28)

where

- \( G_{rp} = \) activation level of PSNS due to RSA \([\text{dimensionless}]\)
- \( P_{th} = \) thoracic pressure signal \([\text{mmHg}]\)
- \( q_{rp} = \) sigmoid steepness constant for activation of PSNS due to RSA \([\text{dimensionless}]\)
- \( s_{r} = \) sigmoid shift constant for activation of PSNS due to RSA \([\text{mmHg}]\)
- \( G_{rp_{min}} = \) minimum activation level of PSNS due to RSA \([\text{dimensionless}]\)

Since \( s_{rp}, P_{th} > 0 \) and \( G_{rp_{min}} \in [0, 1], G_{rp} \in [G_{rp_{min}}, 1] \).

Similar to Equations (1.22) and (1.23), Equation (1.29), incorporating (1.28), shows the change in the tone over time of the PSNS due to RSA (\( T_{rp} \)).

\[ T_{rp}' = \frac{K_{rp} G_{rp} - T_{rp}}{\tau_{rp}} \]  \hspace{1cm} (1.29)

where

- \( T_{rp} = \) tone of PSNS due to RSA \([\text{dimensionless}]\)
- \( G_{rp} = \) activation level of PSNS due to RSA \([\text{dimensionless}]\)
- \( K_{rp} = \) gain constant for tone of PSNS due to RSA \([\text{dimensionless}]\)
- \( \tau_{rp} = \) time constant for tone of PSNS due to RSA \([\text{sec}]\)

Using the same argument as Equations (1.24)-(1.27), \( 0 < T_{rp} < K_{rp} \).

**Heart Rate**

Heart rate (\( H \)) is modeled as the deviation from a weighted intrinsic heart rate (\( H_{I} \)). The weight is based on weighted contributions from each of the nervous system branches, i.e., a linear combination of the efferent responses due to the Baroreflex Mechanism and RSA in Equations (1.22), (1.23), and (1.29). The intrinsic heart rate is the rate at which the heart beats without modulation from the medulla and depends on age, as described in [42] and shown in Equation (1.30).

\[ H_{I} = 118 - 0.57 \times \text{age} \]  \hspace{1cm} (1.30)
Intrinsic heart rate is nonnegative provided \( \text{age} \leq 118/0.57 \approx 207.02 \), which is a reasonable assumption.

The weighted intrinsic heart rate \( \tilde{H} \) is given in Equation (1.31). Stimulation of a PSNS response due to the Baroreflex Mechanism decreases heart rate, hence the negative sign in front of the weighting constant \( H_{bp} \). Stimulation of an SNS response due to the Baroreflex Mechanism and inhibition of the PSNS due to RSA both increase heart rate, hence the positive sign in front of both weighting parameters \( H_{bs} \) and \( H_{rp} \).

\[
\tilde{H} = H_I (1 - H_{bp} T_{bp} + H_{bs} T_{bs} + H_{rp} T_{rp})
\]  
(1.31)

where

- \( \tilde{H} = \text{weighted intrinsic heart rate [bpm]} \)
- \( T_{bp} = \text{tone of PSNS due to Baroreflex Mechanism [dimensionless]} \)
- \( T_{bs} = \text{tone of SNS due to Baroreflex Mechanism [dimensionless]} \)
- \( T_{rp} = \text{tone of PSNS due to RSA [dimensionless]} \)
- \( H_I = \text{intrinsic heart rate [bpm]} \)
- \( H_{bp} = \text{weighting constant for tone of PSNS due to Baroreflex Mechanism [dimensionless]} \)
- \( H_{bs} = \text{weighting constant for tone of SNS due to Baroreflex Mechanism [dimensionless]} \)
- \( H_{rp} = \text{weighting constant for tone of PSNS due to RSA [dimensionless]} \)

Since \( 0 < T_i < K_i \) for \( i = \{bp, bs, rp\} \) and \( H_{bp}, H_{bs}, \) and \( H_{rp} \) are positive, Equation (1.32) is satisfied for the bounds of \( \tilde{H} \), provided \( H_{bp} \leq \frac{1}{K_{bp}} \).

\[
0 \leq H_I (1 - H_{bp} K_{bp}) \leq \tilde{H} \leq H_I (1 + H_{bs} K_{bs} + H_{rp} K_{rp})
\]  
(1.32)

Equation (1.33) describes the change in heart rate over time as an adjustment back to homeostatic levels after being changed due to activated PSNS and SNS responses.

\[
H' = \frac{\tilde{H} - H}{\tau_H}
\]  
(1.33)
where

\[H = \text{heart rate [bpm]}
\]
\[\tilde{H} = \text{weighted intrinsic heart rate [bpm]}
\]
\[\tau_H = \text{time constant for heart rate [bpm]}
\]

To find bounds on \(H\), and show that \(H\) is nonnegative, \(\tilde{H} \in [0, H_I(1 + H_{bs} K_{bs} + H_{rp} K_{rp})]\) is used after integrating Equation (1.33) via integrating factor \(e^{\frac{1}{\tau_H} t}\), as shown in Equations (1.34)-(1.38) for \(t \in [0, \infty)\).

\[
H(t) = \frac{1}{\tau_H} e^{\frac{1}{\tau_H} t} \int_{s=0}^{s=t} \tilde{H}(s)e^{\frac{1}{\tau_H} s} ds
\]  
(1.34)

\[
\tilde{H} \in [0, H_I(1 + H_{bs} K_{bs} + H_{rp} K_{rp})] \implies
\]  
(1.35)

\[
0 \leq H(t) \leq \frac{1}{\tau_H} e^{\frac{1}{\tau_H} t} \int_{s=0}^{s=t} H_I(1 + H_{bs} K_{bs} + H_{rp} K_{rp}) e^{\frac{1}{\tau_H} s} ds
\]  
(1.36)

\[
\implies 0 \leq H(t) \leq \frac{1}{\tau_H} H_I(1 + H_{bs} K_{bs} + H_{rp} K_{rp}) e^{\frac{1}{\tau_H} t} \left(\tau_{Hh} e^{\frac{1}{\tau_H} t} - \tau_{H}\right)
\]  
(1.37)

\[
e^{\frac{1}{\tau_H} t} \in (0, 1) \implies 0 \leq H(t) < H_I(1 + H_{bs} K_{bs} + H_{rp} K_{rp})
\]  
(1.38)

**Circulation Model**

According to [39], since the heart pumps a volume of blood through the body via the circulatory system, heart rate can be modeled by its connection to blood volume (\(V\)). The circulation model describes blood pressure (\(P\)), via blood volume, as a function of heart rate in four compartments: arterial systemic circulation (\(as\)), venous systemic circulation (\(vs\)), arterial pulmonary circulation (\(ap\)), and venous pulmonary circulation (\(vp\)). The compartments are made up of the large arteries and veins entering and exiting the heart. Since large arteries and veins are primarily elastic with no resistance to blood flow, they are considered to be compliance vessels, meaning the blood volume through the vessel is directly proportional to the blood pressure as shown in Equation (1.39).

\[
V = cP
\]  
(1.39)
where

\[ V = \text{volume of blood in vessel} \ [L] \]
\[ P = \text{blood pressure} \ [mmHg] \]
\[ c = \text{compliance constant} \ [L \cdot mmHg^{-1}] \]

The compliance of a vessel \((c)\) describes a vessel’s ability to resist recoil toward its original dimensions on application of a distending or compressing force. A stiff vessel has a small compliance value while a flexible vessel has a large compliance value. Since the four compartments of the circulation model are made up of the large arteries and veins entering and exiting the heart, the blood volume in each compartment is described by Equations (1.40)-(1.43).

\[
V_{as} = c_{as}P_{as} \quad (1.40)
\]
\[
V_{vs} = c_{vs}P_{vs} \quad (1.41)
\]
\[
V_{ap} = c_{ap}P_{ap} \quad (1.42)
\]
\[
V_{vp} = c_{vp}P_{vp} \quad (1.43)
\]

where

\[ V_i = \text{volume of blood in compartment } i \ [L] \]
\[ P_i = \text{blood pressure of compartment } i \ [mmHg] \]
\[ c_i = \text{compliance constant for compartment } i \ [L \cdot mmHg^{-1}] \]
\[ i = \{as, vs, ap, vp\} \]

The change in blood volume with respect to time in a compartment will be the difference between the blood flow into the compartment and the blood flow out of the compartment. Blood flow into or out of the heart is termed cardiac output and is denoted by \(Q_l\) and \(Q_r\) for the left side and right side of the heart, respectively. Blood flow in the body is denoted by \(F_s\) and \(F_p\) for systemic circulation and pulmonary circulation, respectively. Blood flow in the body refers to circulation in the smaller vessels not apart of the four compartments. Since arterial systemic circulation carries oxygenated blood from the left side of the heart to the body, the change in blood volume over time in the \(as\) compartment can be described by Equation (1.44). Since venous systemic circulation carries de-oxygenated blood from the body to the right side of the heart, the change in blood volume over time in the \(vs\)
compartment can be described by Equation (1.45). Since arterial pulmonary circulation carries de-oxygenated blood from the right side of the heart to the lungs, the change in blood volume over time in the ap compartment can be described by Equation (1.46). Since venous pulmonary circulation carries oxygenated blood from the lungs to the left side of the heart, the change in blood volume over time in the vp compartment can be described by Equation (1.47). The change in the blood volume over time in each compartment is illustrated in Figure 9. The far right side of Equations (1.44)-(1.47) are divided by 60 to convert from minutes to seconds.

\[
\begin{align*}
V'_{as} &= c_{as}P'_{as} = \frac{1}{60}(Q_l - F_s) \quad (1.44) \\
V'_{vs} &= c_{vs}P'_{vs} = \frac{1}{60}(F_s - Q_r) \quad (1.45) \\
V'_{ap} &= c_{ap}P'_{ap} = \frac{1}{60}(Q_r - F_p) \quad (1.46) \\
V'_{vp} &= c_{vp}P'_{vp} = \frac{1}{60}(F_p - Q_l) \quad (1.47)
\end{align*}
\]

where

- \( V_i \) = volume of blood in compartment \( i \) [L]
- \( P_i \) = blood pressure of compartment \( i \) [mmHg]
- \( c_i \) = compliance constant for compartment \( i \) [L · mmHg\(^{-1}\)]
- \( i = \{as, vs, ap, vp\} \)
- \( Q_l \) = cardiac output of left side of heart [L · min\(^{-1}\)]
- \( Q_r \) = cardiac output of right side of heart [L · min\(^{-1}\)]
- \( F_s \) = blood flow in systemic circulation [L · min\(^{-1}\)]
- \( F_p \) = blood flow in pulmonary circulation [L · min\(^{-1}\)]

Cardiac output (\( Q \)) is defined as the the volume of blood pumped through a ventricle per minute. It is the product of the heart rate (number of beats per minute) and the stroke volume (volume of blood pumped through a ventricle per beat). The stroke volume (\( V_{str} \)) can be determined by the difference in the end-diastolic volume (\( V_{dia} \)) and the end-systolic volume (\( V_{sys} \)) of a ventricle. The end-diastolic volume of the heart is the maximum volume of blood and the end-systolic volume of the heart is the minimum volume of blood in the heart during a heartbeat. The stroke volume is the difference between the maximum and
minimum volume of blood in the heart during a heartbeat. Considering the atriums and ventricles as compliance vessels, the stroke volume can be described by Equation (1.48). The blood pressure of an atrium at the end of diastole \((P_{dia})\) will be equivalent to the blood pressure of the veins supplying the atrium with blood since they are both compliance vessels. Likewise, the blood pressure of a ventricle at the end of systole \((P_{sys})\) will be equivalent to the blood pressure of the arteries supplied with blood by the ventricle. Also, since the heart is fully contracted (very stiff) at the end of systole, the compliance of the ventricle will be essentially zero.

\[
V_{str} = V_{dia} - V_{sys} = c_{dia}P_{dia} - c_{sys}P_{sys} = c_{dia}P_v - c_{sys}P_a = c_{dia}P_v
\]

where

- \(V_{str}\) = stroke volume \([L \cdot beat^{-1}]\)
- \(V_{dia}\) = end-diastolic volume of relaxed atrium \([L \cdot beat^{-1}]\)
- \(V_{sys}\) = end-systolic volume of contracted ventricle \([L \cdot min^{-1}]\)
- \(P_{dia}\) = end-diastolic blood pressure of relaxed atrium \([mmHg]\)
- \(P_{sys}\) = end-systolic blood pressure of contracted ventricle \([mmHg]\)
- \(P_v\) = blood pressure of veins supplying atrium \([mmHg]\)
- \(P_a\) = blood pressure of arteries supplied by ventricle \([mmHg]\)
- \(c_{dia}\) = end-diastolic compliance of relaxed atrium \([L \cdot mmHg^{-1} \cdot beat^{-1}]\)
- \(c_{sys}\) = end-systolic compliance of contracted ventricle \([L \cdot mmHg^{-1} \cdot beat^{-1}]\)

This gives Equation (1.49) for cardiac output.

\[
Q = HV_{str} = c_{dia}HP_v
\]
where
\[ Q = \text{cardiac output} \quad [L \cdot min^{-1}] \]
\[ H = \text{heart rate} \quad [bpm] \]
\[ V_{str} = \text{stroke volume} \quad [L \cdot beat^{-1}] \]
\[ P_v = \text{blood pressure of veins supplying atrium} \quad [mmHg] \]
\[ c_{dia} = \text{end-diastolic compliance of relaxed atrium} \quad [L \cdot mmHg^{-1} \cdot beat^{-1}] \]

Since the venous pulmonary compartment is the compartment that supplies the atrium of the left side of the heart, Equation (1.50) describes the cardiac output of the left side of the heart. Likewise, since the venous systemic compartment is the compartment that supplies the atrium of the right side of the heart, Equation (1.51) describes the cardiac output of the right side of the heart.

\[ Q_l = c_l H P_{vp} \quad (1.50) \]
\[ Q_r = c_r H P_{vs} \quad (1.51) \]

where
\[ Q_l = \text{cardiac output of left side of heart} \quad [L \cdot min^{-1}] \]
\[ Q_r = \text{cardiac output of right side of heart} \quad [L \cdot min^{-1}] \]
\[ H = \text{heart rate} \quad [bpm] \]
\[ P_{vp} = \text{blood pressure of compartment } vp \quad [mmHg] \]
\[ P_{vs} = \text{blood pressure of compartment } vs \quad [mmHg] \]
\[ c_l = \text{end-diastolic compliance of relaxed left atrium} \quad [L \cdot mmHg^{-1} \cdot beat^{-1}] \]
\[ c_r = \text{end-diastolic compliance of relaxed right atrium} \quad [L \cdot mmHg^{-1} \cdot beat^{-1}] \]

Blood flow in the body (\( F \)) takes place in smaller vessels, such as arterioles, capillaries, and venules, that are rigid with resistance to blood flow. These vessels are considered to be resistance vessels, meaning volume of blood is not proportional to blood pressure. A simple relationship to describe vessels of this sort is Ohm’s Law. Ohm’s Law states that the potential difference, or voltage, across a conductor is proportional to the current through it, with the resistance of the conductor as the constant of proportionality. Applied to circulation, the difference in blood pressure between two points in a vessel is proportional to the blood flow
through the vessel, with the resistance to blood flow \((R)\) as the constant of proportionality. This is described in Equation (1.52). Blood flows out of the heart via arteries (large vessels), then flows through arterioles (small vessels), capillaries (even smaller vessels), venules (small vessels), and back to the heart via veins (large vessels). The two points in consideration are arterioles to venules.

\[
R \cdot F = P_a - P_v \tag{1.52}
\]

\[
\Rightarrow F = \frac{P_a - P_v}{R}
\]

where

\(F\) = blood flow in circulation \([L \cdot min^{-1}]\)

\(P_a\) = blood pressure of arterioles \([mmHg]\)

\(P_v\) = blood pressure of venules \([mmHg]\)

\(R\) = resistance to blood flow in circulation \([mmHg \cdot min \cdot L^{-1}]\)

In systemic circulation, arterioles have the same blood pressure as the arteries supplying them with blood, or the \(as\) compartment. Likewise, venules have the same blood pressure as the veins they supply with blood, or the \(vs\) compartment. Thus blood flow in systemic circulation \((F_s)\) is described by Equation (1.53). In pulmonary circulation, arterioles have the same blood pressure as the arteries supplying them with blood, or the \(ap\) compartment. Likewise, venules have the same blood pressure as the veins they supply with blood, or the \(vp\) compartment. Thus blood flow in pulmonary circulation \((F_p)\) is described by Equation (1.54).

\[
F_s = \frac{P_{as} - P_{vs}}{R_s} \tag{1.53}
\]

\[
F_p = \frac{P_{ap} - P_{vp}}{R_p} \tag{1.54}
\]
where

\( F_s = \) blood flow in systemic circulation \([L/min]\)
\( F_p = \) blood flow in pulmonary circulation \([L/min]\)
\( P_{as} = \) blood pressure of compartment \(as\) \([mmHg]\)
\( P_{vs} = \) blood pressure of compartment \(vs\) \([mmHg]\)
\( P_{ap} = \) blood pressure of compartment \(ap\) \([mmHg]\)
\( P_{vp} = \) blood pressure of compartment \(vp\) \([mmHg]\)
\( R_s = \) resistance to blood flow in systemic circulation \([mmHg \cdot min/L]\)
\( R_p = \) resistance to blood flow in pulmonary circulation \([mmHg \cdot min/L]\)

Substituting Equations (1.50) and (1.51) in for \(Q_l\) and \(Q_r\), respectively, and Equations (1.53) and (1.54) in for \(F_s\) and \(F_p\), respectively, into Equations (1.44)-(1.47) gives the system of ODEs in Equation (1.55) describing circulation.

\[
\begin{align*}
P_{as}' &= \frac{1}{60c_{as}} \left( c_lHP_{vp} - \frac{P_{as} - P_{vs}}{R_s} \right) \\
P_{vs}' &= \frac{1}{60c_{vs}} \left( \frac{P_{as} - P_{vs}}{R_s} - c_rHP_{vs} \right) \\
P_{ap}' &= \frac{1}{60c_{ap}} \left( c_rHP_{vs} - \frac{P_{ap} - P_{vp}}{R_p} \right) \\
P_{vp}' &= \frac{1}{60c_{vp}} \left( \frac{P_{ap} - P_{vp}}{R_p} - c_lHP_{vp} \right)
\end{align*}
\] (1.55)

### 1.5.2 Parameterization of HRV Model

Model parameters are described below and summarized in Table 3. The following parameter values are taken from Randall et al. [75]: \(A, K_b, K_{bp}, K_{bs}, K_{rp}, \tau_b, \tau_{bp}, \tau_{bs}, \tau_{rp},\) and \(\tau_H\). The following parameter values are taken from Li et al. [57]: \(c_{as}, c_{vs}, c_{ap}, c_{vp}, c_l, c_r, R_s, R_p\) and \(V_{tot}\). The following parameter values are varied, as explained in Section 1.6, to explore their effect on model dynamics: \(B, q_w, q_{bp}, q_{bs}, q_{rp}, H_{bp}, H_{bs},\) and \(H_{rp}\). It is assumed that the PSNS and SNS can be completely inhibited, so \(G_{bp_{min}} = G_{bs_{min}} = G_{rp_{min}} = 0\).

Initial conditions for the variables described in Table 1 and the following parameters are derived below: \(s_w, s_{bp}, s_{bs},\) and \(s_{rp}\). Since the model in this study is formulated to describe a healthy system at rest, initial conditions and parameters values are derived from the system
in homeostasis (derivatives are zero) at average arterial systemic blood pressure and average thoracic pressure.

The parameter $s_w$ is chosen to be the average value of $P_c = P_{as}$, as described by Equations (1.9)-(1.15), and calculated as the average of the arterial systemic blood pressure signal, or MAP data. At average arterial systemic blood pressure and thoracic pressure, Equations (1.56)-(1.60) are satisfied, where * denotes the homeostatic value of a variable.

\[
\epsilon_{wc}^* = 1 - \sqrt{1 + \left(\frac{P^*_c}{P^*_c - P^*_th}\right)^{q_w}} = 1 - \sqrt{\frac{2}{A + 1}} \quad (1.56)
\]

\[
\epsilon_{wa}^* = 1 - \sqrt{1 + \left(\frac{P^*_a}{P^*_a - P^*_th}\right)^{q_w}} \quad (1.57)
\]

\[
\epsilon_{bc}' = \frac{K_b \epsilon_{wc}^* - \epsilon_{bc}}{\tau_b} = 0 \implies \epsilon_{bc}^* = K_b \epsilon_{wc}^* \quad (1.58)
\]

\[
\epsilon_{ba}' = \frac{K_b \epsilon_{wa}^* - \epsilon_{ba}}{\tau_b} = 0 \implies \epsilon_{ba}^* = K_b \epsilon_{wa}^* \quad (1.59)
\]

\[
n^* = B(\epsilon_{wc}^* - \epsilon_{bc}) + (1 - B)(\epsilon_{wa}^* - \epsilon_{ba}) \quad (1.60)
\]

where

- $P^*_c$ = average of blood pressure signal [mmHg]
- $P^*_th$ = average of thoracic pressure signal [mmHg]
- $\epsilon_{wc}$ = arterial wall strain of carotid sinuses [dimensionless]
- $\epsilon_{wa}$ = arterial wall strain of aortic arch [dimensionless]
- $\epsilon_{bc}$ = strain of carotid baroreceptors [dimensionless]
- $\epsilon_{ba}$ = strain of aortic baroreceptors [dimensionless]
- $n$ = afferent signal of baroreceptors [sec$^{-1}$]
- $A$ = maximally stressed to unstressed arterial cross-sectional area ratio [dimensionless]
- $B$ = linear combination constant for afferent signal of baroreceptors [sec$^{-1}$]
- $q_w$ = sigmoid steepness constant for wall strain [dimensionless]
- $K_b$ = gain constant for strain of baroreceptors [dimensionless]
- $\tau_b$ = time constant for strain of baroreceptors [sec]
The parameters $s_{bp}$ and $s_{bs}$ are chosen so that the activation levels of the PSNS and SNS due to the Baroreflex Mechanism are 0.8 and 0.2, respectively, at average arterial systemic blood pressure and thoracic pressure, i.e., $G_{bp} = 0.8$ and $G_{bs} = 0.2$, as given in Equations (1.61) and (1.62). Also, at average arterial systemic blood pressure and thoracic pressure Equations (1.63) and (1.64) are satisfied, where $^*$ denotes the homeostatic value of a variable.

$$G_{bp}^* = G_{bp_{min}} + (1 - G_{bp_{min}}) \cdot \left( \frac{(n^*)_{q_{bp}}}{Q_{bp}^{*}_{bp} + (n^*)_{q_{bp}}} \right) = 0.8 \quad (1.61)$$

$$\implies s_{bp} = n^* \left( \frac{1 - G_{bp}^*}{G_{bp}^* - G_{bp_{min}}} \right)$$

$$G_{bs}^* = 1 - (1 - G_{bs_{min}}) \cdot \left( \frac{(n^*)_{q_{bs}}}{Q_{bs}^{*}_{bs} + (n^*)_{q_{bs}}} \right) = 0.2 \quad (1.62)$$

$$\implies s_{bs} = n^* \left( \frac{1 - G_{bs}^*}{G_{bs}^* - G_{bs_{min}}} \right)$$

$$T_{bp}' = \frac{K_{bp} G_{bp} - T_{bp}}{\tau_{bp}} = 0 \implies T_{bp}^* = K_{bp} G_{bp}^* \quad (1.63)$$

$$T_{bs}' = \frac{K_{bs} G_{bs} - T_{bs}}{\tau_{bs}} = 0 \implies T_{bs}^* = K_{bs} G_{bs}^* \quad (1.64)$$
where

\[ n = \text{afferent signal of baroreceptors} \ [sec^{-1}] \]

\[ G_{bp} = \text{activation level of PSNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ G_{bs} = \text{activation level of SNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ T_{bp} = \text{tone of PSNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ T_{bs} = \text{tone of SNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ q_{bp} = \text{sigmoid steepness constant for activation of PSNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ q_{bs} = \text{sigmoid steepness constant for activation of SNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ s_{bp} = \text{sigmoid shift constant for activation of PSNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ s_{bs} = \text{sigmoid shift constant for activation of SNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ G_{bp\min} = \text{minimum activation level of PSNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ G_{bs\min} = \text{minimum activation level of SNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ K_{bp} = \text{gain constant for tone of PSNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ K_{bs} = \text{gain constant for tone of SNS due to Baroreflex Mechanism} \ [\text{dimensionless}] \]

\[ \tau_{bp} = \text{time constant for tone of PSNS due to Baroreflex Mechanism} \ [sec] \]

\[ \tau_{bs} = \text{time constant for tone of SNS due to Baroreflex Mechanism} \ [sec] \]

The parameter \( s_{rp} \) is chosen so that the activation level of the PSNS due to RSA is 0.5, respectively, at average arterial systemic blood pressure and thoracic pressure, i.e., \( G_{rp} = 0.5 \), as given in Equation (1.65). Also, at average arterial systemic blood pressure and thoracic pressure Equations (1.66)-(1.68) are satisfied, where * denotes the homeostatic value of a variable.
\[ G_{rp}^* = 1 - \left(1 - G_{rp_{min}}\right) \cdot \left(\frac{(P_{th})^q_{rp}}{s_{rp} + (P_{th})^q_{rp}}\right) = 0.5 \quad (1.65) \]

\[ \Rightarrow s_{rp} = P_{th}^* \left(\frac{1 - G_{rp}^*}{G_{rp}^* - G_{rp_{min}}}\right) \frac{1}{q_{rp}} \]

\[ T_{rp}' = \frac{K_{rp}G_{rp} - T_{rp}}{\tau_{rp}} = 0 \Rightarrow T_{rp}^* = K_{rp}G_{rp}^* \quad (1.66) \]

\[ \tilde{H}^* = H_I(1 - H_{bp}T_{bp}^* + H_{bs}T_{bs}^* + H_{rp}T_{rp}^*) \quad (1.67) \]

\[ H' = \frac{\tilde{H} - H}{\tau_{H}} = 0 \Rightarrow H^* = \tilde{H}^* \quad (1.68) \]

where

- \( P_{th}^* \) = average of thoracic pressure signal [mmHg]
- \( G_{rp} \) = activation level of PSNS due to RSA [dimensionless]
- \( T_{bp} \) = tone of PSNS due to Baroreflex Mechanism [dimensionless]
- \( T_{bs} \) = tone of SNS due to Baroreflex Mechanism [dimensionless]
- \( T_{rp} \) = tone of PSNS due to RSA [dimensionless]
- \( \tilde{H} \) = weighted intrinsic heart rate [bpm]
- \( H \) = heart rate [bpm]
- \( q_{rp} \) = sigmoid steepness constant for activation of PSNS due to RSA [dimensionless]
- \( s_{rp} \) = sigmoid shift constant for activation of PSNS due to RSA [mmHg]
- \( G_{rp_{min}} \) = minimum activation level of PSNS due to RSA [dimensionless]
- \( K_{rp} \) = gain constant for tone of PSNS due to RSA [dimensionless]
- \( \tau_{rp} \) = time constant for tone of PSNS due to RSA [sec]
- \( \tau_{H} \) = time constant for heart rate [bpm]
- \( H_I \) = intrinsic heart rate [bpm]
- \( H_{bp} \) = weighting constant for tone of PSNS due to Baroreflex Mechanism [dimensionless]
- \( H_{bs} \) = weighting constant for tone of SNS due to Baroreflex Mechanism [dimensionless]
- \( H_{rp} \) = weighting constant for tone of PSNS due to RSA [dimensionless]
Initial conditions of $\epsilon_{bc}$, $\epsilon_{ba}$, $T_{bp}$, $T_{bs}$, and $T_{rp}$ are the homeostatic values at average arterial systemic blood pressure and thoracic pressure. The initial condition of $P_{as}$ is the average of the arterial systemic blood pressure signal, or MAP data. The initial condition of $H$ is the value of the heart data at the first time point.

At average arterial systemic blood pressure, Equations (1.69)-(1.72) are satisfied, where $^*$ denotes the homeostatic value of a variable.

\[
(1.55) = 0 \implies \\
\begin{align*}
&c_l H^* P_{vp}^* = P_{as}^* - P_{vs}^* \\
&c_r H^* P_{vs}^* = P_{as}^* - P_{vp}^* \\
&c_r H^* P_{vs}^* = P_{ap}^* - P_{vp}^* \\
&c_l H^* P_{vp}^* = P_{ap}^* - P_{vp}^*
\end{align*}
\] (1.69) (1.70) (1.71) (1.72)

where

- $P_i =$ blood pressure of compartment $i$ [mmHg]
- $c_i =$ compliance constant for compartment $i$ [L·mmHg$^{-1}$]
- $i = \{as, vs, ap, vp\}$
- $H =$ heart rate [bpm]
- $c_l =$ end-diastolic compliance of relaxed left atrium [L·mmHg$^{-1}$·beat$^{-1}$]
- $c_r =$ end-diastolic compliance of relaxed right atrium [L·mmHg$^{-1}$·beat$^{-1}$]
- $R_s =$ resistance to blood flow in systemic circulation [mmHg·min/L]
- $R_p =$ resistance to blood flow in pulmonary circulation [mmHg·min/L]

Also, since circulation is a closed loop, the sum of the volumes of blood in the four compartments will be constant, as given in Equation (1.73).

\[
V_{tot} = V_{as} + V_{vs} + V_{ap} + V_{vp} = c_{as} P_{as} + c_{vs} P_{vs} + c_{ap} P_{ap} + c_{vp} P_{vp}
\] (1.73)

31
where

\[ V_{\text{tot}} = \text{total blood volume} \ [L] \]
\[ V_i = \text{volume of blood in compartment } i \ [L] \]
\[ P_i = \text{blood pressure of compartment } i \ [mmHg] \]
\[ c_i = \text{compliance constant for compartment } i \ [L \cdot mmHg^{-1}] \]
\[ i = \{as, vs, ap, vp\} \]

Solving Equations (1.69)-(1.73) for \( P_{vs}^*, P_{ap}^*, \) and \( P_{vp}^* \) gives the homeostatic values in Equations (1.74)-(1.76) and are the initial conditions for \( P_{vs}, P_{ap}, \) and \( P_{vp}. \)

\[
P_{vp}^* = \frac{c_r(V_{\text{tot}}R_s - (c_{as}R_s + c_{ap}R_p)P_{as}^*)}{(c_{vs}c_l + c_{ap}c_r + c_{vp}c_r)R_s - c_{ap}c_lR_p} \tag{1.74}
\]
\[
P_{vs}^* = \frac{c_l}{c_r}P_{vp}^* \tag{1.75}
\]
\[
P_{ap}^* = \frac{R_pP_{as}^* - R_pP_{vs}^* + R_sP_{vp}^*}{R_s} \tag{1.76}
\]

where

\[ P_i = \text{blood pressure of compartment } i \ [mmHg] \]
\[ c_i = \text{compliance constant for compartment } i \ [L \cdot mmHg^{-1}] \]
\[ i = \{as, vs, ap, vp\} \]
\[ c_l = \text{end-diastolic compliance of relaxed left atrium} \ [L \cdot mmHg^{-1} \cdot \text{beat}^{-1}] \]
\[ c_r = \text{end-diastolic compliance of relaxed right atrium} \ [L \cdot mmHg^{-1} \cdot \text{beat}^{-1}] \]
\[ R_s = \text{resistance to blood flow in systemic circulation} \ [mmHg \cdot \text{min/L}] \]
\[ R_p = \text{resistance to blood flow in pulmonary circulation} \ [mmHg \cdot \text{min/L}] \]
\[ V_{\text{tot}} = \text{total blood volume} \ [L] \]

1.5.3 HRV Model

Heart rate is modeled by the system of ODEs in Equation (1.77) with auxiliary Equations (1.7), (1.8), (1.14), (1.15), (1.19), (1.20), (1.21), (1.28), (1.30), and (1.31) where ‘ denotes differentiation with respect to time, that describes neuroendocrine control of heart via the Baroreflex Mechanism and RSA, and heart rate as a driver of circulation. Model variables
are summarized in Table 1, auxiliary variables are summarized in Table 2, and parameters are summarized in Table 3.

\[
\begin{align*}
\epsilon'_{bc} &= \frac{K_b \epsilon_{wc} - \epsilon_{bc}}{\tau_b} \\
\epsilon'_{ba} &= \frac{K_b \epsilon_{wa} - \epsilon_{ba}}{\tau_b} \\
T'_{bp} &= \frac{K_{bp} G_{bp} - T_{bp}}{\tau_{bp}} \\
T'_{bs} &= \frac{K_{bs} G_{bs} - T_{bs}}{\tau_{bs}} \\
T'_{rp} &= \frac{K_{rp} G_{rp} - T_{rp}}{\tau_{rp}} \\
H' &= \frac{\bar{H} - H}{\tau_H} \\
P'_{as} &= \frac{1}{60 c_{as}} \left( c_l H P_{vp} - \frac{P_{as} - P_{vs}}{R_s} \right) \\
P'_{vs} &= \frac{1}{60 c_{vs}} \left( \frac{P_{as} - P_{vs}}{R_s} - c_r H P_{vs} \right) \\
P'_{ap} &= \frac{1}{60 c_{ap}} \left( c_r H P_{vs} - \frac{P_{ap} - P_{vp}}{R_p} \right) \\
P'_{vp} &= \frac{1}{60 c_{vp}} \left( \frac{P_{ap} - P_{vp}}{R_p} - c_l H P_{vp} \right)
\end{align*}
\]

The solution to Equation (1.77) is simulated by the ODE solver ode15s in MATLAB [62], a numerical method for stiff ODE systems. Figure 10 shows the numerical solution of the HRV model described by the system of ODEs in Equation (1.77) compared to patient data. The numerical solution shows the time courses of the system variables from Table 1 with reference parameter values from Table 3. Initial conditions are described in Section 1.5.2. Figure 11 shows a larger plot of the numerical solution of the model predicted heart rate (\(H\)).

### 1.5.4 Metrics of HRV

The solution of the HRV model, particularly model predicted heart rate (\(H\)) and arterial systemic blood pressure (\(P_{as}\)), are compared to heart rate and MAP data. The data is not used to validate the model. Instead, it is used to provide a visual and numerical projection
for the model output. Numerically, the model is compared to the data by two metrics: the mean of heart rate and the variance of the RR intervals of heart rate.

As described in Section 1.2.1, an RR interval is the time interval between two consecutive R waves on an ECG. Also, heart rate is derived from an ECG by dividing 60 by the duration of the RR interval at each time point. Thus, the RR intervals for the model predicted heart rate can be found by dividing 60 by the heart rate at each time point, as described by Equation (1.78). The variance in the RR intervals is used as a metric for HRV in this study.

\[ RR = \frac{60}{H} \quad (1.78) \]

where

\[ RR = \text{duration of RR interval [sec]} \]
\[ H = \text{heart rate [bpm]} \]

The the mean of heart rate and the variance of the RR intervals of heart rate for the heart rate data and the model predicted heart rate are summarized in Table 4.

### 1.6 Results

The effect of several parameters on the model output, the mean of heart rate, and the variance of the RR intervals of heart rate was explored. The parameter values explored included the sigmoid steepness constants \((q_w, q_{bp}, q_{bs}, \text{ and } q_{rp})\), the weighting constants \((H_{bp}, H_{bs}, \text{ and } H_{rp})\), and the linear combination constant \((B)\), and were chosen because their values were not available in literature, could not be calculated from patient data, and appear to have a significant effect on the model output. Results are summarized in Table 4 and Figures 12-19.

The solution to the system of ODEs in Equation (1.77) with reference parameter values in Table 3 and initial conditions described in Section 1.5.2 is shown in Figures 10 and 11. There is more variability in the strain of the aortic baroreceptors \((\epsilon_{ba})\), which incorporates respiration via thoracic pressure, than in the strain of the carotid baroreceptors \((\epsilon_{bc})\), which does not incorporate respiration via thoracic pressure. There is also more variability in the tone of the PSNS due to RSA \((T_{rp})\) than the tone of the PSNS and SNS due to the Baroreflex Mechanism \((T_{bp} \text{ and } T_{bs})\), and more variability in \(T_{bp}\) than \(T_{bs}\). Thus, it appears that signals incorporating respiration via thoracic pressure have more variability than the signals that do not, and may be the source of variability in the heart rate signal \((H)\). Parameter exploration further supports this as described below. The model predicted arterial
systemic blood pressure ($P_{as}$) is higher than the data and has more variability than the other model predicted blood pressures. Model predicted venous systemic, arterial pulmonary, and venous pulmonary blood pressures ($P_{vs}$, $P_{ap}$, and $P_{vp}$) follow average values of 5-8 mmHg, 8-20 mmHg, and 8 mmHg, respectively, from literature [33]. The mean of the heart rate data is 68.394 bpm and the mean of the model predicted heart rate ($H$) is 69.836 bpm. The variance of the RR intervals for the heart rate data is 0.00227 bpm$^2$ and the variance of the RR intervals for the model predicted heart rate ($H$) is 0.00102 bpm$^2$. Thus, the model is able to capture the order of magnitude of HRV in the data.

The sigmoid steepness constant for arterial wall strain ($q_w$) determines how quickly cross-sectional area of an artery distends as blood pressure increases. Since pressure and volume are directly proportional in large vessels like the carotid sinuses and aortic arch, an increase in blood pressure in an artery causes an increase in the volume of blood in that artery. If $q_w$ is small, distension is slow and cross-sectional area is not as large for higher pressures. Thus, the heart beats faster to pump the larger volume of blood through the artery. Also, slower distension results in slower changes in baroreceptor strain and a slower afferent signal, causing a slower PSNS and SNS response via the Baroreflex Mechanism to bring heart rate back down. If $q_w$ is large, the opposite occurs. Thus, mean heart rate decreases as $q_w$ increases in Table 4. Also, if $q_w$ is small, causing a higher heart rate ($H$), arterial systemic blood pressure ($P_{as}$) will be larger. A larger arterial systemic blood pressure causes the Baroreflex Mechanism to stimulate the PSNS and inhibit the SNS responses, producing a larger $T_{bp}$ and a smaller $T_{bs}$. Since $T_{bp}$ has more variability than $T_{bs}$, HRV will be larger. If $q_w$ is large, the opposite occurs. Thus, the variance in the RR intervals of heart rate increases as $q_w$ decreases in Table 4. Figure 12 shows the model predicted heart rate compared to heart rate data for increasing values of $q_w$.

The sigmoid steepness constant for the activation of the PSNS due to the Baroreflex Mechanism ($q_{bp}$) determines how quickly the level of PSNS activation increases as the afferent signal increases. An increasing afferent signal indicates increasing baroreceptor strain from increasing blood pressure. If $q_{bp}$ is small, the PSNS is not being stimulated as quickly to lower heart rate. If $q_{bp}$ is large, the PSNS is being stimulated quickly to lower heart rate. Thus, mean heart rate decreases as $q_{bp}$ increases in Table 4. Also, if $q_{bp}$ is small and the PSNS is not being stimulated as quickly, and thus the SNS is not being inhibited as quickly, $T_{bp}$ will be small and $T_{bs}$ will be large. Since $T_{bs}$ has less variability than $T_{bp}$, HRV will be smaller. If $q_{bp}$ is large, the opposite occurs. However, very large values of $q_{bp}$ produce a smaller heart rate ($H$), which in turn produces a smaller arterial systemic blood pressure ($P_{as}$). A smaller arterial systemic blood pressure causes the Baroreflex Mechanism to inhibit the PSNS and stimulate the SNS responses, producing a smaller $T_{bp}$ and larger $T_{bs}$. Therefore, HRV will
be smaller. Thus, the variance in the RR intervals of heart rate increases as $q_{bp}$ is closer to middle values in Table 4. Figure 13 shows the model predicted heart rate compared to heart rate data for increasing values of $q_{bp}$.

The sigmoid steepness constant for the activation of the SNS due to the Baroreflex Mechanism ($q_{bs}$) determines how quickly the level of SNS activation decreases as the afferent signal increases. An increasing afferent signal indicates increasing baroreceptor strain from increasing blood pressure. If $q_{bs}$ is small, the SNS is not being inhibited as quickly to lower heart rate. If $q_{bs}$ is large, the SNS is being inhibited quickly to lower heart rate. Thus, mean heart rate decreases as $q_{bs}$ increases in Table 4. Also, if $q_{bs}$ is small and the SNS is not being inhibited as quickly, and thus the PSNS is not being stimulated as quickly, $T_{bs}$ will be larger and $T_{bp}$ will be smaller. Since $T_{bs}$ has less variability than $T_{bp}$, HRV will be smaller. If $q_{bs}$ is large, the opposite occurs. However, very large values of $q_{bs}$ produce a smaller heart rate ($H$), which in turn produces a smaller arterial systemic blood pressure ($P_{as}$). A smaller arterial systemic blood pressure causes the Baroreflex Mechanism to inhibit the PSNS and stimulate the SNS responses, producing a smaller $T_{bp}$ and larger $T_{bs}$. Therefore, HRV will be smaller. Thus, the variance in the RR intervals of heart rate increases as $q_{bs}$ is closer to middle values in Table 4. Figure 14 shows the model predicted heart rate compared to heart rate data for increasing values of $q_{bs}$.

The sigmoid steepness constant for the activation of the PSNS due to RSA ($q_{rp}$) determines how quickly the level of PSNS activation decreases as thoracic pressure increases. An increasing thoracic pressure indicates inhalation. If $q_{rp}$ is small, the PSNS is not being inhibited as quickly to raise heart rate. If $q_{rp}$ is large, the PSNS is being inhibited quickly to raise heart rate. If $q_{rp}$ is 0, the PSNS is almost not responding to changes in thoracic pressure and is not contributing to changes in heart. Thus, mean heart rate decreases as $q_{rp}$ increases, except for when $q_{rp}$ is 0, in Table 4. Changes in mean heart rate due to variation in $q_{rp}$ are not as large as changes in mean heart rate due to variation in $q_{bp}$ or $q_{bs}$ because the activation of the PSNS due to RSA only has small, transient effects on heart rate whereas activation of the PSNS and SNS due to the Baroreflex Mechanism acts directly on heart rate. Also, if $q_{rp}$ is small, $T_{rp}$ will be smaller. Since $T_{rp}$ has more variability than $T_{bp}$ and $T_{bs}$, HRV will be smaller. If $q_{rp}$ is large, the opposite occurs. Thus, the variance in the RR intervals of heart rate increases as $q_{rp}$ increases in Table 4. Figure 15 shows the model predicted heart rate compared to heart rate data for increasing values of $q_{rp}$.

The weighting constant $H_{bp}$ determines the relative contribution of the tone of the PSNS due to the Baroreflex Mechanism ($T_{bp}$) to heart rate. Since stimulation of a PSNS response due to the Baroreflex Mechanism decreases heart rate, if $H_{bp}$ is small, $T_{bp}$ contributes less to heart rate and heart rate is decreased less. If $H_{bp}$ is large, $T_{bp}$ contributes more to heart rate and heart rate is increased more.

36
rate and heart rate is decreased more. Thus, mean heart rate decreases as $H_{bp}$ increases in Table 4. Also, since $T_{bp}$ has more variability than $T_{bs}$, if $H_{bp}$ is small, $T_{bp}$ contributes less to heart rate, allowing $T_{bp}$ to contribute more to heart rate, and HRV will be smaller. If $H_{bp}$ is large, $T_{bp}$ contributes more to heart rate, allowing $T_{bs}$ to contribute less to heart rate, and HRV will be larger. However, since $T_{bp}$ has less variability than $T_{rp}$, if $H_{bp}$ is small, $T_{bp}$ contributes less to heart rate, allowing $T_{rp}$ to contribute more to heart rate, and HRV will be larger. If $H_{bp}$ is large, $T_{bp}$ contributes more to heart rate, allowing $T_{rp}$ to contribute less to heart rate, and HRV will be smaller. Thus, the variance in the RR intervals of heart rate increases as $H_{bp}$ is closer to middle values in Table 4. Figure 17 shows the model predicted heart rate compared to heart rate data for increasing values of $H_{bp}$.

The weighting constant $H_{bs}$ determines the relative contribution of the tone of the SNS due to the Baroreflex Mechanism ($T_{bs}$) to heart rate. Since stimulation of an SNS response due to the Baroreflex Mechanism increases heart rate, if $H_{bs}$ is small, $T_{bs}$ contributes less to heart rate and heart rate is increased less. If $H_{bs}$ is large, $T_{bs}$ contributes more to heart rate and heart rate is increased more. Thus, mean heart rate increases as $H_{bs}$ increases in Table 4. Also, since $T_{bs}$ has less variability than $T_{bp}$ and $T_{rp}$, if $H_{bs}$ is small, $T_{bs}$ contributes less to heart rate, allowing $T_{bp}$ and $T_{rp}$ to contribute more to heart rate, and HRV will be larger. If $H_{bs}$ is large, $T_{bs}$ contributes more to heart rate, allowing $T_{bp}$ and $T_{rp}$ to contribute less to heart rate, and HRV will be smaller. However, very large values of $H_{bs}$ produce a larger heart rate ($H$), which in turn produces a larger arterial systemic blood pressure ($P_{as}$). A larger arterial systemic blood pressure causes the Baroreflex Mechanism to stimulate the PSNS and inhibit the SNS responses, producing a smaller $T_{bs}$. Therefore, even though $H_{bs}$ is very large, $T_{bs}$ is small and the heart rate signal is more due to $T_{bp}$ and $T_{rp}$, which contain more variability. Thus, the variance in the RR intervals of heart rate increases as $H_{bs}$ further away from middle values in Table 4. Figure 17 shows the model predicted heart rate compared to heart rate data for increasing values of $H_{bs}$.

The weighting constant $H_{rp}$ determines the relative contribution of the tone of the PSNS due to RSA ($T_{rp}$) to heart rate. Since inhibition of a PSNS response due to RSA increases heart rate, if $H_{rp}$ is small, $T_{rp}$ contributes less to heart rate and heart rate is increased less. If $H_{rp}$ is large, $T_{rp}$ contributes more to heart rate and heart rate is increased more. Thus, mean heart rate increases as $H_{rp}$ increases in Table 4. Also, since $T_{rp}$ has more variability than $T_{bp}$ and $T_{bs}$, if $H_{rp}$ is small, $T_{rp}$ contributes less to heart rate and HRV will be smaller. If $H_{rp}$ is large, $T_{rp}$ contributes more to heart rate and HRV will be larger. Thus, the variance in the RR intervals of heart rate increases as $H_{rp}$ increases in Table 4. Figure 18 shows the model predicted heart rate compared to heart rate data for increasing values of $H_{rp}$.
The linear combination constant \( (B) \) determines the relative contribution of carotid and aortic baroreceptor strain to the afferent signal \( (n) \). If \( B \in [0, 0.5) \), aortic baroreceptor strain contributes more to \( n \). If \( B \in (0.5, 1] \), carotid baroreceptor strain contributes more to \( n \). If \( B = 0.5 \), carotid and aortic baroreceptor strain contributes evenly to \( n \). There is not a significant change in the mean heart rate for different values of \( B \) in Table 4 because PSNS and SNS tone due to the Baroreflex Mechanism, and thus heart rate, responds the same to the afferent signal regardless of how the signal is formulated from different locations in the body. HRV is larger for \( B = 1 \), when \( n \) is only a function of carotid baroreceptor strain, than for \( B = 0 \), when \( n \) is only a function of aortic baroreceptor strain, as summarized in Table 4, which is a counterintuitive result. More variability in aortic baroreceptor strain \( (\epsilon_{ba}) \) than in carotid baroreceptor strain \( (\epsilon_{bc}) \) supports the opposite result. Figure 19 shows the model predicted heart rate compared to heart rate data for increasing values of \( B \).

1.7 Discussion

The correlation between loss of HRV and physiological states of stress has not been fully linked to underlying physiological mechanisms, preventing the broad use of this noninvasive, diagnostic metric of health. To gain a better understanding of the physiological mechanisms governing HRV, this thesis combined two previous mathematical models of neuroendocrine control of heart rate and circulation to explain the source of heart rate variability in a resting, healthy state. Respiration was also incorporated as a disturbance to the system to characterize the role of respiration in heart rate variability. The treatment of respiration in this study was novel in the incorporation of a respiration-derived thoracic pressure signal into the Baroreflex Mechanism and RSA. Also, this study was unique in the exploration of the source of HRV in a healthy, resting state rather than the loss of HRV in a stressed state.

Results show that the mean of the heart rate data is 68.394 bpm and the mean of the model predicted heart rate is 69.836 bpm. The variance of the RR intervals for the heart rate data is 0.00227 bpm\(^2\) and the variance of the RR intervals for the model predicted heart rate is 0.00102 bpm\(^2\). Thus, the model is able to capture the order of magnitude of HRV in the data. Results also show that the mean heart rate decreases as the sigmoid steepness constants \( q_w, q_bp, q_bs, \) and \( q_rp \) increase, as the weighting constant \( H_{bp} \) increases, and as the weighting constants \( H_{bs} \) and \( H_{rp} \) decrease. Additionally, the variance of the RR intervals for heart rate, a metric for HRV, increases as \( q_w \) decreases, as \( q_bp, q_bs, \) and \( H_{bp} \) are closer to middle values, as \( q_rp, H_{rp}, \) and \( B \) increase, and as \( H_{bs} \) is further away from middle values. This indicates that there appears to be a trade-off occurring for most parameters associate with the Baroreflex Mechanism. HRV is higher in scenarios that do not produce extreme
heart rate and blood pressure values. For the parameters associated with RSA, a direct correlation between the parameter values and HRV indicates that RSA contributes to higher RSA.

The model in this study has a few notable limitations. First, the model was not fit to the data to determine the best values for the unknown parameter values and sensitivity analysis was not performed to determine which parameters had a significant impact on the outcome of the model. The combination of fitting the model to the data and sensitivity analysis could better drive the exploration of the effect of parameters on the model output. Second, although the incorporation of respiration was novel in this model, it is rudimentary. There is still a large gap in the understanding of neuroendocrine control of respiration and its link to heart rate. Thus an afferent signal due to RSA was not incorporated in this model. Also, the effects of respiration on the circulation component of the model was not explored. Third, the counterintuitive result of larger HRV when the afferent signal did not incorporate aortic baroreceptor strain is not understood from the formulation of this model. Further exploration of the formulation of the afferent signal and more metrics of HRV could help make this result more clear.

The appearance of trade-offs in the results of this thesis mimic the type of results in Li et al. [57]. In future work, this model could be viewed as a control system, penalized from deviating from homeostasis, to rigorously describe the trade-offs occurring between maintaining homeostatic values and deviations from homeostasis during respiration. Exaggerated, but healthy, data, such as the exercise data from Li et al. [57] and the Valsalva Maneuver data from Randall et al. [75], could be used to force a more exaggerated model output and help validate the model. Ultimately, this thesis has demonstrated the need to further study the physiological control mechanisms governing heart rate in a healthy, resting state.
Chapter 2

The Contribution of Environmental Pathways to Clostridioides difficile Transmission

2.1 Introduction

Transmission of a pathogen between hosts is the most important process driving the dynamics of an infectious disease. However, transmission is difficult to study. Transmission events are unobservable and are influenced by multiple interacting factors. Mathematical models provide a framework to investigate complex interactions driving transmission, study infectious disease dynamics, evaluate control interventions, and design surveillance strategies. Such mathematical models are termed epidemiological models. The aim of this study is to formulate an epidemiological model to investigate the contribution of environmental pathways to the transmission of Clostridioides difficile (abbreviated C. diff) in healthcare settings.

C. diff is the leading cause of infectious diarrhea and is the most frequently identified healthcare-associated, i.e., nosocomial, infection in United States hospitals. C. diff is typically contracted after antibiotic use, when a healthy gut microbiota that prevents colonization is compromised. Colonized patients, both symptomatic and asymptomatic, shed endospores that survive for long periods of time on surfaces outside the host and are resistant to commonly used disinfectants. Transmission pathways can include contact with environmental reservoirs of endospores on fomites, objects and surfaces that can harbor infectious agents.
The difficulty in studying environmental transmission of nosocomial pathogens, a lack of understanding of these dynamics, and the serious nature of \textit{C. diff} infections hinders the ability to control certain nosocomial infections, including \textit{C. diff} infections. This study adds environmental reservoirs to a previous epidemiological model of \textit{C. diff} transmission and focuses on the effect of fomite touch frequency on \textit{C. diff} transmission. Specifically, this study investigates the contribution of high-touch frequency and low-touch frequency fomites in a hospital ward to new cases of \textit{C. diff} colonization among hospital patients. Additionally, this study determines the factors that influence their relative contributions.

The dynamics of transmission are modeled deterministically using a six-dimensional system of ODEs representing the four patient population classes: resistant individuals ($R$), susceptible individuals ($S$), asymptptomatically colonized individuals ($C$), and diseased individuals ($D$), and the two pathogen environmental reservoirs: pathogen density on high-touch frequency fomites ($P_H$) and pathogen density on low-touch frequency fomites ($P_L$). Due to the small population size of 30 beds in the considered hospital ward, the system is also simulated stochastically using the Gillespie Stochastic Simulation Algorithm (GSSA) and the results are compared to the average population behavior described by the deterministic system.

Results show that on average, over three-quarters of asymptptomatically colonized patients are colonized due to a contact with a high-touch frequency fomite and under one-quarter are colonized due to a contact with a low-touch fomite, despite the extra daily cleaning high-touch frequency fomites receive. Individual trajectories of the system from the stochastic simulations showed behaviors and extreme cases not captured by the deterministic system.

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2.2 Background

2.2.1 Natural History of \textit{C. diff} Infection

\textit{Clostridioides difficile} (formerly \textit{Clostridium difficile} [52]) is an anaerobic, gram-positive bacillus spread among humans via the fecal-oral route. \textit{C. diff} is of particular interest because
it is the leading cause of infectious diarrhea and is the most frequently identified healthcare-associated infection in United States hospitals [55]. It was first identified in the 1930s by [35], who named the bacterium Bacillus difficile due to the difficulty of culturing the bacterium in vitro. It was originally thought that the relationship between humans and the bacterium was commensal [35] since most infants have C. diff present in their gut (are colonized) but do not display any symptoms (are not diseased) [77]. However, subsequent studies began to indicate otherwise, leading to recent data that demonstrates the serious nature of the disease. In 2008, it was estimated that C. diff may have been responsible for an extra $4.8 billion in healthcare costs in the United States that year [23]. In 2011, it was estimated that 453,000 C. diff infections and 29,300 C. diff-associated deaths occurred in the United States that year [55]. In 2013, the Centers for Disease Control and Prevention (CDC) published an analysis of the top antibiotic-resistant threats in the United States, classifying the threats according to their current and projected health and economic impacts. C. diff was classified at the highest rank of ‘Urgent Threat’, requiring immediate and aggressive public health action [15].

According to [56], C. diff produces endospores: non-reproductive, metabolically inactive structures able to survive harsh conditions such as high temperatures and acidic environments for several weeks or months. Spores can survive in water and are resistant to most commonly used disinfectants. When ingested, spores survive the environment of the stomach and travel to the large intestine. In individuals with a diverse gut microbiota, spores do not germinate and remain in the colon as a commensal species, causing no harm or symptoms for the host. In individuals without a diverse gut microbiota, the absence of competition with other bacteria for resources in the gut stimulate spores to germinate: become active, reproducing, vegetative cells. Such individuals are termed colonized. However, if the host is able to mount an appropriate immune response against toxins produced by vegetative cells, they do not experience symptoms of colonization. Such individuals are termed asymptotically colonized. If the host is not be able to mount an appropriate immune response, vegetative cells adapt to their new environment on the interior walls of the colon. This adaption includes remodeling structural components of their cell wall that degrade the lining of the colon and releasing exotoxins TcdA and TcdB. Toxins TcdA and TcdB cause fluid accumulation and inflammation of the colon, termed colitis. Symptoms of colitis due to C. diff colonization without an appropriate immune response include diarrhea, abdominal pain and cramps, nausea, vomiting, dehydration, malaise, fever, and leukocytosis. Symptomatically colonized individuals are termed infectious or diseased.

Since the prevention of the germination of C. diff spores in the colon is primarily due to the presence of a diverse gut microbiota, recent antibiotic use, which compromises gut
microbiota, is the principle risk factor for colonization. Although the primary antibiotics associated with colonization are ampicillin, amoxicillin, cephalosporins, clindamycin, and fluoroquinolones, all antibiotics have been linked to \( C. \text{diff} \) colonization, even those used to treat \( C. \text{diff} \) infection \[54\]. Symptoms typically start displaying one week after antibiotic use \[22\] and 85-90% of infections occur within 30 days of antibiotic use \[16\]. Most infections are healthcare-associated due to patient clustering, the large proportion of elderly patients, and the large proportion (30-40%) of patients using antibiotics \[54\].

Metronidazole and vancomycin have been the primary antibiotics used to treat patients with \( C. \text{diff} \) infection since the 1970s \[54\]. Fidaxomicin was approved by the Food and Drug Administration (FDA) in 2011 as another possible antibiotic treatment \[54\]. A 10-14 day treatment is successful in approximately 50% of cases \[40, 53\]. Since recent antibiotic use is the principle risk factor for colonization, recurrent infections are likely. There is a 20% chance of a recurrent infection after the initial infection and a 60% chance after multiple prior infections \[27, 64\]. Risk factors for a recurrent \( C. \text{diff} \) infection include ongoing use of antibiotics not associated with \( C. \text{diff} \) infection and a severe initial infection \[64\]. Due to the persistence of spores and an ineffective immune response, not antibiotic resistance, it is difficult to treat subsequent recurrent infections \[61\]. Multiple recurrent infections result in severe colitis. Severe colitis can lead to colon perforation and the need for an emergency colectomy, which is associated with an 80% mortality rate \[66\]. The most effective way to eliminate \( C. \text{diff} \) from the gut is to cease all antibiotics and allow the gut microbiota to recover spontaneously, however gut restoration may take up to 12 weeks, during which patients may experience recurrent infections \[25\].

There is no effective vaccination against the toxins TcdA and TcdB released by the bacteria, but as of 2017 three candidate vaccines are undergoing clinical evaluation for \( C. \text{diff} \) infection prevention \[89\].

### 2.2.2 Environmental Pathways of \( C. \text{diff} \) Transmission

Evidence suggests that transmission pathways of \( C. \text{diff} \) infection include compulsorily interacting with fomites in healthcare settings \[69, 70\]. Colonized patients, both symptomatic and asymptomatic, shed \( C. \text{diff} \) spores that can survive for long periods on surfaces outside the host and can spread to other surfaces via hands of patients, visitors, and healthcare workers \[29, 47\]. A study by \[4\] swabbed fomites in patient rooms and bathrooms, nurses stations, and utility rooms in a hospital. They found that 74% of surfaces tested in the vicinity of infected patients were contaminated with \( C. \text{diff} \) spores. They also found that 29% of all surfaces tested in a case ward, including surfaces beyond patient areas such as utility
room sinks and chair arms, and 90% of floors tested in a case ward were contaminated with
*C. diff* spores. An analysis by [91] found that frequency of *C. diff* infections is correlated with
the frequency of *C. diff* recovered from environmental surfaces in rooms of diseased patients.
A study by [24] surveyed six healthcare facilities and found that rooms of colonized patients
were more likely to be contaminated than rooms of non-colonized patients. An investigation
by [82] tracked patients admitted over six months into an intensive care unit. Of the patients
who acquired infection, 11% occupied a room that was previously occupied by a patient with
*C. diff* infection, whereas 4.6% occupied a room that was previously occupied by a patient
without *C. diff* infection. They suggested that a room housing a patient infected with *C. diff*
had a significant effect on the acquisition of infection by the subsequent occupant. A study
by [90] documented *C. diff* environmental contamination after cleaning rooms of infected
patients. They found that room contamination and *C. diff* infection rates decreased over
four weeks of effective cleaning. An analysis by [68] evaluated daily cleaning with bleach
wipes in hospital wards with high-incidence of *C. diff* infection. The intervention reduced
incidence by 85%.

The acknowledgment of the importance of environmental reservoirs in the transmission
of *C. diff* infection has resulted in an influx of research on the most effective cleaning
and disinfecting methods. The most effective chemical for killing *C. diff* spores is a
chlorine-derived disinfectant [58], while non-chlorine-derived chemicals may stimulate spore
production [93]. The CDC recommends daily cleaning of the immediate vicinity around an
infected patient, including toilets, and disinfecting of an infected patient’s entire room upon
transfer or discharge [36, 79]. Disinfecting should utilize a disinfectant or sporicide from the
Environmental Protection Agency’s (EPA) List K, which comprises chlorine-derived cleaners
effective against *C. diff* spores [26]. The CDC also recommends considering additional
disinfection with no-touch technologies, such as UV light and hydrogen peroxide systems
[36, 79].

Compliance with these guidelines is often suboptimal. In a study by [12], rooms in sixteen
intensive care units were evaluated after at least two patients had occupied a room with
disinfecting upon each discharge. They found that only 57.1% of tested sites were effectively
cleaned. An investigation by [81] swabbed fomites highly interacted with by patients in nine
acute-care hospitals and two long-term care facilities in four states to determine the typical
microbial burden on high-touch surfaces after daily cleaning and disinfecting upon discharge.
They observed that after daily cleaning, 34% of sites tested still contained pathogen and after
disinfecting upon discharge, 17% of sites tested still contained pathogen.
Suboptimal cleaning may be due to the variation in cleaning protocols for different parts of hospital rooms. The CDC’s Guidelines for Environmental Infection Control in Healthcare Facilities [36] and the CDC’s Guideline for Disinfection and Sterilization in Healthcare Facilities [79] include recommended cleaning strategies for a variety of fomites: high-touch surfaces in patient rooms and bathrooms (i.e., bed rails, tray table, IV pole, doorknobs, sink, toilet, etc.), other surfaces in patient rooms (i.e., curtains, furniture, thermostats, soap and paper towel dispensers, trash cans, etc.), equipment in patient rooms (i.e., blood pressure cuffs, monitors, etc.), equipment traveling between patient rooms (i.e., housekeeping carts, wheelchairs, etc.), surfaces not in patient rooms (i.e., utility rooms, nurses stations, etc.), and cleaning equipment (i.e., mops, vacuums, etc.). Each type of surface requires a different disinfectant depending on vicinity to patients and probable pathogen presence. Chlorine-derived cleaners are only used when necessary since liquid disinfectants can damage electronic equipment, corrode metals, harm the environment, and encourage development of biocide resistant pathogens. Since chlorine-derived cleaners may be harmful to the user, [36, 79] recommend the use of goggles, gloves, and gowns, when using chlorine-derived disinfectants. In addition, cleaning, the removal of organic debris using vigorous scrubbing, must take place before disinfection, the inactivation of pathogens, to ensure that disinfection is not compromised by protection of pathogen by debris [10]. Disinfecting agents should remain on surfaces several minutes to ensure disinfection of \textit{C. diff} spores. Further, each type of surface has a different cleaning schedule based on vicinity to patients and probable pathogen presence. High-touch surfaces are typically cleaned daily since they carry heavy contamination [87], whereas other surfaces not as highly contaminated are only disinfected upon transfer or discharge. Since cleaning protocols for different parts of hospital rooms vary widely, it is difficult to decontaminate all surfaces without error. Thus, bacteria accumulates on surfaces not cleaned as thoroughly or often. A study by [11] evaluated rooms in three hospitals. They found that sites that were not disinfected upon discharge of a patient tended to be surfaces not deemed high-touch.

Since \textit{C. diff} spores can survive for long periods on surfaces not adequately cleaned or disinfected and have a large presence in healthcare settings correlated with infection rates, they can be a continuous source of transmission. This raises the question of what kinds of fomites in a healthcare setting contribute more to the transmission of \textit{C. diff} infection, fomites that are interacted with more and tend to be cleaned more often, or fomites that are interacted with less and tend to be cleaned less often. In this work, fomites are classified as one of two types: high-touch frequency and low-touch frequency fomites, respectively. Examples of high-touch frequency fomites include bed rails, tray tables, IV poles, doorknobs,
sinks, and toilets. Examples of low-touch frequency fomites include curtains, furniture, thermostats, soap and paper towel dispensers, and trash cans.

2.3 Previous Mathematical Models

2.3.1 Models Incorporating Environmental Pathways

In most epidemiological models of nosocomial infections, transmission is assumed to be only direct, i.e., through physical contact between susceptible and infected individuals. Wolkewitz et al. [95], Starr et al. [84], Rubin et al. [78], and Huang et al. [41] formulated epidemiological models that also included environmental pathways in the transmission of nosocomial infections.

Vancomycin-resistant enterococci (VRE) is a bacterium that colonizes the intestine, skin, urinary tract, and open wounds, among other locations, and typically occurs in people with weakened immune systems. Even though VRE does not form spores like C. diff, vegetative cells are capable of cellular respiration in the presence or absence of oxygen and can thus tolerate a variety of environmental conditions. Wolkewitz et al. [95] formulated a deterministic ODE model to describe the transmission of VRE among patients in a healthcare setting including environmental pathways. Patients were classified as uncolonized or colonized and healthcare workers and surfaces were classified as decontaminated or contaminated. Patients became colonized via a contact with a contaminated surface or healthcare worker. Healthcare workers became contaminated via a contact with a colonized patient or a contaminated surface. Surfaces became contaminated via a contact from a colonized patient or contaminated healthcare worker. The model tracked the number of contaminated healthcare workers and surfaces, rather than pathogen level. Cleaning reduced the number of contaminated surfaces and decontamination, such as hand-washing, reduced the number of contaminated healthcare workers. The model was used to study the effect of various intervention strategies that affect colonization, contamination, or decontamination rates.

Starr et al. [84] formulated a stochastic model to describe the transmission of C. diff among patients in a healthcare setting including environmental pathways. Patients were divided into classes based on infection status including immune without antibiotic exposure, immune with antibiotic exposure, susceptible and uncolonized, susceptible and colonized, and toxin positive. Individual patients transitioned to different classes at probabilities determined by class sizes and contact rates. Patients became colonized via contact with a susceptible and colonized or toxin positive patient, from the same or different hospital room, or from
the contaminated environment. The contaminated environment was considered independent of patients’ status and experienced neither contamination growth via patient shedding or decay via cleaning. The study analyzed the effects of changing parameter values on system dynamics.

Rubin et al. [78] formulated an agent-based model (ABM) to describe the transmission of \textit{C. diff} among patients in a healthcare setting including environmental pathways. ABMs simulate actions and interactions of individuals with particular characteristics, rather than classes of individuals, to generate population-level dynamics. Patients were classified as susceptible, asymptotically colonized, or symptomatic and occupied individual rooms. Patients became colonized via occupancy of a room with contaminated surfaces or with a contaminated healthcare worker. The level of environmental contamination (fraction of contaminated surfaces) in a room was a function of patient shedding and routine and terminal cleaning, which proportionally increased or decreased the fraction of contaminated surfaces. Healthcare workers acquired pathogen (number of spores) if they visited a room with contaminated surfaces. The model was used to study the effect of various intervention strategies on system dynamics.

Methicillin-resistant \textit{Staphylococcus aureus} (MRSA) is a bacteria that is often part of the normal microbiota in the upper respiratory tract, on skin, and in gut mucosa. MRSA can cause disease if it takes over the tissues it normally colonizes or invades other tissues. Even though MRSA does not form spores like \textit{C. diff}, it can tolerate a variety of environmental conditions and is often spread through objects used by colonized people. Huang et al. [41] formulated a deterministic ODE model and a stochastic differential equation (SDE) model to describe the transmission of MRSA among patients in a healthcare setting including environmental pathways. Patients were classified as uncolonized without antibiotic exposure, uncolonized with antibiotic exposure, colonized without antibiotic exposure, and colonized with antibiotic exposure. Healthcare workers were classified as uncontaminated or contaminated. Patients became colonized via direct contact with a contaminated healthcare worker or indirect contact with the contaminated environment. Healthcare workers became contaminated via direct contact with a colonized patient or indirect contact with the contaminated environment. The model tracked density of bacteria in aerobic colony counts per square centimeter, which increased via shedding of colonized patients and contamination by healthcare workers, and decreased via disinfection. The model was used to explore the role antibiotic exposure and environmental contamination play in the transmission of MRSA.
2.3.2 Lanzas et al. (2011)

Several studies have found evidence to support the hypothesis that asymptomatic patients are a reservoir for *C. diff* bacteria. A study by [91] found that environmental contamination in hospitals continues despite treatment of symptomatic patients, suggesting that asymptomatic patients shed spores into the environment. An analysis by [76] observed that 51% of long-term care facility residents without *C. diff* infection were actually asymptomatically colonized and spores from asymptomatic patients were easily transferred to investigators’ hands. A study by [21] found that 3-18% of healthcare patients may be asymptomatically colonized with *C. diff*. The asymptomatic patient reservoir may be significantly contributing to new infections as well. According to [22], the best diagnostic test for *C. diff* colonization is relatively intensive and expensive. Other diagnostic tests that are less intensive or expensive are not as reliable. Thus, most healthcare facilities only test symptomatic admissions and patients for *C. diff*. Therefore, asymptomatic patients shed *C. diff* spores and contaminate the environment, but do not prompt implementation of control measures. An investigation by [18] provided evidence that asymptomatic patients newly admitted to a hospital are an important source of transmission of *C. diff*.

Lanzas et al. [50] formulated an epidemiological model of *C. diff* transmission to evaluate the relative contributions of asymptomatic and symptomatic patients to new colonizations within a healthcare setting. The study used data collected from six medicine wards at Barnes-Jewish Hospital in St. Louis, Missouri during the calendar year 2008 to help parameterize the model. The data included patient demographics, dates of hospital and ward admission, dates of discharges and transfers, laboratory tests, and medication exposures. Each ward contained around 30 beds each. On average, 153 patients were admitted per ward per month and 2.2 incident cases of symptomatic *C. diff* infection were reported per ward per month. In total there were 11,046 patients in the data set with 157 cases of *C. diff* infection.

Lanzas et al. included the following patient classes in their model: resistant to colonization (*R*), susceptible to colonization (*S*), asymptomatically colonized with protection against *C. diff* infection (*C*\(^+\)), asymptomatically colonized without protection against *C. diff* infection (*C*\(^-\)), and diseased (*D*). A schematic of the model is given in Figure 20. Resistant individuals (*R*) have not received antibiotic treatment and therefore have a normal gut microbiota and are resistant to *C. diff* colonization. Susceptible individuals (*S*) have received antibiotic treatment and therefore do not have a normal gut microbiota and are susceptible to *C. diff* colonization. Asymptomatically colonized individuals with protection against *C. diff* infection (*C*\(^+\)) have *C. diff* present in the gut, have had an appropriate immune response to the toxins produced by the bacteria, and do not display symptoms. Asymptomatically
colonized individuals without protection against \textit{C. diff} infection ($C^-$) have \textit{C. diff} present in the gut, have not had an appropriate immune response to the toxins produced by the bacteria, and are not displaying symptoms. Diseased individuals ($D$) are colonized individuals who are displaying symptoms of \textit{C. diff} infection. Since diseased individuals ($D$) receive antibiotic treatment, they return to the susceptible class ($S$) if the treatment is successful. Otherwise, they remain in the diseased class ($D$). A system of five ODEs deterministically described the transitions between the patient classes. The system was also simulated stochastically due to the small population size of the considered hospital ward.

The results of model analysis and simulations demonstrated that the three types of colonized patients ($C^+, C^-, D$) contributed similarly to new colonizations and the proportion of patients admitted as $C^-$ most strongly influenced the number of new cases. The study emphasized that asymptomatic patients are an important source of transmission of \textit{C. diff}.

The model in this thesis adds environmental reservoirs to the model formulated by Lanzas et al. and focuses on the effect of fomite touch frequency on \textit{C. diff} transmission. Specifically, this study investigates the contribution of high-touch frequency and low-touch frequency fomites, both of which can harbor spores shed by symptomatic and asymptomatic patients, in a hospital ward to new cases of \textit{C. diff} colonization among hospital patients. Additionally, this study determines the factors that influence their relative contributions.

\section*{2.4 Model Formulation}

\subsection*{2.4.1 Description of \textit{C. diff} Model}

This work aims to gain a better understanding of the dynamics of \textit{C. diff} transmission through environmental pathways by investigating the contribution of high-touch frequency and low-touch frequency fomites, both of which can harbor spores shed by symptomatic and asymptomatic patients, in a hospital ward to new cases of \textit{C. diff} colonization within hospital patients. Additionally, this study aims to determine the factors that influence their relative contributions. In order to address these inquiries, this work develops and analyzes an epidemiological model that incorporates four classes for the patient population and two classes for environmental reservoirs of \textit{C. diff}. Classes are summarized in Table 5 and a schematic of the model is given in Figure 21.

The four patient classes are similar to the patient classes in Lanzas et al. [50]: resistant ($R$), susceptible ($S$), asymptotically colonized ($C$), and diseased ($D$). Because antibiotic use is the most significant risk factor for colonization by \textit{C. diff}, resistant individuals ($R$) are defined as individuals that have not received antibiotic treatment. Therefore, they
have a normal gut microbiota and resistance to *C. diff* colonization. Likewise, susceptible individuals (*S*) are defined as individuals that have received antibiotic treatment. Therefore, they do not have a normal gut microbiota and are susceptible to *C. diff* colonization. Since a patient’s microbiota returns to normal after they have ceased taking antibiotics, susceptible individuals (*S*) can return to the resistant class (*R*). If a susceptible individual (*S*) is exposed to *C. diff* there is a chance they become colonized. Asymptomatically colonized individuals (*C*) are defined as individuals that have *C. diff* present in the gut but are not displaying symptoms. Diseased individuals (*D*) are defined as individuals that have *C. diff* present in the gut and are displaying symptoms of *C. diff* infection. Since diseased individuals (*D*) receive antibiotic treatment for *C. diff* infection, they return to the susceptible class (*S*) if the treatment is successful. Otherwise, they remain in the diseased class (*D*). Lanzas et al. [50] differentiated between colonized individuals with (*C*+) and without (*C*−) an appropriate immune response against *C. diff* infection. This model does not make this distinction because the goal of this work is not to evaluate the contribution of asymptomatic patients to the transmission of *C. diff*, as was the goal of Lanzas et al. [50]. Instead, this work investigates the contribution of environmental pathways, to which asymptomatic patients contribute, to the transmission of *C. diff* infection. Both types of asymptotically colonized patients (*C*+ and *C*−) shed spores that contribute to the bacterial spore population, and it is assumed that they both shed spores at the same rate. Instead of differentiating between colonized individuals with (*C*+) and without (*C*−) protection against *C. diff* infection, the transition rate from the asymptotically colonized class (*C*) to the diseased class (*D*) incorporates the fraction of colonized individuals who do not mount a sufficient immune response against the toxins produced by the bacteria. The remaining asymptotically colonized individuals are assumed to have mounted a sufficient immune response and stay in the asymptotically colonized class (*C*) for the duration of their hospital stay. Patients may be admitted into or discharged from any patient class. Discharge accounts for release from the hospital, transfer to another ward, or death.

Unlike previous models, this model incorporates two classes for the environmental reservoirs of *C. diff* to model the bacteria population as well as the patient population. The two classes for the environmental reservoirs are: spore density on high-touch frequency fomites (*P* _H_) and spore density on low-touch frequency fomites (*P* _L_). High-touch frequency fomites are interacted with more often by patients and are assumed to be cleaned daily and disinfected when a patient is discharged. Low-touch frequency fomites are interacted with less often by patients and are assumed to be disinfected when a patient is discharged. Examples of high-touch frequency fomites include bed rails, tray tables, IV poles, doorknobs, sinks, and toilets. Examples of low-touch frequency fomites include curtains, furniture,
thermostats, soap and paper towel dispensers, and trash cans. Both asymptomatically colonized (C) and diseased (D) individuals contribute to the level of pathogen on both types of surfaces. If a susceptible individual (S) is exposed to C. diff there is a chance they become asymptomatically colonized (C). This depends on which type of surface they have come in contact with, the spore density on that surface, the chance of transferring C. diff spores off of the surface, and the chance of becoming colonized from those spores. (This could also depend on the duration of a contact with a fomite, but is not considered in this model.)

2.4.2 Parameterization of C. diff Model

Model parameters are described below and summarized in Table 6.

Patient Parameters

The admission proportions for each patient class \((a_R, a_S, a_C, a_D)\) are taken from [85], who used and updated values from Lanzas et al. [50]. Lanzas et al. [50] determined admission proportions based on collected data from Barnes-Jewish Hospital in St. Louise, Missouri. In particular, they determined the proportion of patients admitted as susceptible \((a_S)\) was 0.22 and the proportions of patients admitted as asymptomatically colonized with and without protection were 0.01 each, together making the proportion of patients admitted as asymptomatically colonized \((a_C)\) 0.02. However, [3] suggests that \(a_C\) is actually as high as 0.15. In [85], \(a_C\) was updated from 0.02 to 0.15. \(a_S\) was subsequently updated from 0.22 to 0.09 since the sum of all of the admission proportions must be 1.

Lanzas et al. [50] determined from their data that a prescription for an antibiotic was written every two days, on average. Thus, the antibiotic prescription rate \((\alpha)\) is the inverse of the length between prescriptions, or 0.5 per day. After ceasing antibiotic treatment, the gut returns to normal after 30 days, on average, according to [73]. Thus, the rate at which the gut restores its resistance to C. diff colonization \((\theta)\) is the inverse of the time to restoration, or 0.033 per day. For approximately 80% of patients with C. diff infection, symptoms resolve within a 10 day treatment of vancomycin or metronidazole according to [63]. Thus, the successful treatment rate \((\varepsilon)\) is the product of the proportion of successfully treated patients and the inverse of the treatment duration, or 0.08 per day. Lanzas et al. [50] determined from their data that approximately 60% of patients had an appropriate immune response to the toxins produced by C. diff. According to [16], those that do not mount an appropriate immune response start to display symptoms after 6 days, on average. Thus, the disease rate of asymptomatically colonized patients \((\phi)\) is the product of the compliment
of the proportion of patients with an appropriate immune response and the inverse of the incubation period, or 0.024 per day.

Lanzas et al. [50] determined the average length of stay for patients of each class from their data. The discharge rate for each patient class \((k_R, k_S, k_C, k_D)\) is the inverse of their average duration in the hospital. The discharge rates for the susceptible and asymptotically colonized classes are assumed to be the same \((k_S = k_C = k)\) because asymptotically colonized patients \((C)\) are not tested for \(C.\) diff and therefore cannot be differentiated from susceptible patients \((S)\). Also, asymptotically colonized patients \((C)\) are asymptomatic so they do not require additional treatment for \(C.\) diff infection and do not need to remain in the hospital longer than susceptible patients \((S)\) due to \(C.\) diff infection. The total discharge rate \((\delta(t))\), derived in Section 2.4.3) is a function of time since it depends on the size of the patient classes, which are functions of time.

It is assumed that the total ward population is constant at the capacity of the hospital ward \((N = 30)\), so admission into the hospital ward can only occur if a patient is discharged. Thus, the admission rates into patient classes are a product of the admission proportions \((a_R, a_S, a_C, a_D)\) and the total discharge rate \((\delta(t))\).

**Shedding Parameters**

Asymptomatically colonized \((C)\) and diseased \((D)\) patients expel \(C.\) diff spores from the body through bowel movements and diarrhea, respectively. This process is known as bacterial shedding. Contamination of surfaces occurs when shed spores are deposited on surfaces through direct contact with soiled hands of patients. Since \(C.\) diff spores can survive on surfaces for long periods of time, it is assumed in the model that natural spore death is negligible and spores are only killed through cleaning or disinfecting. A study by [17] observed the number of hand-touch contacts by patients, healthcare workers, and visitors with any hospital environmental item. Over a period of 66 hours, they observed 12 patients make 470 contacts, 311 of which were with high-touch frequency fomites and 159 were with low-touch frequency fomites. Based on this data, patients have 9.424 contacts per day per individual with high-touch frequency fomites and 4.818 contacts per day per individual with low-touch frequency fomites. An analysis by [80] cultured stool, skin, and environmental samples for \(C.\) diff from patients with \(C.\) diff infection before, during, and after treatment. They found that a contact with an asymptomatic patient resulted in 3.333 spores on average and a contact with a symptomatic patient resulted in 7 spores on average on the hand of the person contacting the patient. With the average surface area of a hand being 0.054 square meters, according to [44], this results in 0.006 spores per square centimeter per contact.
with an asymptomatically colonized patient \((C)\) and 0.013 spores per square centimeter per contact with a diseased patient \((D)\). The shedding rates \((\rho_{CH}, \rho_{CL}, \rho_{DH}, \rho_{DL})\) of asymptomatically colonized \((C)\) or diseased \((D)\) individuals onto high-touch or low-touch frequency fomites are the product of the contacts per day with a fomite and the spores per square centimeter per contact from a patient. These calculations are summarized in Table 7.

Cleaning Parameters

The model assumes that both types of fomites are disinfected after a patient is discharged and only high-touch surfaces are cleaned (not disinfected) daily. However, since this model is a continuous time model, these are not discrete disinfecting or cleaning events but per day rates. An analysis by [81] swabbed fomites highly interacted with by patients in nine acute-care hospitals and two long-term care facilities in four states to determine the typical microbial burden on high-touch surfaces after daily cleaning and disinfecting upon discharge. They observed that after daily cleaning, 34% of sites tested contained pathogen and after disinfecting upon discharge, 17% of sites tested contained pathogen. For this model, the rate at which \(C.\ diff\) is killed on high-touch surfaces due to daily cleaning \((\mu)\) is set to 0.66 per day, meaning 34% of spores remain on surfaces and 66% of spores are killed per day due to daily cleaning.

Also, this model does not describe the behavior of individual patients and spores in individual rooms. It describes average mass action dynamics for homogeneously mixed classes of patients and classes of surfaces that contain spores. Thus, when considering disinfection upon discharge, which would only kill spores on surfaces in the discharged patient’s room, a term is needed to describe the proportion of all spores that are associated with a single patient and that are killed when disinfected. Therefore, the disinfecting rate upon discharge is the product of the total discharge rate \((\delta(t))\), the total ward population \((N)\), and the proportion of spores killed per individual discharged \((\sigma)\). From [81], the proportion of spores killed per individual discharge is set to 0.83 per individual, meaning 17% of spores remain on surfaces and 83% of spores are killed after disinfecting upon the discharge of an individual.

Force of Infection Parameters

The force of infection of an epidemiological model is the rate at which susceptible individuals contract a disease. In this model the force of infection is the rate at which susceptible individuals \((S)\) become asymptomatically colonized \((C)\) and is assumed to have a type II
functional response [37], where the rate of successful colonization increases as pathogen level in the environment increases and the colonization rate saturates at high levels of pathogen. Equation (2.1) is an example of a type II functional response where the rate of successful colonization is the rate at which a contact with a contaminated fomite results in a transfer of spores.

\[
\lambda = \frac{P}{K + P}
\]  \hspace{1cm} (2.1)

where
\begin{align*}
\lambda &= \text{successful colonization rate} \\
P &= \text{pathogen density on contacted fomite} \\
K &= \text{half-saturation constant}
\end{align*}

Figure 22 graphically illustrates the type II functional response in Equation (2.1) for two different values of the half-saturation constant \(K\). The half-saturation constant \(K\) is the level of pathogen that would make the successful colonization rate half of its maximum value. Equation (2.1) assumes that if there is a transfer of spores from a contact with a contaminated fomite, the individual who contacted the contaminated surface will become colonized. The maximum colonization rate is 1, thus, \(K\) would be the pathogen level at which the rate is 0.5, or at which 50% of susceptibles \((S)\) will become asymptotically colonized \((C)\) when they contact a contaminated fomite. In a study by [51], susceptible mice were held in cages contaminated with \(C.\ diff\) spores isolated from a multi-hospital outbreak. They found that 5-10 spores per square centimeter in a cage resulted in 50% of the mice in the cage becoming colonized. This model uses 7.5 spores per square centimeter for the half-saturation constant \(K\).

The force of infection in Equation (2.1) is not a realistic representation of the transmission of \(C.\ diff\). In reality, an individual may pick up spores off of a surface but not become colonized. Multiplying the rate at which a contact results in a transfer of spores by the rate at which a transfer of spores results in a colonization \((\beta)\) will give a more realistic force of infection, or successful colonization rate. If a susceptible individual \((S)\) comes into contact with a high-touch frequency fomite, the successful colonization rate is described by Equation (2.2). If a susceptible individual \((S)\) comes into contact with a low-touch frequency fomite, the successful colonization rate is described by Equation (2.3).
\[
\lambda_H = \beta \omega \frac{P_H}{K + P_H} \\
\lambda_L = \beta \frac{P_L}{K + P_L}
\]  

(2.2)

(2.3)

where

\[
\lambda_H = \text{successful colonization rate due to high-touch fomites [day}^{-1}\text{]}
\]

\[
\lambda_L = \text{successful colonization rate due to low-touch fomites [day}^{-1}\text{]}
\]

\[
P_H = \text{pathogen density on high-touch fomites [spores} \cdot \text{cm}^{-2}\text{]}
\]

\[
P_L = \text{pathogen density on low-touch fomites [spores} \cdot \text{cm}^{-2}\text{]}
\]

\[
K = \text{half-saturation constant [spores} \cdot \text{cm}^{-2}\text{]}
\]

\[
\beta = \text{colonization rate upon transfer of spores from a fomite [day}^{-1}\text{]}
\]

\[
\omega = \text{weighting constant for high-touch fomites [dimensionless]}
\]

A high-touch frequency fomite is defined as a surface that is contacted more often. Thus, the force of infection, or successful colonization rate due to high-touch fomites has an extra weighting parameter \((\omega \geq 1)\) to account for the higher frequency of contacts. In the study [17], patients made 470 contacts with surfaces in a hospital room, 311 of which were with high-touch frequency fomites and 159 were with low-touch frequency fomites. Therefore, a patient is 1.96 times more likely to contact a high-touch frequency fomite than a low-touch frequency fomite. The parameter \(\omega\) is set to 1.96 to weight the force of infection for high-touch frequency fomites. Since patients interact with both high-touch and low-touch frequency fomites, the overall force of infection is the sum of the successful colonization rates for each surface, described in Equation (2.4).

\[
\lambda = \beta \left( \omega \frac{P_H}{K + P_H} + \frac{P_L}{K + P_L} \right)
\]  

(2.4)
where

\[ \lambda = \text{successful colonization rate due to high-touch and low-touch fomites} \ [\text{day}^{-1}] \]
\[ P_H = \text{pathogen density on high-touch fomites} \ [\text{spores} \cdot \text{cm}^{-2}] \]
\[ P_L = \text{pathogen density on low-touch fomites} \ [\text{spores} \cdot \text{cm}^{-2}] \]
\[ K = \text{half-saturation constant} \ [\text{spores} \cdot \text{cm}^{-2}] \]
\[ \beta = \text{colonization rate upon transfer of spores from a fomite} \ [\text{day}^{-1}] \]
\[ \omega = \text{weighting constant for high-touch fomites} \ [\text{dimensionless}] \]

To estimate the value of \( \beta \), the force of infection is evaluated at half of the maximum colonization rate (\( \lambda_{\text{max}} \)), when pathogen levels are equal to the half-saturation constant. It is assumed that \( \lambda_{\text{max}} = 1 \). Using \( P_H = P_L = K \) and \( \lambda = 0.5 \cdot \lambda_{\text{max}} = 0.5 \) in Equation (2.4) and solving for \( \beta \) gives Equation (2.5).

\[
0.5 = \beta \left( 1.96 \frac{K}{K + K} + \frac{K}{K + K} \right) \tag{2.5}
\]

\[ \implies \beta = 0.338 \]

Thus, 33.8% of contacts with contaminated fomites that resulted in a transfer of spores result in colonization per day.

2.4.3 C. diff Model

The dynamics of \( C. \ diff \) transmission, including environmental pathways through contact with high-touch and low-touch frequency fomites, are modeled deterministically using a six-dimensional system of ODEs describing the mass action transitions between the four patient classes: resistant individuals \( (R) \), susceptible individuals \( (S) \), asymptomatically colonized individuals \( (C) \), and diseased individuals \( (D) \), and the two environmental reservoir classes: spore density on high-touch frequency fomites \( (P_H) \) and spore density on low-touch frequency fomites \( (P_L) \). The model is given by the system in Equation (2.6), where \( ' \) denotes
differentiation with respect to time. Classes are described in Table 5 and parameters are described in Table 6.

\[
\begin{align*}
R' &= a_R \delta N - (k_R + \alpha)R + \theta S \\
S' &= a_S \delta N + \alpha R - (k + \theta)S - \beta \left( \frac{P_H}{K+P_H} + \frac{P_L}{K+P_L} \right) S + \varepsilon D \\
C' &= a_C \delta N + \beta \left( \frac{P_H}{K+P_H} + \frac{P_L}{K+P_L} \right) S - (k + \phi)C \\
D' &= a_D \delta N + \phi C - (k_D + \varepsilon)D \\
P'_H &= \rho_{CH} C + \rho_{DH} D - (\sigma \delta N + \mu) P_H \\
P'_L &= \rho_{CL} C + \rho_{DL} D - \sigma \delta N P_L
\end{align*}
\]  

(2.6)

The total ward population is the sum of the patients in each patient class, given in Equation (2.7). Taking the derivative of Equation (2.7) with respect to time, plugging in the expressions for \( R' \), \( S' \), \( C' \), and \( D' \) from the system in Equation (2.6), and using the fact that the sum of the admission proportions must be one \( a_R + a_S + a_C + a_D = 1 \) gives the equation for \( N' \) in Equation (2.8). It is assumed that the total ward population is constant, so \( N' = 0 \). Thus, Equation (2.9) gives the equation for \( \delta(t) \), the total discharge rate.

\[
N = R + S + C + D
\]  

(2.7)

\[
\implies N' = R' + S' + C' + D' = \delta N - k_R R - k(S + C) - k_D D
\]  

(2.8)

\[
N' = 0 \implies \delta(t) = \frac{1}{N}(k_R R(t) + k(S(t) + C(t)) + k_D D(t))
\]  

(2.9)
where

\[
\begin{align*}
N &= \text{total ward population [individuals]} \\
R &= \text{resistant [individuals]} \\
S &= \text{susceptible [individuals]} \\
C &= \text{asymptotically colonized [individuals]} \\
D &= \text{diseased [individuals]} \\
\delta(t) &= \text{total discharge rate [day}^{-1}] \\
k_R &= \text{discharge rate of resistant individuals [day}^{-1}] \\
k &= \text{discharge rate of susceptible and asymptotically colonized individuals [day}^{-1}] \\
k_D &= \text{discharge rate of diseased individuals [day}^{-1}]
\end{align*}
\]

The discharge rates \(k_R\), \(k\), and \(k_D\) and the total ward population \(N\) are constant, and \(R\), \(S\), \(C\), and \(D\) depend on time. Thus, \(\delta(t)\) must depend on time. Substituting Equation (2.9) into the system in Equation (2.6) gives the system in Equation (2.10).

\[
\begin{align*}
R' &= (a_R - 1)k_R - \alpha)R + (a_R k + \theta)S + a_R kC + a_R k_D D \\
S' &= (a_S k_R + \alpha)R + ((a_S - 1)k - \theta - \beta \left( \frac{P_H}{K + P_H} + \frac{P_L}{K + P_L} \right) K + P_L) + a_S kC + (a_S k_D + \varepsilon)D \\
C' &= a_C k_R R + \left( a_C k + \beta \left( \frac{P_H}{K + P_H} + \frac{P_L}{K + P_L} \right) \right) S + ((a_C - 1)k - \phi)C + a_C k_D D \\
D' &= a_D k_R R + a_D k S + (a_D k + \phi)C + ((a_D - 1)k_D - \varepsilon)D \\
P'_H &= -k_R \sigma P_H R - k \sigma P_H S + (\rho_{CH} - k \sigma P_H)C + (\rho_{DH} - k_D \sigma P_H) D - \mu P_H \\
P'_L &= -k_R \sigma P_L R - k \sigma P_L S + (\rho_{CL} - k \sigma P_L)C + (\rho_{DL} - k_D \sigma P_L) D
\end{align*}
\]

The solution to Equation (2.10) is simulated by the ODE solver ode45 in MATLAB [62], a medium order numerical method for nonstiff ODE systems. Figure 23 shows the numerical solution of the \(C.\ diff\) model described by the system of ODEs in Equation (2.10) for a total ward population of \(N = 30\). The numerical solution shows the time courses over 40 days of the system variables from Table 5 with reference parameter values from Table 6. Initial conditions for the patient classes are determined by the admission proportions and are rounded to the nearest, nonzero integer: \(S_0 = a_S \cdot N \approx 3\) individuals, \(C_0 = a_C \cdot N \approx 5\) individuals, \(D_0 = [a_D \cdot N] = 1\) individuals, \(R_0 = N - S_0 - C_0 - D_0 = 21\) individuals. The
initial conditions for the environmental reservoir classes are $P_{H_0} = P_{L_0} = 0.01$ spores per cm$^2$.

### 2.4.4 Predicted Metrics of $C.\text{ diff}$ Model

#### Incidence

For an infectious disease, incidence measures the number of new infections over a period of time. In this study, the incidence of new diseased cases is calculated as well as the incidence of new asymptotically colonized cases, since both patient classes contribute to the transmission of $C.\text{ diff}$ in a healthcare setting. However, from the formulation of the model, only new asymptotically colonized cases can be linked with the environmental reservoir class that caused the colonization. Incidence of diseased ($I_D$) is calculated as the integral over the time period of the rate at which asymptotically colonized patients become diseased, or the solution to the ODE in Equation (2.11). Likewise, incidence of asymptotically colonized ($I_C$) is calculated as the integral over the time period of the rate at which susceptible patients become asymptotically colonized, or the solution to the ODE in Equation (2.12). Since the rate at which susceptible patients become asymptotically colonized depends on the rates attributed to contacts with high-touch and low-touch frequency fomites (Equations (2.2) and (2.3), respectively), the incidence of asymptotically colonized due to a contact with a fomite ($I_{CH}$ and $I_{CL}$) is calculated as the integral over the time period of the rate due to a contact with that fomite, or the solutions to the ODEs in Equations (2.13) and (2.14). For the incidence of asymptotically colonized, $I_C = I_{CH} + I_{CL}$.

$$I'_D = \phi C \quad (2.11)$$

$$I'_C = \beta \left( \omega \frac{P_H}{K + P_H} + \frac{P_L}{K + P_L} \right) S \quad (2.12)$$

$$I'_{CH} = \beta \left( \omega \frac{P_H}{K + P_H} \right) S \quad (2.13)$$

$$I'_{CL} = \beta \left( \frac{P_L}{K + P_L} \right) S \quad (2.14)$$
where

\[ I_D = \text{incidence of new diseased [individuals]} \]
\[ I_C = \text{incidence of new asymptomatic colonizations [individuals]} \]
\[ I_{CH} = \text{incidence of new asy. colonizations due to high-touch fomites [individuals]} \]
\[ I_{CL} = \text{incidence of new asy. colonizations due to low-touch fomites [individuals]} \]
\[ S = \text{susceptible [individuals]} \]
\[ C = \text{asymptomatically colonized [individuals]} \]
\[ P_H = \text{pathogen density on high-touch fomites [spores \cdot cm^{-2}]} \]
\[ P_L = \text{pathogen density on low-touch fomites [spores \cdot cm^{-2}]} \]
\[ \phi = \text{disease rate [spores \cdot cm^{-2}]} \]
\[ K = \text{half-saturation constant [spores \cdot cm^{-2}]} \]
\[ \beta = \text{colonization rate upon transfer of spores from a fomite [day^{-1}]} \]
\[ \omega = \text{weighting constant for high-touch fomites [dimensionless]} \]

To have perspective on the incidence values, the total number of patients who go through the hospital ward in the time period is needed. Since the hospital population is assumed to be constant at the capacity of the ward, admission of a patient can only occur if a patient is discharged. Thus, the total number of patients will be the total number of patients discharged, or the integral of the rate at which patients are discharged. The solution to the ODE in Equation (2.15) gives the total number of patients.

\[ M' = \delta N = k_R R + k(S + C) + k_D D \] (2.15)
where

\[
M = \text{total number of patients [individuals]}
\]

\[
N = \text{total ward population of hospital ward [individuals]}
\]

\[
R = \text{resistant [individuals]}
\]

\[
S = \text{susceptible [individuals]}
\]

\[
C = \text{asymptomatically colonized [individuals]}
\]

\[
D = \text{diseased [individuals]}
\]

\[
\delta(t) = \text{total discharge rate [day}^{-1}\text{]}
\]

\[
k_R = \text{discharge rate of resistant individuals [day}^{-1}\text{]}
\]

\[
k = \text{discharge rate of susceptible and asymptomatically colonized individuals [day}^{-1}\text{]}
\]

\[
k_D = \text{discharge rate of diseased individuals [day}^{-1}\text{]}
\]

Incidence results for the \textit{C. diff} model described by the system of ODEs in Equation (2.10) for a total ward population of \( N = 30 \) over 40 days of the system variables from Table 5 with reference parameter values from Table 6 and initial conditions \( R_0 = 21, S_0 = 3, C_0 = 5, D_0 = 1, \) and \( P_{H_0} = P_{L_0} = 0.01 \) are summarized in Table 10.

**Basic Reproduction Number**

The basic reproduction number \((R_0)\) is defined as the expected number of secondary cases produced by a single case in a completely susceptible population. This metric conveys the transmissibility of a pathogen. If \( R_0 < 1 \) then a few infected individuals introduced to a completely susceptible population will fail to replace themselves and the epidemic will die out in the long run. If \( R_0 > 1 \) then a few infected individuals introduced to a completely susceptible population will infect others beyond replacing themselves and the epidemic will spread. Generally, the larger the value of \( R_0 \), the harder it is to control an epidemic. For example, \( R_0 \) is cited to be 1.8 for the 1918 influenza outbreak [6] and is cited to be 12-18 for measles [32]. \( R_0 \) can be used to calculate important figures like the proportion of the population that needs to be vaccinated to prevent the spread of a disease.

For this model, the basic reproduction number is the average number of secondary colonizations produced by a primary \textit{C. diff} colonization (\( C \) or \( D \) patient) in a \textit{C. diff}-free hospital ward. \( R_0 \) is based on the linearization of the ODE model about a disease-free equilibrium. At a disease-free equilibrium, there would be an absence of colonization and pathogen. Plugging \( C = D = P_{H} = P_{L} = 0 \) into Equation (2.10) and setting Equation (2.10) equal to zero does not give a non-trivial, biologically feasible disease-free equilibrium point.
In this study, biologically feasible refers to satisfying the constrain $N = R + S + C + D$. Without a disease-free equilibrium, there cannot be a scenario in which $C. \text{diff}$ infections are non-existent. As a result, the basic reproduction number cannot be calculated. This is due to the fact that one of the assumptions needed to have the existence of a disease-free equilibrium is not met by the model [8]. A criterion for the existence of a disease-free equilibrium is that all new infections are secondary infections arising from infected hosts and not due to immigration of individuals into a diseased compartment. Since patients admitted into the hospital could be asymptomatically colonized or diseased, all new colonizations are not necessarily secondary colonizations.

### 2.5 Stochastic Simulations

#### 2.5.1 Gillespie Stochastic Simulation Algorithm

The GSSA [30] was formulated to answer the following question:

> If a fixed volume $V$ contains a spatially uniform mixture of $N$ chemical species which can interact through $M$ specified chemical reaction channels, then given the numbers of molecules of each species present at some initial time, what will these molecular population levels be at any later time?

A deterministic model would describe the time course of such a system as a continuous time, wholly predictable process governed by a set of coupled ODEs called the ‘reaction-rate equations’. The solution of the system of ODEs would provide the molecular population levels at a given time. A stochastic model would describe the time course of such a system as a discrete, random-walk process governed by a single ODE called the ‘master equation’. The solution of the master equation would give the probability distribution of the molecular population levels at a given time. The deterministic model would describe the average behavior of the stochastic model. The stochastic model is more realistic than the deterministic model since collisions between molecules occur randomly and molecular population levels change by integer values in discrete time steps. This is especially true for small molecular population levels, when dynamics may be sensitive to stochasticity. However, master equations can be difficult to work with and there are no efficient algorithms to solve them. The GSSA provides a way to make exact numerical calculations within the framework of the stochastic model without directly solving the master equation. The GSSA uses a Markov Chain Monte Carlo (MCMC) procedure to sample from the solution of the
master equation at each time point, creating a trajectory for a possible time course of a system.

The GSSA views reactions between chemical species as discrete events. Based only on the current molecular population levels, not past levels, the MCMC procedure determines the molecular population levels at the next time step by probabilistically determining that time step and what type of reaction will occur then. For chemical species 1, ..., N and reactions 1, ..., M, the state of the system at time $t$, given by $X(t) = [X_1(t), X_2(t), ..., X_N(t)]$, is updated by the following steps of the GSSA:

**Step 0.** Set the reaction counter as $n = 0$ and define the initial time as $t = 0$, the initial state as $X(0)$, and the reaction probabilities $c_j$ for $j = \{1, ..., M\}$. ($c_j$ is the probability that a particular combination of chemical species will react via the $j$th channel in the small time step $(t, t + \tau)$.)

**Step 1.** Calculate the propensity functions $a_j$ and the sum of the propensities $a_0$. ($a_j$ is the probability that a reaction will occur via the $j$th channel in $(t, t + \tau)$ given the system is in the present state $X(t)$. $a_j = c_j h_j$ where $h_j$ is the number of combinations of chemical species available to react via the $j$th channel when the system is in the present state $X(t)$.)

**Step 2.** Generate two random numbers, $r_1$ and $r_2$, from a uniform distribution on $[0, 1]$. Calculate the time to the next reaction, $\tau$, and the reaction that occurs next, $j$. (The calculations of $\tau$ and $j$ are described below.)

**Step 3.** Set the reaction counter to $n = n + 1$ and the next time to $t = t + \tau$, update the state to $X(t + \tau)$ based on what reaction occurred, and return to Step 1 unless $a_0 = 0$ or $t + \tau = t_{final}$.

**Calculation of time to next reaction**

The occurrence of reactions are assumed to follow a Poisson point process, meaning reactions occur at known, constant rates and independently of the time since the last reaction. The probability density function of the Poisson distribution, which describes the probability of a reaction occurring, is given by Equation (2.16).

$$P(x|\lambda) = \frac{\lambda^x}{x!} e^{-\lambda}, \quad x \in [0, \infty)$$  

(2.16)
where

\[ P = \text{probability of reaction occurring} \]
\[ x = \text{number of times reaction occurs} \]
\[ \lambda = \text{number of times reaction occurs on average} \]

Equation (2.16) represents the probability of a reaction occurring within a given interval exactly \( x \) times given that the reaction occurs within the given interval \( \lambda \) times on average.

The exponential distribution in Equation (2.17) describes the probability of the time interval between reactions in a Poisson point process ([19] proves this relationship) and has a mean of \( 1/\lambda \).

\[ P(\tau | \lambda) = \lambda e^{-\lambda \tau}, \quad \tau \in [0, \infty) \tag{2.17} \]

where

\[ P = \text{probability of time interval} \]
\[ \tau = \text{time interval to next reaction} \]
\[ \lambda = \text{number of times reaction occurs on average} \]

Equation (2.17) represents the probability of the time interval \( \tau \) being the interval to the next reaction given the reaction occurs in the interval \( \lambda \) times on average. The probability that any of the \( M \) reactions will occur in the time interval \( (t, t + \tau) \), given the system is in the present state \( X(t) \), is the sum of the propensity functions \( a_0 = \sum_{j=1}^{M} a_j \). Thus, the mean of the Poisson distribution is \( a_0 \) and the mean of the exponential distribution is \( 1/a_0 \). The time to the next reaction \( (\tau) \) is chosen from the exponential distribution in Equation (2.18).

\[ P(\tau | a_0) = a_0 e^{-a_0 \tau} \tag{2.18} \]

where

\[ P = \text{probability of time interval} \]
\[ \tau = \text{time interval to next reaction} \]
\[ a_0 = \text{sum of propensity functions} \]

Taking the random number \( r_1 \), chosen in Step 2 of the Gillespie Algorithm, as \( P(\tau | a_0) \) gives the value for \( \tau \) in Equation (2.19).
\[ \tau = \frac{1}{a_0} \ln \left( \frac{a_0}{r_1} \right) \]  

(2.19)

where

\[ \tau = \text{time interval to next reaction} \]
\[ r_1 = \text{random number chosen from uniform distribution on } [0,1] \]
\[ a_0 = \text{sum of propensity functions} \]

Calculation of which reaction occurs

The probability that reaction \( j = \{1, ..., M\} \) is the next reaction is \( a_j/a_0 \). Consider lining up the probabilities for all \( j = \{1, ..., M\} \) on the number line between 0 and 1. The \( j \) for which the random number \( r_2 \), from Step 2 of the Gillespie Algorithm, is greater than \( \sum_{k=1}^{j-1} a_k/a_0 \) and less than or equal to \( \sum_{k=1}^{j} a_k/a_0 \) will be the reaction that occurs next.

2.5.2 Stochastic Simulations of C. diff Model

The ODE model given by the system in Equation (2.10) assumes accuracy based on average behavior. However, hospital wards have small population sizes, including the considered ward size of \( N = 30 \) in this study. Thus, dynamics can be sensitive to stochasticity, i.e., a particular outbreak of C. diff in a hospital ward may not necessarily follow the behavior of an average outbreak. Instead of describing potential time courses of molecular population levels incorporating the probabilistic occurrence of reactions, in this study stochastic simulations via the GSSA show particular time courses of the transmission of C. diff incorporating the probabilistic occurrence of events, or interactions among the state variables \( X(t) = [R(t), S(t), C(t), D(t), P_H(t), P_L(t)] \). Examples of events include the discharge of a patient, the prescription of an antibiotic, and the shedding of spores onto a fomite. The state variables are involved in 15 different events, summarized in Table 8, along with the event propensity functions and how the state variables are updated when an event occurs. The propensity function of an event is the product of the rate at which that event occurs and the size of the affected state variable at that time. For example, for the prescription of an antibiotic event, the propensity function is the product of the rate at which antibiotics are prescribed (\( \alpha \)) and the size of the affected state variable (\( R(t) \)). When this event occurs at time \( t + \tau \), one resistant individual becomes susceptible, \( R(t + \tau) = R(t) - 1 \) and \( S(t + \tau) = S(t) + 1 \), and all other state variables are unchanged.
Since it is assumed that the total ward population is constant at the capacity of the hospital ward, admission into the hospital ward can only occur if a patient is discharged. Thus, a discharge event triggers an admission. When a patient is discharged, the class a new patient is admitted into is randomly chosen, weighted by the admission proportions. To track the total number of patients that go through the hospital ward, a counter variable starting at $N = 30$, increases by one with each discharge event. Also, when a patient is discharged, both high-touch and low-touch frequency fomites are disinfected. Thus, as a result of a discharge event, the spore density on high-touch ($P_H$) and low-touch ($P_L$) frequency fomites is reduced by the proportion of spores killed when fomites are disinfected due to an individual discharge ($\sigma$).

To track colonization events, or incidence, four counter variables were created in the algorithm. When a colonization event happens due to a type of fomite, the counter for the cases due to that type of fomite and the counter for the total number of colonizations increase by one. When a disease event happens, the counter for the total number of diseased increases by one. Incidence results are compared to the incidence results of the ODE model and are summarized in Table 10. When a daily cleaning event occurs, the spore density on high-touch frequency fomites ($P_H$) is reduced by the proportion of spores killed due to daily cleaning per individual, $\mu/N$. The daily cleaning event occurs at a rate of once per day and affects all patient state variables. Thus, the propensity function is

$$N = 1 \cdot (R(t) + S(t) + C(t) + D(t)).$$

Shedding rates, $\rho_{ij}, i = \{C, D\}, j = \{H, L\}$, are determined by multiplying the contacts per day per individual, $cpd_{j}, j = \{H, L\}$ by the spores per square centimeter transferred per contact, $spc_{i}, i = \{C, D\}$. Thus, the propensity function for a shedding event is the contacts per day per individual, $cpd_{j}, j = H, L$, multiplied by the number of individuals in the patient class for the shedding patient ($C$ or $D$). The pathogen density of the fomite shed on increases by the spores per square centimeter transferred per contact, $spc_{i}, i = \{C, D\}$.

Figure 24 shows 100 potential trajectories of the $C.\text{diff}$ model generated by the GSSA with the events in Table 8 for a total ward population of $N = 30$. The 100 potential trajectories show possible time courses over 40 days of the system variables from Table 5 with reference parameter values from Table 6. Initial conditions for the patient classes are determined by the admission proportions and are rounded to the nearest, nonzero integer: $S_0 = a_S \cdot N \approx 3$ individuals, $C_0 = a_C \cdot N \approx 5$ individuals, $D_0 = \lceil a_D \cdot N \rceil = 1$ individuals, $R_0 = N - S_0 - C_0 - D_0 = 21$ individuals. The initial conditions for the environmental reservoir classes are $P_{H0} = P_{L0} = 0.01$ spores per cm$^2$. Figure 25 shows the shaded area that the middle 95% of the 100 trajectories falls within. Figures 26, 27, and 28 show the ODE solution compared to the 100 potential trajectories generated by the GSSA and the middle 95% of the trajectories.
2.6 Results

The model of *C. diff* transmission including environmental pathways in a hospital ward is described deterministically by the system of ODEs in Equation (2.10) and simulated stochastically by the GSSA with events in Table 8 for system variables in Table 5. Five different scenarios consider a total ward population of $N = 30$ over 40 days. Parameter values and initial conditions are varied in each scenario as summarized in Table 9. In all scenarios, the average behavior of the stochastic simulations generated by the GSSA match the ODE behavior. Average behavior shows that in all scenarios around three-quarters of the incidence of asymptomatically colonized is due to a contact with a high-touch frequency fomite and around one-quarter is due to a contact with a low-touch frequency fomite. This demonstrates that even with the extra daily cleaning of high-touch frequency fomites, most colonizations result from the larger frequency of contacts with these surfaces. Individual trajectories generated by the GSSA show behaviors that the ODE cannot show, and demonstrate that extreme cases can occur. Two metrics are used to describe the variation in the individual trajectories: the range of the middle 95% of trajectories at each time point and the variance in the trajectories at each time point. The range of the middle 95% of trajectories at each time point is the difference in the 97.5th percentile and the 2.5th percentile at that time. The mean and maximum of each metric for the asymptomatically colonized and diseased patient classes are given in Tables 15 and 16. For reference, the data from Lanzas et al. [50] had 2.2 diseased cases per ward per month, on average, in six wards over 12 months and 11,046 total patients, resulting in an incidence of diseased as 1.43%.

Scenario #0 uses the reference parameter values from Table 6 and initial conditions described in Section 2.4.3. Figures 23-28, show the time courses and Tables 10, 15, and 16 summarize the results of Scenario #0. The ODE and the average of the 100 trajectories predict around 7 asymptomatically colonized individuals in approximately 250 total patients over 40 days. Individual trajectories show that incidence of asymptomatically colonized ranges from 1 to 15 individuals. Going from 7 to 1 individual is an approximate 86% decrease and going from 7 to 15 individuals is an approximate 114% increase in the number of individuals. The average and maximum range of the middle 95% of trajectories is 8.29 and 11, respectively, meaning that at any given time the difference between the number of asymptomatically colonized individuals between two time courses could be 8.29 individuals on average, and could be as high as 11 individuals. This does not take into account the 5% of the most extreme trajectories. Likewise, the ODE and the average of the 100 trajectories predict around 5-6 diseased individuals in approximately 250 total patients over 40 days. Individual trajectories show that incidence of diseased ranges from 0 to 7 individuals (not
shown in Table 10). Going from 5.5 to 0 individuals is a 100% decrease and going from 5.5 to 7 individuals is an approximate 27% increase in the number of individuals. The average and maximum range of the middle 95% of trajectories is 3.69 and 5, respectively, meaning that at any given time the difference between the number of diseased individuals between two time courses could be 3.69 individuals on average, and could be as high as 5 individuals. Again, this does not take into account the 5% of the most extreme trajectories.

Since the difficulty of quantifying the density of bacteria on surfaces can lead to under-estimation, Scenario #1 considers an increased initial pathogen level in the environmental reservoir, i.e., larger initial conditions for the high-touch and low-touch frequency fomites ($P_{H_0}$ and $P_{L_0}$). Figure 29 and Tables 11, 15, and 16 summarize the results of Scenario #1. Time courses for Scenario #1 show a slight initial decrease in the environmental reservoir classes ($P_H$ and $P_L$) not seen in the time courses of Scenario #0, but incidence results are otherwise nearly identical to Scenario #0, except for increased range of the middle 95% of trajectories and variance in trajectories. The average and maximum range of the middle 95% of trajectories for asymptomatically colonized is 8.86 and 12 individuals, respectively, and the average and maximum range of the middle 95% of trajectories for diseased is 3.75 and 5 individuals, respectively. It appears that incidence is similar to Scenario #0 because initially, there are not enough asymptomatically colonized and diseased individuals shedding onto fomites to counteract cleaning and disinfecting and maintain the higher pathogen levels. Thus, pathogen levels drop quickly to levels of Scenario #0.

Only symptomatic individuals are tested for *C. diff* upon admission so the proportion of individuals that are asymptomatically colonized may be underestimated. Thus, Scenario #2 considers an increased proportion of individuals admitted as asymptomatically colonized ($a_C$). Since the sum of all of the admission proportions must be one, $a_S$ and $a_D$ are decreased. Figure 30 and Tables 12, 15, and 16 summarize the results of Scenario #2. The ODE and the average of the 100 trajectories predict around 8 asymptomatically colonized individuals (7 in Scenario #0) in approximately 250 total patients over 40 days. Individual trajectories show that incidence of asymptomatically colonized ranges from 2 to 17 individuals (1 to 15 in Scenario #0). The average and maximum range of the middle 95% of trajectories is 9.37 and 12 (8.29 and 11 in Scenario #0), respectively. Mean and maximum variance in the trajectories of asymptomatically colonized also increased from Scenario #0. Likewise, the ODE and the average of the 100 trajectories predict around 8 diseased individuals (5-6 in Scenario #0) in approximately 250 total patients over 40 days. Individual trajectories show that incidence of diseased ranges from 0 to 5 individuals (0 to 7 in Scenario #0 and not shown in Table 12). The average and maximum range of the middle 95% of trajectories is 3.53 and 4 (3.69 and 5 in Scenario #0), respectively. Mean variance in the
trajectories of diseased also decreased from Scenario #0. Scenario #2 is the only scenario in which the incidence of asymptotically colonized and diseased are almost identical. In all other scenarios, the incidence of asymptotically colonized is higher. Scenario #2 also provides an interesting individual trajectory. The individual trajectory with the maximum incidence of asymptotically colonized has over 94% due to a contact with a high-touch frequency fomite. (Some scenarios have individual trajectories with 100% of asymptotically colonized incidence due to high-touch frequency fomites, however, this occurs in the trajectories with the minimum asymptotically colonized incidence as 1.)

In an ideal world, every admitted patient would be tested for C. diff and asymptotically colonized and diseased individuals would be isolated from other patients. Scenario #3 considers the proportions of asymptotically colonized and diseased individuals to be zero. Since the sum of all of the admission proportions must be one, \( a_S \) is increased. This case also allows the analysis of the transmission of C. diff in a closed setting without immigration of outside colonized individuals. Figure 31 and Tables 13, 15, and 16 summarize the results of Scenario #3. The ODE and the average of the 100 trajectories predict around 1-2 asymptotically colonized individuals (7 in Scenario #0) in approximately 250 total patients over 40 days. Individual trajectories show that incidence of asymptotically colonized ranges from 0 to 7 individuals (1 to 15 in Scenario #0). The average and maximum range of the middle 95% of trajectories is 2.39 and 6 (8.29 and 11 in Scenario #0), respectively. Mean and maximum variance in the trajectories of asymptotically colonized also decreased from Scenario #0. Likewise, the ODE and the average of the 100 trajectories predict around 1 diseased individual (5-6 in Scenario #0) in approximately 250 total patients over 40 days. Individual trajectories show that incidence of diseased ranges from 0 to 4 individuals (0 to 7 in Scenario #0 and not shown in Table 13). The average and maximum range of the middle 95% of trajectories is 1.47 and 3 (3.69 and 5 in Scenario #0), respectively. Mean and maximum variance in the trajectories of diseased also decreased from Scenario #0. Scenario #3 is the only scenario in which the time courses for the asymptotically colonized and diseased patient classes and the high-touch and low-touch frequency fomites environmental reservoir classes go to zero, meaning when pathogen is not reintroduced through admissions, cleaning and disinfecting is able to eliminate pathogen from the hospital ward. Scenario #3 also provides an interesting individual trajectory. The individual trajectory with the minimum incidence of asymptotically colonized has no new asymptotically colonized or diseased individuals, meaning the initial colonized patients present in the hospital ward recover without infecting other susceptible patients.

Often, compliance with the varied cleaning and disinfecting protocols of hospital surfaces is suboptimal. Scenario #4 considers reduced efficacy of cleaning and disinfecting, i.e.,
smaller values for the rate at which spores are killed on high-touch frequency fomites due to daily cleaning ($\mu$) and the proportion of spores killed when high-touch and low-touch frequency fomites are disinfected due to a discharge ($\sigma$). Figure 32 and Tables 14, 15, and 16 summarize the results of Scenario #4. The ODE and the average of the 100 trajectories predict around 14-15 asymptomatically colonized individuals (7 in Scenario #0) in approximately 250 total patients over 40 days. Individual trajectories show that incidence of asymptomatically colonized ranges from 4 to 31 individuals (1 to 15 in Scenario #0). The average and maximum range of the middle 95% of trajectories is 9.38 and 12 (8.29 and 11 in Scenario #0), respectively. Mean and maximum variance in the trajectories of asymptomatically colonized also increased from Scenario #0. Likewise, the ODE and the average of the 100 trajectories predict around 6 diseased individuals (5-6 in Scenario #0) in approximately 250 total patients over 40 days. Individual trajectories show that incidence of diseased ranges from 0 to 6 individuals (0 to 7 in Scenario #0 and not shown in Table 14). The average and maximum range of the middle 95% of trajectories is 3.76 and 5 (3.69 and 5 in Scenario #0), respectively. Mean and maximum variance in the trajectories of diseased also increased from Scenario #0. Scenario #4 has the largest mean and maximum range of the middle 95% of trajectories and variance of trajectories of the five scenarios. Scenario #4 also provides an interesting individual trajectory. The individual trajectory with the maximum incidence of asymptomatically colonized has over 14% of the 217 total patients becoming asymptomatically colonized. In the same trajectory, both types of fomites contributed almost equally to the incidence of asymptomatically colonized.

2.7 Discussion

The difficulty of studying environmental transmission of nosocomial pathogens, a lack of understanding of these dynamics, and the serious nature of C. diff infections has hindered the ability to control C. diff infections in healthcare settings. To gain a better understanding of the dynamics of C. diff transmission, this thesis investigated the contribution of environmental pathways to C. diff transmission in a healthcare setting by adding the environmental reservoir classes of high-touch and low-touch frequency fomites to the previous epidemiological model by Lanzas et al. [50]. Additionally, this study aimed to determine the factors that influence the relative contributions of the two types of fomites by considering five scenarios. Due to a small hospital ward size, patient and pathogen populations were simulated stochastically using the GSSA and compared with the average population behavior described by a system of ODEs. The treatment of environmental pathways in disease transmission in this study was novel in the distinction of types of surfaces, including the
tracking of bacterial spore populations on those surfaces, the distinction between cleaning and disinfecting of the surfaces, and the associated transmission, shedding, and cleaning parameters. An abundance of studies dealing with patient-surface contacts and transfer of pathogen allowed this novelty.

Results show that on average, over three-quarters of asymptomatically colonized patients are colonized due to a contact with a high-touch frequency fomite and under one-quarter are colonized due to a contact with a low-touch fomite, despite the extra daily cleaning high-touch frequency fomites receive. Individual trajectories of the system from the stochastic simulations showed behaviors and extreme cases not captured by the ODE solution. Specifically, individual trajectories showed that incidence of asymptomatically colonized could vary between 1 and 15 individuals, when the average was 7 individuals (2.8% of the total number of patients), for the reference scenario and could get as high as 31 individuals (14% of the total number of patients) in another scenario. The stochastic simulations also showed that in the reference scenario, the number of asymptomatically colonized patients at any given time could differ by about 8 individuals on average between two different time courses, not accounting for the 5% of most extreme cases. The scenario with an increase in the initial pathogen level in the environmental reservoirs, did not differ significantly from the reference scenario. The scenario with an increased proportion of admitted asymptomatically colonized patients had higher incidence and larger variability in the trajectories than the reference scenario. The scenario with no admitted asymptomatically colonized or diseased patients had lower incidence and lower variability in the trajectories, and saw pathogen eliminated from the hospital ward. The scenario with reduced efficacy of cleaning and disinfecting had significantly higher incidence and variability in the trajectories. Forthcoming sensitivity analysis (by Cara Sulyok) will expectantly provide more insight into the results of the five scenarios and provide other interesting scenarios to analyze.

The model in this study has a few notable limitations. First, the validity of the model has not been assessed, i.e., the predictive accuracy of the results have not been compared to available incidence data.

Second, due to the formulation of the model, fomites were linked to new asymptomatically colonized cases but not linked to new diseased cases. To be able to keep track of disease incidence due to a type of fomite, the model would need two asymptomatically colonized (\(C_H\) and \(C_L\)) and two diseased (\(D_H\) and \(D_L\)) patient classes. Instead of combining the successful colonization rates \(\lambda_H\) and \(\lambda_L\) in Equations (2.2) and (2.3) to give the successful colonization rate \(\lambda\) in Equation (2.4) to describe the rate at which susceptibles (\(S\)) become asymptomatically colonized (\(C\)), \(\lambda_H\) would describe the rate at which susceptibles (\(S\)) become asymptomatically colonized due to high-touch frequency fomites (\(C_H\)) and \(\lambda_L\) would
describe the rate at which susceptibles become asymptomatically colonized due to low-touch frequency fomites ($C_L$). The rates at which $C_H$ patients move to the $D_H$ class and $C_L$ patients move to the $D_L$ class would be the same: the disease rate $\phi$.

Third, the description of the transmission of $C.\ diff$ among patients through contacts with fomites is incomplete. A major contributor to the transmission of $C.\ diff$ through environmental pathways is healthcare workers, which are not explicitly considered in this study. Healthcare workers directly contact patients and fomites, and transfer spores between them. To include healthcare workers in this model, a class for healthcare workers would need to be added, as well as a description of how that class interacts with the patient and environmental reservoir classes, and how colonization of patients occurs through those interactions. Many of the studies used to calculate parameter values for this model also contain data on contacts with fomites and transfer of spores for healthcare workers. Thus, the addition of healthcare workers to this model could be achieved without too much effort. Visitors of patients should also be considered and could be added to the model in a similar way as healthcare workers. Also, patients as a source of infection, beyond shedding onto fomites, was not considered in this study.

The model in this study could be improved upon by considering further classifications of surfaces beyond high-touch and low-touch frequency fomites. The CDC’s Guidelines for Environmental Infection Control in Health-Care Facilities [36] and the CDC’s Guideline for Disinfection and Sterilization in Healthcare Facilities [79] include recommended cleaning strategies for a variety of fomites. Further, contact time with a fomite would improve the description of transmission. However, more data would be needed on contacts with and transfer of spores from these different fomites to be able to calculate parameter values.

In reality patients and surfaces are not homogeneously mixed and interacting at average rates, as this model describes. Another way to improve upon the model in this study is to consider describing the same dynamics in an ABM. An ABM would be able to consider patients and surfaces in individual rooms and track spores on high-touch and low-touch frequency fomites associated to particular patients.

In future work, this model could be used to analyze the relative effectiveness of disease control strategies, especially strategies associated with cleaning and disinfecting fomites. Ultimately, this thesis has demonstrated the need to further study the role of environmental pathways in the transmission of $C.\ diff$ in a healthcare setting.
Bibliography


Appendices
## A Tables

### A.1 Chapter 1 Tables

**Table 1: Variables.** Variables for the model formulated to explore physiological control mechanisms governing HRV. All variables are nonnegative.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Units</th>
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</thead>
<tbody>
<tr>
<td>(\epsilon_{bc})</td>
<td>strain of carotid baroreceptors</td>
<td>dimensionless</td>
</tr>
<tr>
<td>(\epsilon_{ba})</td>
<td>strain of aortic baroreceptors</td>
<td>dimensionless</td>
</tr>
<tr>
<td>(T_{bp} \in (0, K_{bp}))</td>
<td>tone of PSNS due to Baroreflex Mechanism</td>
<td>dimensionless</td>
</tr>
<tr>
<td>(T_{bs} \in (0, K_{bs}))</td>
<td>tone of SNS due to Baroreflex Mechanism</td>
<td>dimensionless</td>
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<tr>
<td>(T_{rp} \in (0, K_{rp}))</td>
<td>tone of PSNS due to RSA</td>
<td>dimensionless</td>
</tr>
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<td>bpm</td>
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<td>(P_{as})</td>
<td>blood pressure of arterial systemic circulation</td>
<td>mmHg</td>
</tr>
<tr>
<td>(P_{vs})</td>
<td>blood pressure of venous systemic circulation</td>
<td>mmHg</td>
</tr>
<tr>
<td>(P_{ap})</td>
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<td>mmHg</td>
</tr>
<tr>
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<td>blood pressure of venous pulmonary circulation</td>
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### Table 2: Auxiliary Variables

Auxiliary variables for the model formulated to explore physiological control mechanisms governing HRV. All auxiliary variables are nonnegative.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description [Units]</th>
</tr>
</thead>
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<tr>
<td>$P_{th}$</td>
<td>thoracic pressure signal [mmHg] (model input)</td>
</tr>
<tr>
<td>$P_c$</td>
<td>pressure on carotid baroreceptors [mmHg]</td>
</tr>
<tr>
<td>$P_a$</td>
<td>pressure on aortic baroreceptors [mmHg]</td>
</tr>
<tr>
<td>$\epsilon_{wc} \in (0, 1)$</td>
<td>arterial wall strain of carotid sinuses [dimensionless]</td>
</tr>
<tr>
<td>$\epsilon_{wa} \in (0, 1)$</td>
<td>arterial wall strain of aortic arch [dimensionless]</td>
</tr>
<tr>
<td>$n$</td>
<td>afferent signal of baroreceptors [sec$^{-1}$]</td>
</tr>
<tr>
<td>$G_{bp} \in [G_{bp_{min}}, 1]$</td>
<td>activation level of PSNS due to Baroreflex Mechanism [dimensionless]</td>
</tr>
<tr>
<td>$G_{bs} \in [G_{bs_{min}}, 1]$</td>
<td>activation level of SNS due to Baroreflex Mechanism [dimensionless]</td>
</tr>
<tr>
<td>$G_{rp} \in [G_{rp_{min}}, 1]$</td>
<td>activation level of PSNS due to RSA [dimensionless]</td>
</tr>
<tr>
<td>$\bar{H} \in [0, H_I(1 + H_{bs}K_{bs} + H_{rp}K_{rp})]$</td>
<td>weighted intrinsic heart rate [bpm]</td>
</tr>
</tbody>
</table>
Table 3: **Parameters.** Parameters for the model formulated to explore physiological control mechanisms governing HRV with reference values. All variables are nonnegative. *Continued on next three pages.*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description [Units]</th>
<th>Reference Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A &gt; 1$</td>
<td>maximally stressed to unstressed arterial cross-sectional area ratio [dimensionless]</td>
<td>5</td>
<td>[75]</td>
</tr>
<tr>
<td>$B \in [0, 1]$</td>
<td>linear combination constant for afferent signal of baroreceptors [sec$^{-1}$]</td>
<td>0.5</td>
<td>—</td>
</tr>
<tr>
<td>$q_w$</td>
<td>sigmoid steepness constant for arterial wall strain [dimensionless]</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>$q_{bp}$</td>
<td>sigmoid steepness constant for activation of PSNS due to Baroreflex Mechanism [dimensionless]</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>$q_{bs}$</td>
<td>sigmoid steepness constant for activation of SNS due to Baroreflex Mechanism [dimensionless]</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>$q_{rp}$</td>
<td>sigmoid steepness constant for activation of PSNS due to RSA [dimensionless]</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>$s_w$</td>
<td>sigmoid shift constant for arterial wall strain [mmHg]</td>
<td>$P_c^*$</td>
<td>data</td>
</tr>
<tr>
<td>$s_{bp}$</td>
<td>sigmoid shift constant for activation of PSNS due to Baroreflex Mechanism [sec$^{-1}$]</td>
<td>$n^* \left( \frac{1 - G_{bp}^<em>}{G_{bp}^</em> - G_{bp_{min}}} \right)^{-\frac{1}{q_{bp}}}$</td>
<td>calculated in Section 1.5.2</td>
</tr>
<tr>
<td>$s_{bs}$</td>
<td>sigmoid shift constant for activation of SNS due to Baroreflex Mechanism [sec$^{-1}$]</td>
<td>$n^* \left( \frac{1 - G_{bs}^<em>}{G_{bs}^</em> - G_{bs_{min}}} \right)^{-\frac{1}{q_{bs}}}$</td>
<td>calculated in Section 1.5.2</td>
</tr>
</tbody>
</table>
Table 3 Continued: Parameters. Parameters for the model formulated to explore physiological control mechanisms governing HRV with reference values. All variables are nonnegative. *Continued on next two pages.*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description [Units]</th>
<th>Reference Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>(s_{rp})</td>
<td>sigmoid shift constant for activation of PSNS due to RSA ([mmHg])</td>
<td>(P_{th}^{<em>} \left( \frac{1 - G_{rp}^{</em>}}{G_{rp}^{<em>} - G_{rp_{min}}^{</em>}} \right)^{\frac{1}{\tau_{rp}}})</td>
<td>calculated in Section 1.5.2</td>
</tr>
<tr>
<td>(G_{bp_{min}} \in [0, 1])</td>
<td>minimum activation level of PSNS due to Baroreflex Mechanism ([\text{dimensionless}])</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>(G_{bs_{min}} \in [0, 1])</td>
<td>minimum activation level of SNS due to Baroreflex Mechanism ([\text{dimensionless}])</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>(G_{rp_{min}} \in [0, 1])</td>
<td>minimum activation level of PSNS due to RSA ([\text{dimensionless}])</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>(K_{b} &lt; 1)</td>
<td>gain constant for strain of baroreceptors ([\text{dimensionless}])</td>
<td>0.1</td>
<td>[75]</td>
</tr>
<tr>
<td>(K_{bp})</td>
<td>gain constant for tone of PSNS due to Baroreflex Mechanism ([\text{dimensionless}])</td>
<td>5</td>
<td>[75]</td>
</tr>
<tr>
<td>(K_{bs})</td>
<td>gain constant for tone of SNS due to Baroreflex Mechanism ([\text{dimensionless}])</td>
<td>5</td>
<td>[75]</td>
</tr>
<tr>
<td>(K_{rp})</td>
<td>gain constant for tone of PSNS due to RSA ([\text{dimensionless}])</td>
<td>1</td>
<td>[75]</td>
</tr>
<tr>
<td>(\tau_{b})</td>
<td>time constant for strain of baroreceptors ([\text{sec}])</td>
<td>0.9</td>
<td>[75]</td>
</tr>
<tr>
<td>(\tau_{bp})</td>
<td>time constant for tone of PSNS due to Baroreflex Mechanism ([\text{sec}])</td>
<td>1.8</td>
<td>[75]</td>
</tr>
</tbody>
</table>
Table 3: Parameters. Continued. Parameters for the model formulated to explore physiological control mechanisms governing HRV with reference values. All variables are nonnegative.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description [Units]</th>
<th>Reference Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \tau_{bs} )</td>
<td>time constant for tone of SNS due to Baroreflex Mechanism [sec]</td>
<td>10</td>
<td>[75]</td>
</tr>
<tr>
<td>( \tau_{rp} )</td>
<td>time constant for tone of PSNS due to RSA [sec]</td>
<td>6</td>
<td>[75]</td>
</tr>
<tr>
<td>( \tau_{H} )</td>
<td>time constant for heart rate [sec]</td>
<td>0.5</td>
<td>[75]</td>
</tr>
<tr>
<td>( age )</td>
<td>age of patient [years]</td>
<td>patient specific data</td>
<td></td>
</tr>
<tr>
<td>( H_I )</td>
<td>intrinsic heart rate [bpm]</td>
<td>( 118 - 0.57 \cdot age )</td>
<td>[42]</td>
</tr>
<tr>
<td>( H_{bp} &lt; \frac{1}{K_{bp}} )</td>
<td>weighting constant for tone of PSNS due to Baroreflex Mechanism [dimensionless]</td>
<td>0.15</td>
<td>—</td>
</tr>
<tr>
<td>( H_{bs} )</td>
<td>weighting constant for tone of SNS due to Baroreflex Mechanism [dimensionless]</td>
<td>0.29</td>
<td>—</td>
</tr>
<tr>
<td>( H_{rp} )</td>
<td>weighting constant for tone of PSNS due to RSA [dimensionless]</td>
<td>0.29</td>
<td>—</td>
</tr>
<tr>
<td>( c_{as} )</td>
<td>compliance constant for arterial systemic circulation ([L \cdot mmHg^{-1}])</td>
<td>0.01016</td>
<td>[57]</td>
</tr>
<tr>
<td>( c_{vs} )</td>
<td>compliance constant for venous systemic circulation ([L \cdot mmHg^{-1}])</td>
<td>0.65</td>
<td>[57]</td>
</tr>
<tr>
<td>( c_{ap} )</td>
<td>compliance constant for arterial pulmonary circulation ([L \cdot mmHg^{-1}])</td>
<td>0.0361</td>
<td>[57]</td>
</tr>
<tr>
<td>( c_{vp} )</td>
<td>compliance constant for venous pulmonary circulation ([L \cdot mmHg^{-1}])</td>
<td>0.1408</td>
<td>[57]</td>
</tr>
</tbody>
</table>
### Table 3 Continued: Parameters

Parameters for the model formulated to explore physiological control mechanisms governing HRV with reference values. All variables are nonnegative.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description [Units]</th>
<th>Reference Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c_l$</td>
<td>end-diastolic compliance for relaxed left atrium ([L \cdot mmHg^{-1} \cdot beat^{-1}])</td>
<td>0.0274</td>
<td>[57]</td>
</tr>
<tr>
<td>$c_r$</td>
<td>end-diastolic compliance for relaxed right atrium ([L \cdot mmHg^{-1} \cdot beat^{-1}])</td>
<td>0.0474</td>
<td>[57]</td>
</tr>
<tr>
<td>$R_s$</td>
<td>resistance to blood flow in systemic circulation ([mmHg \cdot min \cdot L^{-1}])</td>
<td>6.5</td>
<td>[57]</td>
</tr>
<tr>
<td>$R_p$</td>
<td>resistance to blood flow in pulmonary circulation ([mmHg \cdot min \cdot L^{-1}])</td>
<td>0.5</td>
<td>[57]</td>
</tr>
<tr>
<td>$V_{tot}$</td>
<td>total blood volume ([L])</td>
<td>5.058</td>
<td>[57]</td>
</tr>
</tbody>
</table>
Table 4: Results. Effect of parameter values on the mean of the model predicted heart rate and the variance of the RR intervals of the model predicted heart rate for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77). Reference parameter values are summarized in Table 3, including $q_w = 3$, $q_{bp} = q_{bs} = q_{rp} = 10$, $H_{bp} = 0.15$, $H_{bs} = H_{rp} = 0.29$, and $B = 0.5$. The mean of the heart rate data is 68.384 bpm and the variance of the RR intervals of the heart rate data is 0.00227 bpm$^2$. Continued on next page.

<table>
<thead>
<tr>
<th>Varied Parameter</th>
<th>Mean of Model Predicted Heart Rate [bpm]</th>
<th>Variance of RR Intervals of Model Predicted Heart Rate [bpm$^2$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>reference parameter values</td>
<td>69.836</td>
<td>0.00102</td>
</tr>
<tr>
<td>$q_w = 0$</td>
<td>83.276</td>
<td>0.00110</td>
</tr>
<tr>
<td>$q_w = 0.1$</td>
<td>81.838</td>
<td>0.00110</td>
</tr>
<tr>
<td>$q_w = 10$</td>
<td>66.012</td>
<td>0.00067</td>
</tr>
<tr>
<td>$q_{bp} = 0$</td>
<td>87.024</td>
<td>0.00099</td>
</tr>
<tr>
<td>$q_{bp} = 1$</td>
<td>71.909</td>
<td>0.00132</td>
</tr>
<tr>
<td>$q_{bp} = 25$</td>
<td>68.333</td>
<td>0.00086</td>
</tr>
<tr>
<td>$q_{bs} = 0$</td>
<td>113.100</td>
<td>0.00090</td>
</tr>
<tr>
<td>$q_{bs} = 1$</td>
<td>74.780</td>
<td>0.00106</td>
</tr>
<tr>
<td>$q_{bs} = 25$</td>
<td>67.418</td>
<td>0.00100</td>
</tr>
<tr>
<td>$q_{rp} = 0$</td>
<td>69.757</td>
<td>0.00018</td>
</tr>
<tr>
<td>$q_{rp} = 1$</td>
<td>70.123</td>
<td>0.00041</td>
</tr>
<tr>
<td>$q_{rp} = 25$</td>
<td>69.745</td>
<td>0.00116</td>
</tr>
</tbody>
</table>
Table 4 Continued: Results. Effect of parameter values on the mean of the model predicted heart rate and the variance of the RR intervals of the model predicted heart rate for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77). Reference parameter values are summarized in Table 3, including \( q_w = 3 \), \( q_b = q_{bs} = q_{rp} = 10 \), \( H_{bp} = 0.15 \), \( H_{bs} = H_{rp} = 0.29 \), and \( B = 0.5 \). The mean of the heart rate data is 68.384 bpm and the variance of the RR intervals of the heart rate data is 0.00227 bpm\(^2\).

<table>
<thead>
<tr>
<th>Varied Parameter</th>
<th>Mean of Model Predicted Heart Rate [bpm]</th>
<th>Variance of RR Intervals of Model Predicted Heart Rate [bpm(^2)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>( H_{bp} = 0 )</td>
<td>119.980</td>
<td>0.00044</td>
</tr>
<tr>
<td>( H_{bp} = 0.05 )</td>
<td>98.472</td>
<td>0.00081</td>
</tr>
<tr>
<td>( H_{bp} = 0.19 )</td>
<td>64.494</td>
<td>0.00079</td>
</tr>
<tr>
<td>( H_{bs} = 0 )</td>
<td>59.408</td>
<td>0.00128</td>
</tr>
<tr>
<td>( H_{bs} = 0.1 )</td>
<td>63.882</td>
<td>0.00105</td>
</tr>
<tr>
<td>( H_{bs} = 0.4 )</td>
<td>72.600</td>
<td>0.00114</td>
</tr>
<tr>
<td>( H_{rp} = 0 )</td>
<td>64.947</td>
<td>0.00008</td>
</tr>
<tr>
<td>( H_{rp} = 0.1 )</td>
<td>66.460</td>
<td>0.00013</td>
</tr>
<tr>
<td>( H_{rp} = 0.4 )</td>
<td>72.158</td>
<td>0.00190</td>
</tr>
<tr>
<td>( B = 0 )</td>
<td>69.687</td>
<td>0.00084</td>
</tr>
<tr>
<td>( B = 1 )</td>
<td>70.030</td>
<td>0.00125</td>
</tr>
</tbody>
</table>
A.2 Chapter 2 Tables

Table 5: Classes. Patient and environmental reservoir classes for the model of \textit{C. diff} transmission including environmental pathways in a hospital ward. The total population size of the hospital ward is \(N = R + S + C + D\). For this study, \(N = 30\) individuals.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description [Units]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)</td>
<td>Resistant [individuals]</td>
</tr>
<tr>
<td>(S)</td>
<td>Susceptible [individuals]</td>
</tr>
<tr>
<td>(C)</td>
<td>Asymptomatically Colonized [individuals]</td>
</tr>
<tr>
<td>(D)</td>
<td>Diseased [individuals]</td>
</tr>
<tr>
<td>(P_H)</td>
<td>\textit{C. diff} spore density on high-touch frequency fomites ([spores \cdot cm^{-2}])</td>
</tr>
<tr>
<td>(P_L)</td>
<td>\textit{C. diff} spore density on low-touch frequency fomites ([spores \cdot cm^{-2}])</td>
</tr>
</tbody>
</table>
Table 6: Parameters. Parameters for the model of *C. diff* transmission including environmental pathways in a hospital ward with reference values. *Continued on next page.*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description [Units]</th>
<th>Reference Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_R$</td>
<td>proportion of admitted individuals who are resistant [dimensionless]</td>
<td>0.75</td>
<td>[85]</td>
</tr>
<tr>
<td>$a_S$</td>
<td>proportion of admitted individuals who are susceptible [dimensionless]</td>
<td>0.09</td>
<td>[85]</td>
</tr>
<tr>
<td>$a_C$</td>
<td>proportion of admitted individuals who are asymptomatically colonized [dimensionless]</td>
<td>0.15</td>
<td>[85]</td>
</tr>
<tr>
<td>$a_D$</td>
<td>proportion of admitted individuals who are diseased [dimensionless]</td>
<td>0.01</td>
<td>[85]</td>
</tr>
<tr>
<td>$k_R$</td>
<td>discharge rate of resistant individuals [day$^{-1}$]</td>
<td>0.33</td>
<td>[50]</td>
</tr>
<tr>
<td>$k$</td>
<td>discharge rate of susceptible and asymptomatically colonized individuals [day$^{-1}$]</td>
<td>0.15</td>
<td>[50]</td>
</tr>
<tr>
<td>$k_D$</td>
<td>discharge rate of diseased individuals [day$^{-1}$]</td>
<td>0.068</td>
<td>[50]</td>
</tr>
<tr>
<td>$\delta = \delta(t)$</td>
<td>total discharge rate [day$^{-1}$]</td>
<td>$\frac{1}{N}(k_R R + k_S S + k_C C + k_D D)$</td>
<td>calculated in Section 2.4.3</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>antibiotic prescription rate [day$^{-1}$]</td>
<td>0.5</td>
<td>[50]</td>
</tr>
<tr>
<td>$\theta$</td>
<td>restoration rate of colonization resistance [day$^{-1}$]</td>
<td>0.033</td>
<td>[73]</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>successful treatment rate of infection [day$^{-1}$]</td>
<td>0.08</td>
<td>[63]</td>
</tr>
<tr>
<td>$\phi$</td>
<td>disease rate of asymptomatically colonized individuals with insufficient immune response [day$^{-1}$]</td>
<td>0.024</td>
<td>[16], [50]</td>
</tr>
</tbody>
</table>
Table 6 Continued: Parameters. Parameters for the model of *C. diff* transmission including environmental pathways in a hospital ward with reference values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description [Units]</th>
<th>Reference Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho_{CH}$</td>
<td>shedding rate of asymptomatically colonized individuals onto high-touch fomites [spores \cdot cm^{-2} \cdot individuals^{-1} \cdot day^{-1}]</td>
<td>0.057</td>
<td>[17, 44, 80]</td>
</tr>
<tr>
<td>$\rho_{CL}$</td>
<td>shedding rate of asymptomatically colonized individuals onto low-touch fomites [spores \cdot cm^{-2} \cdot individuals^{-1} \cdot day^{-1}]</td>
<td>0.029</td>
<td>[17, 44, 80]</td>
</tr>
<tr>
<td>$\rho_{DH}$</td>
<td>shedding rate of diseased individuals onto high-touch fomites [spores \cdot cm^{-2} \cdot individuals^{-1} \cdot day^{-1}]</td>
<td>0.123</td>
<td>[17, 44, 80]</td>
</tr>
<tr>
<td>$\rho_{DL}$</td>
<td>shedding rate of diseased individuals onto low-touch fomites [spores \cdot cm^{-2} \cdot individuals^{-1} \cdot day^{-1}]</td>
<td>0.063</td>
<td>[17, 44, 80]</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>proportion of spores killed when high-touch and low-touch fomites are disinfected due to discharge [individuals^{-1}]</td>
<td>0.83</td>
<td>[81]</td>
</tr>
<tr>
<td>$\mu$</td>
<td>rate of spores killed on high-touch surfaces due to daily cleaning [day^{-1}]</td>
<td>0.66</td>
<td>[81]</td>
</tr>
<tr>
<td>$K$</td>
<td>half-saturation constant [spores \cdot cm^{-2}]</td>
<td>7.5</td>
<td>[51]</td>
</tr>
<tr>
<td>$\beta$</td>
<td>colonization rate upon transfer of spores from a fomite [day^{-1}]</td>
<td>0.338</td>
<td>calculated in Section 2.4.3</td>
</tr>
<tr>
<td>$\omega$</td>
<td>weighting constant for high-touch fomites [dimensionless]</td>
<td>1.96</td>
<td>[17]</td>
</tr>
</tbody>
</table>
Table 7: Shedding Parameters. Calculation of the shedding rate parameters for the model of *C. diff* transmission including environmental pathways in a hospital ward. The shedding rates of asymptotically colonized or diseased individuals onto high-touch or low-touch frequency fomites are the product of the spores per square centimeter per contact from a patient and the contacts per day per individual with a fomite.

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Fomite Type</th>
<th>Spores per cm² per contact* (spc)</th>
<th>Contacts per day per individual** (cpd)</th>
<th>Shedding rate = spc · cpd</th>
</tr>
</thead>
<tbody>
<tr>
<td>asymptically colonized high-touch</td>
<td>spc₈ = 0.006</td>
<td>cpd₇ = 9.424</td>
<td>ρ₈₇ = 0.057</td>
<td></td>
</tr>
<tr>
<td>asymptically colonized low-touch</td>
<td>spc₈ = 0.006</td>
<td>cpd₅ = 4.818</td>
<td>ρ₈₅ = 0.029</td>
<td></td>
</tr>
<tr>
<td>diseased high-touch</td>
<td>spc₉ = 0.013</td>
<td>cpd₇ = 9.424</td>
<td>ρ₉₇ = 0.123</td>
<td></td>
</tr>
<tr>
<td>diseased low-touch</td>
<td>spc₉ = 0.013</td>
<td>cpd₅ = 4.818</td>
<td>ρ₉₅ = 0.063</td>
<td></td>
</tr>
</tbody>
</table>

*based on patient type

**based on fomite type
Table 8: GSSA Events. Events, state space updates, and propensity functions for the GSSA for stochastic simulations of the model of C. diff transmission including environmental pathways in a hospital ward. The state space is \( X(t) = [R(t), S(t), C(t), D(t), P_H(t), P_L(t)] \). When event 1, 2, 3, or 4 occurs, the class a new patient is admitted as is determined randomly, weighted by the admission proportions \( (a_R, a_S, a_C, a_D) \). Thus, the state space may be updated in one of four possible ways. Also, a counter for the total number of patients is updated by 1. This counter starts at the hospital ward size of \( N = 30 \). Continued on next page.

<table>
<thead>
<tr>
<th>No.</th>
<th>Event</th>
<th>State Update</th>
<th>Propensity Function</th>
</tr>
</thead>
</table>
| 1   | resistant individual discharged  
(triggers patient admission and fomite disinfection) | \([0, 0, 0, 0, \sigma P_H, \sigma P_L]^*, [-1, 1, 0, 0, -\sigma P_H, -\sigma P_L]^{**}, [-1, 0, 1, 0, -\sigma P_H, -\sigma P_L]^{†}, \text{or} [-1, 0, 0, 1, -\sigma P_H, -\sigma P_L]^{††}\) | \(k_R R\) |
| 2   | susceptible individual discharged  
(triggers patient admission and fomite disinfection) | \([1, -1, 0, 0, -\sigma P_H, -\sigma P_L]^*, [0, 0, 0, 0, -\sigma P_H, -\sigma P_L]^{**}, [0, -1, 1, 0, -\sigma P_H, -\sigma P_L]^{‡}, \text{or} [0, -1, 0, 1, -\sigma P_H, -\sigma P_L]^{‡‡}\) | \(k_S\) |
| 3   | asymptotically colonized individual discharged  
(triggers patient admission and fomite disinfection) | \([1, 0, -1, -\sigma P_H, -\sigma P_L]^*, [0, 1, -1, 0, -\sigma P_H, -\sigma P_L]^{**}, [0, 0, 0, 0, -\sigma P_H, -\sigma P_L]^{†}, \text{or} [0, 0, -1, 1, -\sigma P_H, -\sigma P_L]^{‡‡}\) | \(k_C\) |
| 4   | diseased individual discharged  
(triggers patient admission and fomite disinfection) | \([1, 0, 0, -1, -\sigma P_H, -\sigma P_L]^*, [0, 1, 0, -1, -\sigma P_H, -\sigma P_L]^{**}, [0, 0, 1, -1, -\sigma P_H, -\sigma P_L]^{†}, \text{or} [0, 0, 0, 0, -\sigma P_H, -\sigma P_L]^{‡‡}\) | \(k_D D\) |

*state update if admitted patient is resistant  
**state update if admitted patient is susceptible  
†state update if admitted patient is asymptomatically colonized  
‡state update if admitted patient is diseased
Table 8 Continued: GSSA Events. Events, state space updates, and propensity functions for the GSSA for stochastic simulations of the model of *C. diff* transmission including environmental pathways in a hospital ward. The state space is $X(t) = [R(t), S(t), C(t), D(t), P_H(t), P_L(t)]$. When event 7 or 8 occurs, counters for the number of new colonized cases due to high-touch or low-touch fomites, respectively, and the total number of new colonized cases are updated by 1 to calculate incidence. When event 9 occurs, a counter for the number of new diseased cases is updated by 1 to calculate incidence. These counters start at 0.

<table>
<thead>
<tr>
<th>No.</th>
<th>Event</th>
<th>State Update</th>
<th>Propensity Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>antibiotic prescribed</td>
<td>$[-1, 1, 0, 0, 0, 0]$</td>
<td>$\alpha R$</td>
</tr>
<tr>
<td>6</td>
<td>gut restored against colonization</td>
<td>$[1, -1, 0, 0, 0, 0]$</td>
<td>$\theta S$</td>
</tr>
<tr>
<td>7</td>
<td>new colonized case due to high-touch fomites</td>
<td>$[0, -1, 1, 0, 0, 0]$</td>
<td>$\beta \omega \frac{P_H}{K+P_H} S$</td>
</tr>
<tr>
<td>8</td>
<td>new colonized case due to low-touch fomites</td>
<td>$[0, -1, 1, 0, 0, 0]$</td>
<td>$\beta \frac{P_H}{K+P_H} S$</td>
</tr>
<tr>
<td>9</td>
<td>individual becomes diseased</td>
<td>$[0, 0, -1, 1, 0, 0]$</td>
<td>$\phi C$</td>
</tr>
<tr>
<td>10</td>
<td>individual recovers from infection</td>
<td>$[0, 1, 0, -1, 0, 0]$</td>
<td>$\varepsilon D$</td>
</tr>
<tr>
<td>11</td>
<td>high-touch surfaces cleaned</td>
<td>$[0, 0, 0, 0, -\frac{\mu}{N} P_H, 0]$</td>
<td>$N$</td>
</tr>
<tr>
<td>12</td>
<td>asymptotically colonized individual sheds on high-touch fomite</td>
<td>$[0, 0, 0, 0, spc_C, 0]$</td>
<td>$cpd_H C$</td>
</tr>
<tr>
<td>13</td>
<td>asymptotically colonized individual sheds on low-touch fomite</td>
<td>$[0, 0, 0, 0, spc_C]$</td>
<td>$cpd_L C$</td>
</tr>
<tr>
<td>14</td>
<td>diseased individual sheds on high-touch fomite</td>
<td>$[0, 0, 0, 0, spc_D, 0]$</td>
<td>$cpd_H D$</td>
</tr>
<tr>
<td>15</td>
<td>diseased individual sheds on low-touch fomite</td>
<td>$[0, 0, 0, 0, spc_D]$</td>
<td>$cpd_L D$</td>
</tr>
</tbody>
</table>
Table 9: Scenarios. Five scenarios with different parameter values or initial conditions considered for the model of *C. diff* transmission including environmental pathways in a hospital ward.

<table>
<thead>
<tr>
<th>No.</th>
<th>Scenario Description</th>
<th>Changed Parameter Values and Initial Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Reference scenario</td>
<td>Parameters: $a_R = 0.75$, $a_S = 0.09$, $a_C = 0.15$, $a_D = 0.01$, $\sigma = 0.83$, $\mu = 0.66$ (same as in Table 6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial Conditions: $R_0 = 21$, $S_0 = 3$, $C_0 = 5$, $D_0 = 1$, $P_{H_0} = P_{L_0} = 0.01$</td>
</tr>
<tr>
<td>1</td>
<td>Increase initial pathogen level in environmental reservoir</td>
<td>Initial Conditions: $P_{H_0} = P_{L_0} = 0.1$</td>
</tr>
<tr>
<td>2</td>
<td>Increase proportion of admitted asymptotically colonized</td>
<td>Parameters: $a_R = 0.75$, $a_S = 0$, $a_C = 0.25$, $a_D = 0$</td>
</tr>
<tr>
<td>3</td>
<td>Decrease proportions of admitted asymptotically colonized and diseased</td>
<td>Parameters: $a_R = 0.75$, $a_S = 0.25$, $a_C = 0$, $a_D = 0$</td>
</tr>
<tr>
<td>4</td>
<td>Decrease efficacy of cleaning and disinfecting</td>
<td>Parameters: $\sigma = 0.42$, $\mu = 0.33$</td>
</tr>
</tbody>
</table>
Table 10: Results from Scenario #0. Incidence of new diseased and asymptotically colonized patients for the \( C. \ diff \) model described by the system of ODEs in Equation (2.10) and the GSSA trajectories described by the events in Table 8 for a total ward population of \( N = 30 \) over 40 days, system variables from Table 5, reference parameter values from Table 6, and initial conditions \( R_0 = 21, \ S_0 = 3, \ C_0 = 5, \ D_0 = 1, \ P_{H0} = P_{L0} = 0.01 \).

<table>
<thead>
<tr>
<th>Metric</th>
<th>ODE Model</th>
<th>Mean Value of GSSA Trajectories</th>
<th>Trajectory with Max Incidence of Asy. Colonized</th>
<th>Trajectory with Min Incidence of Asy. Colonized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients (( M )) [\textit{individuals}]</td>
<td>249.93</td>
<td>249.41</td>
<td>242</td>
<td>219</td>
</tr>
<tr>
<td>Incidence of Diseased [\textit{individuals}]</td>
<td>5.42 (2.17% of ( M ))</td>
<td>5.83 (2.34% of ( M ))</td>
<td>4 (1.65% of ( M ))</td>
<td>2 (0.91% of ( M ))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized (( I_C )) [\textit{individuals}]</td>
<td>7.02 (2.81% of ( M ))</td>
<td>6.99 (2.80% of ( M ))</td>
<td>15 (6.20% of ( M ))</td>
<td>1 (0.46% of ( M ))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized due to High-Touch Fomites [\textit{individuals}]</td>
<td>5.40 (2.16% of ( M ), 76.90% of ( I_C ))</td>
<td>5.44 (2.18% of ( M ), 77.83% of ( I_C ))</td>
<td>11 (4.55% of ( M ), 73.33% of ( I_C ))</td>
<td>1 (0.46% of ( M ), 100% of ( I_C ))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized due to Low-Touch Fomites [\textit{individuals}]</td>
<td>1.62 (0.65% of ( M ), 23.10% of ( I_C ))</td>
<td>1.55 (0.62% of ( M ), 22.17% of ( I_C ))</td>
<td>4 (1.65% of ( M ), 26.67% of ( I_C ))</td>
<td>0 (0% of ( M ), 0% of ( I_C ))</td>
</tr>
<tr>
<td>Ending Pathogen Levels [\textit{spores} \cdot \textit{cm}^{-2}]</td>
<td>( P_H = 0.09 )</td>
<td>( P_H = 0.11 )</td>
<td>( P_H = 0.05 )</td>
<td>( P_H = 0.05 )</td>
</tr>
<tr>
<td></td>
<td>( P_L = 0.05 )</td>
<td>( P_L = 0.07 )</td>
<td>( P_L = 0.03 )</td>
<td>( P_L = 0.03 )</td>
</tr>
</tbody>
</table>
Table 11: Results from Scenario #1. Incidence of new diseased and asymptotically colonized patients for the C. diff model described by the system of ODEs in Equation (2.10) and the GSSA trajectories described by the events in Table 8 for a total ward population of $N = 30$ over 40 days, system variables from Table 5, reference parameter values from Table 6, and initial conditions $R_0 = 21$, $S_0 = 3$, $C_0 = 5$, $D_0 = 1$, $P_H = P_L = 0.1$.

<table>
<thead>
<tr>
<th>Metric</th>
<th>ODE Model</th>
<th>Mean Value of GSSA Trajectories</th>
<th>Trajectory with Max Incidence of Asy. Colonized</th>
<th>Trajectory with Min Incidence of Asy. Colonized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients ($M$) [individuals]</td>
<td>249.92</td>
<td>249.58</td>
<td>239</td>
<td>277</td>
</tr>
<tr>
<td>Incidence of Diseased [individuals]</td>
<td>5.42 (2.17% of $M$)</td>
<td>5.72 (2.29% of $M$)</td>
<td>9 (3.77% of $M$)</td>
<td>2 (0.72% of $M$)</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized ($I_C$) [individuals]</td>
<td>7.03 (2.81% of $M$)</td>
<td>6.97 (2.79% of $M$)</td>
<td>15 (6.28% of $M$)</td>
<td>1 (0.36% of $M$)</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized due to High-Touch Fomites [individuals]</td>
<td>5.40 (2.16% of $M$, 76.89% of $I_C$)</td>
<td>5.38 (2.16% of $M$, 77.19% of $I_C$)</td>
<td>11 (4.60% of $M$, 73.33% of $I_C$)</td>
<td>1 (0.36% of $M$, 100% of $I_C$)</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized due to Low-Touch Fomites [individuals]</td>
<td>1.62 (0.65% of $M$, 23.11% of $I_C$)</td>
<td>1.59 (0.64% of $M$, 22.81% of $I_C$)</td>
<td>4 (1.67% of $M$, 26.67% of $I_C$)</td>
<td>0 (0% of $M$, 0% of $I_C$)</td>
</tr>
<tr>
<td>Ending Pathogen Levels [spores · cm(^{-2})]</td>
<td>$P_H = 0.09$, $P_L = 0.05$</td>
<td>$P_H = 0.08$, $P_L = 0.05$</td>
<td>$P_H = 0.07$, $P_L = 0.06$</td>
<td>$P_H = 0.10$, $P_L = 0.10$</td>
</tr>
</tbody>
</table>
Table 12: Results from Scenario #2. Incidence of new diseased and asymptotically colonized patients for the \( C. \) \textit{diff} model described by the system of ODEs in Equation (2.10) and the GSSA trajectories described by the events in Table 8 for a total ward population of \( N = 30 \) over 40 days, system variables from Table 5, reference parameter values from Table 6 except for \( a_R = 0.75, a_S = 0, a_C = 0.25, \) and \( a_D = 0, \) and initial conditions \( R_0 = 21, S_0 = 3, C_0 = 5, D_0 = 1, P_{H_0} = P_{L_0} = 0.01. \)

<table>
<thead>
<tr>
<th>Metric</th>
<th>ODE Model</th>
<th>Mean Value of GSSA Trajectories</th>
<th>Trajectory with Max Incidence of Asy. Colonized</th>
<th>Trajectory with Min Incidence of Asy. Colonized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients (( M )) ( [\text{individuals}] )</td>
<td>248.81</td>
<td>248.30</td>
<td>240</td>
<td>268</td>
</tr>
<tr>
<td>Incidence of Diseased ( [\text{individuals}] )</td>
<td>8.10 (3.26% of ( M ))</td>
<td>8.11 (3.27% of ( M ))</td>
<td>11 (4.58% of ( M ))</td>
<td>11 (4.10% of ( M ))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized (( I_C )) ( [\text{individuals}] )</td>
<td>7.98 (3.21% of ( M ))</td>
<td>8.11 (3.27% of ( M ))</td>
<td>17 (7.08% of ( M ))</td>
<td>2 (0.75% of ( M ))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized due to High-Touch Fomites ( [\text{individuals}] )</td>
<td>6.13 (2.46% of ( M ), 76.86% of ( I_C ))</td>
<td>6.29 (2.53% of ( M ), 77.56% of ( I_C ))</td>
<td>16 (6.67% of ( M ), 94.12% of ( I_C ))</td>
<td>2 (0.75% of ( M ), 100% of ( I_C ))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized due to Low-Touch Fomites ( [\text{individuals}] )</td>
<td>1.85 (0.74% of ( M ), 23.14% of ( I_C ))</td>
<td>1.82 (0.73% of ( M ), 22.44% of ( I_C ))</td>
<td>1 (0.42% of ( M ), 5.88% of ( I_C ))</td>
<td>0 (0% of ( M ), 0% of ( I_C ))</td>
</tr>
<tr>
<td>Ending Pathogen Levels ( [\text{spores \cdot cm}^{-2}] )</td>
<td>( P_H = 0.13 ), ( P_L = 0.08 )</td>
<td>( P_H = 0.14 ), ( P_L = 0.08 )</td>
<td>( P_H = 0.06 ), ( P_L = 0.03 )</td>
<td>( P_H = 0.05 ), ( P_L = 0.03 )</td>
</tr>
</tbody>
</table>
Table 13: Results from Scenario #3. Incidence of new diseased and asymptotically colonized patients for the \textit{C. diff} model described by the system of ODEs in Equation (2.10) and the GSSA trajectories described by the events in Table 8 for a total ward population of \( N = 30 \) over 40 days, system variables from Table 5, reference parameter values from Table 6 except \( a_R = 0.75, a_S = 0.25, a_C = 0, \) and \( a_D = 0, \) and initial conditions \( R_0 = 21, S_0 = 3, C_0 = 5, D_0 = 1, P_{H_0} = P_{L_0} = 0.01. \)

<table>
<thead>
<tr>
<th>Metric</th>
<th>ODE Model</th>
<th>Mean Value of GSSA Trajectories</th>
<th>Trajectory with Max Incidence of Asy. Colonized</th>
<th>Trajectory with Min Incidence of Asy. Colonized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients (( M )) [\textit{individuals}]</td>
<td>255.25</td>
<td>256.25</td>
<td>244</td>
<td>247</td>
</tr>
<tr>
<td>Incidence of Diseased [\textit{individuals}]</td>
<td>0.89 ((0.35% \text{ of } M))</td>
<td>0.83 ((0.32% \text{ of } M))</td>
<td>2 ((0.82% \text{ of } M))</td>
<td>0 ((0% \text{ of } M))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized (( I_C )) [\textit{individuals}]</td>
<td>1.53 ((0.60% \text{ of } M))</td>
<td>1.57 ((0.61% \text{ of } M))</td>
<td>7 ((2.87% \text{ of } M))</td>
<td>0 ((0% \text{ of } M))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized due to High-Touch Fomites [\textit{individuals}]</td>
<td>1.18 ((0.46% \text{ of } M, 77.00% \text{ of } I_C))</td>
<td>1.21 ((0.47% \text{ of } M, 77.07% \text{ of } I_C))</td>
<td>5 ((2.05% \text{ of } M, 71.43% \text{ of } I_C))</td>
<td>0 ((0% \text{ of } M, –% \text{ of } I_C))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized due to Low-Touch Fomites [\textit{individuals}]</td>
<td>0.35 ((0.14% \text{ of } M, 23.00% \text{ of } I_C))</td>
<td>0.36 ((0.14% \text{ of } M, 22.93% \text{ of } I_C))</td>
<td>2 ((0.82% \text{ of } M, 28.57% \text{ of } I_C))</td>
<td>0 ((0% \text{ of } M, –% \text{ of } I_C))</td>
</tr>
<tr>
<td>Ending Pathogen Levels [\textit{spores \cdot cm^{-2}}]</td>
<td>( P_H = 0, ) ( P_L = 0 )</td>
<td>( P_H = 0, ) ( P_L = 0 )</td>
<td>( P_H = 0.06, ) ( P_L = 0.03 )</td>
<td>( P_H = 0.03, ) ( P_L = 0.02 )</td>
</tr>
</tbody>
</table>
Table 14: Results from Scenario #4. Incidence of new diseased and asymptotically colonized patients for the \( C. \ diff \) model described by the system of ODEs in Equation (2.10) and the GSSA trajectories described by the events in Table 8 for a total ward population of \( N = 30 \) over 40 days, system variables from Table 5, reference parameter values from Table 6 except for \( \sigma = 0.42 \) and \( \mu = 0.33 \), and initial conditions \( R_0 = 21, S_0 = 3, C_0 = 5, D_0 = 1, P_H = P_L = 0.01. \)

<table>
<thead>
<tr>
<th>Metric</th>
<th>ODE Model</th>
<th>Mean Value of GSSA Trajectories</th>
<th>Trajectory with Max Incidence of Asy. Colonized</th>
<th>Trajectory with Min Incidence of Asy. Colonized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients ( (M) ) ([\text{individuals}])</td>
<td>249.15</td>
<td>247.70</td>
<td>217</td>
<td>287</td>
</tr>
<tr>
<td>Incidence of Diseased ([\text{individuals}])</td>
<td>6.31 (2.53% of ( M ))</td>
<td>6.12 (2.47% of ( M ))</td>
<td>13 (5.99% of ( M ))</td>
<td>5 (1.74% of ( M ))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized ( (I_C) ) ([\text{individuals}])</td>
<td>14.75 (5.92% of ( M ))</td>
<td>14.21 (5.74% of ( M ))</td>
<td>31 (14.29% of ( M ))</td>
<td>4 (1.39% of ( M ))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized due to High-Touch Fomites ([\text{individuals}])</td>
<td>11.33 (4.55% of ( M ), 76.82% of ( I_C ))</td>
<td>10.73 (4.33% of ( M ), 75.51% of ( I_C ))</td>
<td>16 (7.37% of ( M ), 51.61% of ( I_C ))</td>
<td>4 (1.39% of ( M ), 100% of ( I_C ))</td>
</tr>
<tr>
<td>Incidence of Asy. Colonized due to Low-Touch Fomites ([\text{individuals}])</td>
<td>3.42 (1.37% of ( M ), 23.18% of ( I_C ))</td>
<td>3.48 (1.40% of ( M ), 24.49% of ( I_C ))</td>
<td>15 (6.91% of ( M ), 48.39% of ( I_C ))</td>
<td>0 (0% of ( M ), 0% of ( I_C ))</td>
</tr>
<tr>
<td>Ending Pathogen Levels ([\text{spores} \cdot \text{cm}^{-2}])</td>
<td>( P_H = 0.22, P_L = 0.13 )</td>
<td>( P_H = 0.24, P_L = 0.14 )</td>
<td>( P_H = 0.02, P_L = 0.02 )</td>
<td>( P_H = 0.11, P_L = 0.06 )</td>
</tr>
</tbody>
</table>
Table 15: Ranges of Middle 95% of Trajectories. The mean and maximum ranges of the middle 95% of the 100 trajectories generated by the GSSA for the asymptotically colonized and diseased patient classes for Scenarios #0-#4. The range at each time point is the difference between the 97.5th percentile and 2.5th percentile at that time.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.29</td>
<td>11</td>
<td>3.69</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>8.86</td>
<td>12</td>
<td>3.75</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>9.37</td>
<td>12</td>
<td>3.53</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>2.39</td>
<td>6</td>
<td>1.47</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>9.38</td>
<td>12</td>
<td>3.76</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 16: Variances of Trajectories. The mean and maximum variances of the 100 trajectories generated by the GSSA for the asymptotically colonized and diseased patient classes for Scenarios #0-#4.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.61</td>
<td>7.08</td>
<td>1.13</td>
<td>1.59</td>
</tr>
<tr>
<td>1</td>
<td>5.25</td>
<td>7.49</td>
<td>1.17</td>
<td>1.84</td>
</tr>
<tr>
<td>2</td>
<td>5.99</td>
<td>8.72</td>
<td>1.07</td>
<td>1.60</td>
</tr>
<tr>
<td>3</td>
<td>0.53</td>
<td>2.12</td>
<td>0.20</td>
<td>0.59</td>
</tr>
<tr>
<td>4</td>
<td>6.00</td>
<td>8.56</td>
<td>1.22</td>
<td>2.19</td>
</tr>
</tbody>
</table>
Figure 1: PQRST Wave on ECG. The basic pattern of a heart beat seen on an ECG signal is made up of three parts: a P wave, a QRS wave complex, and a T wave. The R wave represents the depolarization of the main mass of the ventricles, when the heart pumps out most of the blood. The RR interval is the time interval between R waves.
Figure 2: RR Interval Example #1. There are five heart beats (PQRST patterns) in six seconds on the ECG signal, resulting in an average heart rate of 50 bpm. The variance in the RR intervals is 0.0167 square seconds. The heart rate at time 1.28 seconds, at the end of the first RR interval, is $\frac{60}{1.28} = 46.875$ bpm. The heart rate at time 2.36 seconds, at the end of the second RR interval, is $\frac{60}{1.08} = 55.556$ bpm. The heart rate at the end of the remaining RR intervals is similarly calculated, resulting in the heart rate signal of bpm over time.
Figure 3: RR Interval Example #2. There are nine heart beats (PQRST patterns) in six seconds on the ECG signal, resulting in an average heart rate of 90 bpm. The variance in the RR intervals is 0.0006 square seconds. The heart rate at time 0.67 seconds, at the end of the first RR interval, is $60 / 0.67 = 89.552$ bpm. The heart rate at time 1.37 seconds, at the end of the second RR interval, is $60 / 0.70 = 85.714$ bpm. The heart rate at the end of the remaining RR intervals is similarly calculated, resulting in the heart rate signal of bpm over time.
Figure 4: Circulation. De-oxygenated blood travels from the body to the right side of the heart via systemic veins. Next, de-oxygenated blood travels from the right side of the heart to the lungs, to pick up oxygen, via pulmonary arteries. Then, oxygenated blood travels from the lungs to the left side of the heart via pulmonary veins. Last, blood travels from the right side of the heart to the body, to deliver oxygen to tissues, via systemic arteries.
Figure 5: Patient Data. ECG, ECG-derived respiration, respiration-derived thoracic pressure, blood pressure, and ECG-derived heart rate data for one control patient.
Figure 6: Schematic. Schematic of the model formulated to explore physiological control mechanisms governing HRV. Three processes are represented: the Baroreflex Mechanism, RSA, and circulation. The input into the model is thoracic pressure data, derived from ECG-derived respiration data.
Figure 7: Type III Functional Response. A type III functional response describing arterial cross-sectional area as a function of blood pressure. Cross-sectional area increase as blood pressure increases and saturates at low and high pressures. The steepness constant $q$ describes how quickly cross-sectional area increases with increasing blood pressure.
Figure 8: Activation Level of PSNS and SNS. A type III functional response describing activation level of the PSNS and SNS due to the Baroreflex Mechanism as a function of the afferent signal of baroreceptors (and pressure). The activation level of the PSNS increases as the afferent signal increases and the activation level of the SNS decreases as the afferent signal increases. Activation levels saturate at low and high signals.
Figure 9: Four Compartments of Circulation. Arterial systemic circulation carries oxygenated blood from the left side of the heart to the body, thus the change in blood volume in the \( \text{as} \) compartment is the difference between the cardiac output of the left side of the heart (\( Q_l \)) and the blood flow in systemic circulation (\( F_s \)). Arterial pulmonary circulation carries oxygenated blood from the right side of the heart to the lungs, thus the change in blood volume in the \( \text{ap} \) compartment is the difference between the cardiac output of the right side of the heart (\( Q_r \)) and the blood flow in pulmonary circulation (\( F_p \)). The change in blood volume in the venous systemic circulation compartment (\( \text{vs} \)) and the venous pulmonary circulation compartment (\( \text{vp} \)) are defined similarly.
Figure 10: Model Output. Time courses of the variables described in Table 1 for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77) with reference parameter values from Table 3 and initial conditions described in Section 1.5.2.
Figure 11: **Model Output.** Time course of the model predicted heart rate for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77) with reference parameter values from Table 3 and initial conditions described in Section 1.5.2.
Figure 12: Model Output for Varied $q_w$. Time course of the model predicted heart rate for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77) for three different values of the parameter $q_w$. The reference parameter value is $q_w = 3$. 
Figure 13: Model Output for Varied $q_{bp}$. Time course of the model predicted heart rate for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77) for three different values of the parameter $q_{bp}$. The reference parameter value is $q_{bp} = 10$. 
Figure 14: Model Output for Varied $q_{bs}$. Time course of the model predicted heart rate for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77) for three different values of the parameter $q_{bs}$. The reference parameter value is $q_{bs} = 10$. 
Figure 15: Model Output for Varied $q_{rp}$. Time course of the model predicted heart rate for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77) for three different values of the parameter $q_{rp}$. The reference parameter value is $q_{rp} = 10$. 
Figure 16: Model Output for Varied $H_{bp}$. Time course of the model predicted heart rate for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77) for three different values of the parameter $H_{bp}$. The reference parameter value is $H_{bp} = 0.15$. 
Figure 17: Model Output for Varied $H_{bs}$. Time course of the model predicted heart rate for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77) for three different values of the parameter $H_{bs}$. The reference parameter value is $H_{bs} = 0.29$. 
Figure 18: Model Output for Varied $H_{rp}$. Time course of the model predicted heart rate for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77) for three different values of the parameter $H_{rp}$. The reference parameter value is $H_{rp} = 0.29$.  

124
Figure 19: Model Output for Varied $B$. Time course of the model predicted heart rate for the model formulated to explore physiological control mechanisms governing HRV given in Equation (1.77) for two different values of the parameter $B$. The reference parameter value is $B = 0.5$. 
B.2 Chapter 2 Figures

Figure 20: Lanzas et al. Model Schematic. Schematic from Lanzas et al. [50] of the epidemiological model for C. diff transmission in a hospital ward. Five patient classes are included: resistant (R), susceptible (S), asymptptomatically colonized with protection (C+), asymptptomatically colonized without protection (C−), and diseased (D). Admissions and discharges for each patient class are not shown.
Figure 21: Schematic. Schematic of the model of *C. diff* transmission including environmental pathways in a hospital ward. Four patient classes are included: resistant (*R*), susceptible (*S*), asymptptomatically colonized (*C*), and diseased (*D*) and two environmental reservoir classes are included: high-touch frequency fomites (*P_H*) and low-touch frequency fomites (*P_L*). Admissions and discharges for each patient class are not shown.
Figure 22: Type II Functional Response. A type II functional response, describing the force of infection for the model of *C. diff* transmission including environmental pathways in a hospital ward, shows the colonization rate increasing as pathogen level increases. Colonization rate saturates at high levels of pathogen. The half-saturation constant $K$ is the level of pathogen that would make the colonization rate half of its maximum value. For smaller values of $K$ (represented by the black line), this value is reached at a smaller pathogen level. For larger values of $K$ (represented by the blue line), this value is reached at a larger pathogen level.
Figure 23: ODE Solution of Scenario #0. The numerical solution of the *C. diff* model described by the system of ODEs in Equation (2.10) for a total ward population of *N* = 30 shows the time courses over 40 days of the system variables from Table 5 with reference parameter values from Table 6 and initial conditions *R₀* = 21, *S₀* = 3, *C₀* = 5, *D₀* = 1, *P_H₀* = *P_L₀* = 0.01.
Figure 24: GSSA Trajectories of Scenario #0. The 100 potential trajectories of the C. diff model generated by the GSSA with the events in Table 8 for a total ward population of $N = 30$ shows 100 possible time courses over 40 days of the system variables from Table 5 with reference parameter values from Table 6 and initial conditions $R_0 = 21$, $S_0 = 3$, $C_0 = 5$, $D_0 = 1$, $P_{H_0} = P_{L_0} = 0.01$. 
Figure 25: Middle 95% of GSSA Trajectories of Scenario #0. The middle 95% of 100 potential trajectories of the C. diff model generated by the GSSA with the events in Table 8 for a total ward population of $N = 30$ shows 100 possible time courses over 40 days of the system variables from Table 5 with reference parameter values from Table 6 and initial conditions $R_0 = 21$, $S_0 = 3$, $C_0 = 5$, $D_0 = 1$, $P_{H_0} = P_{L_0} = 0.01$. The shaded area shows the difference between the 97.5th percentile and 2.5th percentile at each time point.
Figure 26: Resistant and Susceptible Time Courses of Scenario #0. The ODE solution of the resistant ($R$) and susceptible ($S$) patient classes is compared to the 100 potential trajectories generated by the GSSA and the middle 95% of the trajectories. The time courses are for a total ward population of $N = 30$ over 40 days, with reference parameter values from Table 6 and initial conditions $R_0 = 21$ and $S_0 = 3$. 
Figure 27: Asymptomatically Colonized and Diseased Time Courses of Scenario #0. The ODE solution of the asymptomatically colonized \((C)\) and diseased \((D)\) patient classes is compared to the 100 potential trajectories generated by the GSSA and the middle 95% of the trajectories. The time courses are for a total ward population of \(N = 30\) over 40 days, with reference parameter values from Table 6 and initial conditions \(C_0 = 5\) and \(D_0 = 1\).
Figure 28: High-Touch and Low-Touch Frequency Fomites Time Courses of Scenario #0. The ODE solution of the high-touch frequency fomites ($P_H$) and low-touch frequency fomites ($P_L$) environmental reservoir classes is compared to the 100 potential trajectories generated by the GSSA and the middle 95% of the trajectories. The time courses are for a total ward population of $N = 30$ over 40 days, with reference parameter values from Table 6 and initial conditions $P_{H0} = P_{L0} = 0.01$. 
Figure 29: Middle 95% of GSSA Trajectories of Scenario #1. The middle 95% of 100 potential trajectories of the *C. diff* model generated by the GSSA with the events in Table 8 for a total ward population of *N* = 30 shows 100 possible time courses over 40 days of the system variables from Table 5 with reference parameter values from Table 6 and initial conditions 

\[ R_0 = 21, \quad S_0 = 3, \quad C_0 = 5, \quad D_0 = 1, \quad P_{H_0} = P_{L_0} = 0.1. \]

The shaded area shows the difference between the 97.5th percentile and 2.5th percentile at each time point.
Figure 30: Middle 95% of GSSA Trajectories of Scenario #2. The middle 95% of 100 potential trajectories of the *C. diff* model generated by the GSSA with the events in Table 8 for a total ward population of *N* = 30 shows 100 possible time courses over 40 days of the system variables from Table 5 with reference parameter values from Table 6 except for *a*$_R$ = 0.75, *a*$_S$ = 0, *a*$_C$ = 0.25, and *a*$_D$ = 0, and initial conditions *R*$_0$ = 21, *S*$_0$ = 3, *C*$_0$ = 5, *D*$_0$ = 1, *P*$_{H_0}$ = *P*$_{L_0}$ = 0.01. The shaded area shows the difference between the 97.5th percentile and 2.5th percentile at each time point.
Figure 31: Middle 95% of GSSA Trajectories of Scenario #3. The middle 95% of 100 potential trajectories of the C. diff model generated by the GSSA with the events in Table 8 for a total ward population of $N = 30$ shows 100 possible time courses over 40 days of the system variables from Table 5 with reference parameter values from Table 6 except for $a_R = 0.75$, $a_S = 0.25$, $a_C = 0$, and $a_D = 0$, and initial conditions $R_0 = 21$, $S_0 = 3$, $C_0 = 5$, $D_0 = 1$, $P_{H0} = P_{L0} = 0.01$. The shaded area shows the difference between the 97.5th percentile and 2.5th percentile at each time point.
Figure 32: Middle 95% of GSSA Trajectories of Scenario #4. The middle 95% of 100 potential trajectories of the \textit{C. diff} model generated by the GSSA with the events in Table 8 for a total ward population of $N = 30$ shows 100 possible time courses over 40 days of the system variables from Table 5 with reference parameter values from Table 6 except for $\sigma = 0.42$ and $\mu = 0.33$, and initial conditions $R_0 = 21$, $S_0 = 3$, $C_0 = 5$, $D_0 = 1$, $P_{H0} = P_{L0} = 0.01$. The shaded area shows the difference between the 97.5th percentile and 2.5th percentile at each time point.
Vita

Lindsey Fox was raised in Weaverville, North Carolina and graduated from North Buncombe High School. In 2009, she started her undergraduate career at East Tennessee State University (ETSU) in Johnson City, Tennessee as a pre-medicine student, intending to go to medical school. However, Lindsey discovered a passion for using mathematics as a tool to study her interests in biology and physiology, and decided to pursue graduate school. Under the advisement of Dr. Anahita Ayasoufi, her undergraduate thesis utilized numerical simulations to study the effect of blood vessel geometry on plaque formation in the carotid sinus. Alongside her science coursework, Lindsey studied pottery in Florence, Italy. She graduated from ETSU as a University Honors Scholar in 2013 with a Bachelor of Science degree in Mathematics and minors in Art and Biology.

In 2013, Lindsey began her graduate career at the University of Tennessee (UT) in Knoxville, Tennessee. She studied Mathematical Biology and Numerical Mathematics. Under the advisement of Dr. Judy Day, her graduate work involved formulating two mathematical models, one to explore the origin and control mechanisms of heart rate variability and one to quantify the contribution of environmental pathways to Clostridiodoides difficile transmission in healthcare settings. While working as a Graduate Teaching Associate, mostly teaching an introductory level Statistics course, Lindsey discovered a passion for teaching Mathematics and decided to pursue a career in academia. She graduated from UT in 2017 with a Master of Science degree in Mathematics and again in 2019 with a Doctor of Philosophy degree in Mathematics, with a concentration in Mathematical Ecology/Biology. Lindsey will be joining the Mathematics Department at Eckerd College in Saint Petersburg, Florida in Fall 2019.