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Modeling Nosocomial Disease Outbreaks using a Combined Differential Equations and Agent Based-Modeling Approach

Cody FitzGerald

Senior Honors Thesis

University of New Hampshire

Honors College

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Contents

Chapter 1

Introduction

1.1 Abstract

A nosocomial infection is an infection that a patient develops while in a hospital or healthcare related setting, also known as a hospital acquired infection (HAI).This project has two foci: firstly to model a HAI within an individual, then secondly to understand community-level propagation effects of a nosocomial infection within a hospital ward. An analysis of a novel system of coupled nonlinear ordinary differential equations (representing the HAI attack and immune response within an individual) was first completed. More specifically the model includes an s parameter that allows frailty to be patient specific. After the dynamic behaviors of the model were fully characterized, an agent based-modeling approach was used to understand community level dynamics. Of particular interest was the interplay between the time span of an infection and the distribution of immune responses across agents[1].

1.1.1 Motivation

Understanding and modeling disease dynamics has always been a point of scientific interest, but it is more important than ever due to the rise of antibiotic resistant bacteria, the globalization of travel, and the international food distribution system. Though antibiotics were once hailed as miracle drugs, bacterial populations are able to quickly form a natural resistance in some cases rendering the "miracle drugs" useless [1]. The rise of antibiotic resistance creates an evolving conflict between pharmaceutical developers and bacterial populations [1]. Due to the

cost of developing new antibiotics, the inevitably short amount of time a drug would be effective before a resistant strain of bacteria adapts, and the lack of economic incentives, antibiotic drug development is no longer a major research focus for most large pharmaceutical companies [1]. The market is failing to create new antibiotics while hospitals are becoming more dangerous due to the risk of nosocomial infections that are untreatable with available antibiotics.

Centuries ago, the global population was geographically isolated and travel was localized in scope. This is no longer the case with widespread access to cars, trains, ships, and aircraft. Nearly everywhere on Earth is accessible by some mode of transport within a few days. The global population can now travel more easily than ever before, but this perceived luxury is actually a threat. Aging airport infrastructure along with a lack of public health surveillance allows the possibility for travelers to spread an infectious disease endemic to their home but novel to their destination. Common examples of global outbreaks from the last two decades include SARS, Avian Influenza, and Ebola. Though infectious diseases usually get the most academic attention and media coverage, the same logic applies to nosocomial diseases or antibiotic resistance.

Increased human travel potential is not the only thing worsening the outlook for nosocomial diseases. Meat production is heavily reliant on antibiotics [1]. In 2015, Chinese scientists found MCR-1 in bacterial samples from humans and pigs [2]. MCR-1 is a gene that gives its host resistance to all known antibiotics [2]. Perhaps even more disturbing is the fact that the MCR-1 gene can easily be transferred between bacterial species [2]. MCR-1 has been found in bacterial samples from humans, food, and animals on four different continents: North America, Europe, Africa, and Asia [3]. MCR-1 has yet to be found in the US[3].

As a result of the lack of new antibiotics, the meat production industry, the globalization of travel, and novel mutations naturally arising in bacterial populations, nosocomial infections will never be completely vanquished[1]. It is crucial to understand not only how the infection operates within an individual, but also communal spreading patterns of the infection. Previous research has looked at infections within an individual or modeled infections within a traditional mathematical epidemiological framework (such as SEIR modeling), but the combination between the two has received little attention [4, 5]. Another area of poor scientific coverage is the distribution of immune responses within a population and its effect on a population's resiliency with regard to a

nosocomial infection.

1.1.2 The Model and Parameter Explanation

The model consists of two coupled nonlinear ordinary differential equations which use y(t) to denote the relative severity of the infection and w(t) to denote the relative immune response. Both y(t) and w(t) are qualitative in nature, but may be interpreted on a scale from 0 to 10. y(t) = 0 means that the individual has no infection whatsoever and y(t) = 10 indicates the maximum infection a patient could experience. Similarly, w(t) = 0 indicates no immune response, while w(t) = 10 implies that the patient's immune system is waging an all out war against the infection. λ_1 represents a time scaling parameter which allows the infection equation to be customizable for infections with different temporal behavior. λ_2 plays the same role except for the immune response.

$$\frac{dy}{dt} = \frac{1}{\lambda_1} y(10-y)(\frac{y}{1+w} - 1)$$

$$\frac{dw}{dt} = \frac{1}{\lambda_2} w(10-w)(-1+sy-w)$$

The infection equation contains a logistic growth equations with a changing carrying capacity. It is directly related to the immune response by the 1+w term in the denominator. When y > 1+w, the patient will continue to grow sick and when y < 1+w the immune response will start to "win" allowing the patient to begin to get healthier.

The unique feature of the immune response equation is the s parameter. The s parameter can be thought of as the sensitivity of the immune response to the infection. If y(t) < $\frac{1}{s}$ the immune response will decline to zero, but if y(t) > $\frac{1}{s}$ the immune system will combat the infection. To put in a more clinical context, an immune response is unnecessary for small infections that will die out regardless, but for larger infections an immune response is necessary.

Parameter	Meaning
y(t)	Relative Severity of the Infection
w(t)	Relative Severity of Immune Response
s	sensitivity parameter
λ_1	time scaling parameter for infection
λ_2	time scaling parameter for immune response

1.1.3 Equilibrium Solutions

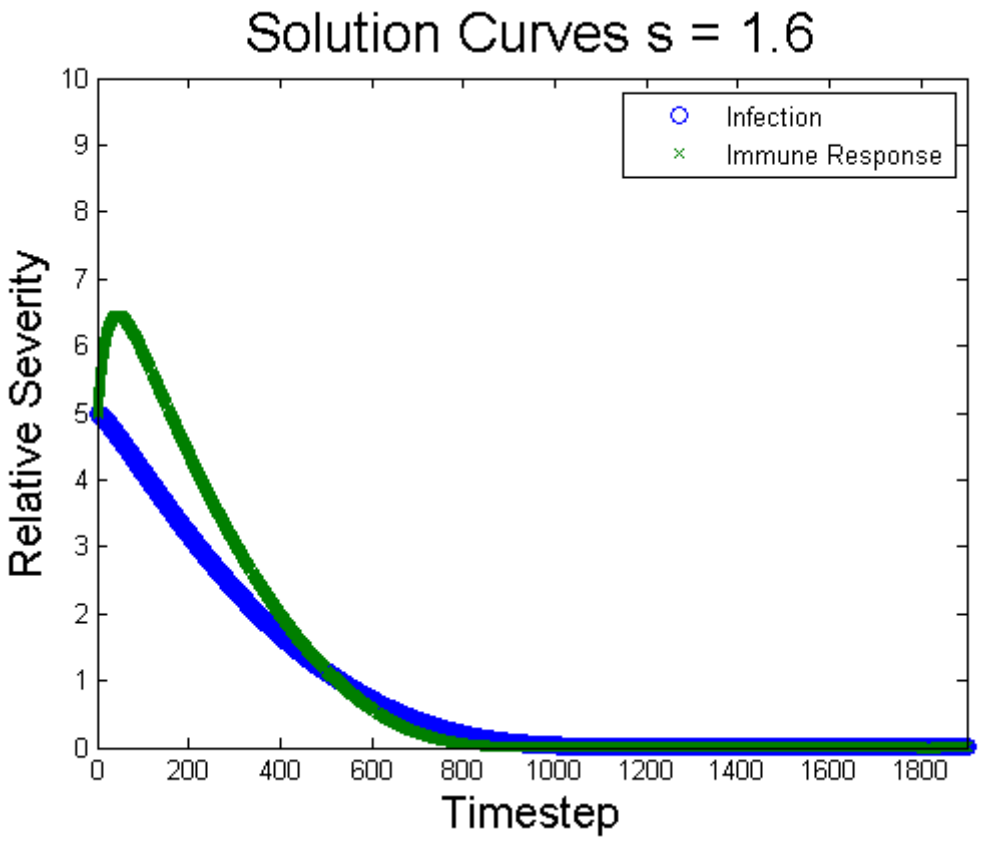
To analyze the dynamics of the coupled ordinary differential equations, a linear stability analysis was completed to find all equilibrium solutions. There are two categories: those that dependent on s and those that do not. Firstly, the s parameter independent equilibrium solutions are described in the following table.

Equilibrium Solution	Meaning	Stability
(0,0)	No infection or immune response	stable
(1,0)	Non-infective yet continual cold	stable
(10,0)	Death	unstable
(0,10)	No infection and full immune response (unrealistic)	unstable
(10,10)	Intense sickness or death	unstable

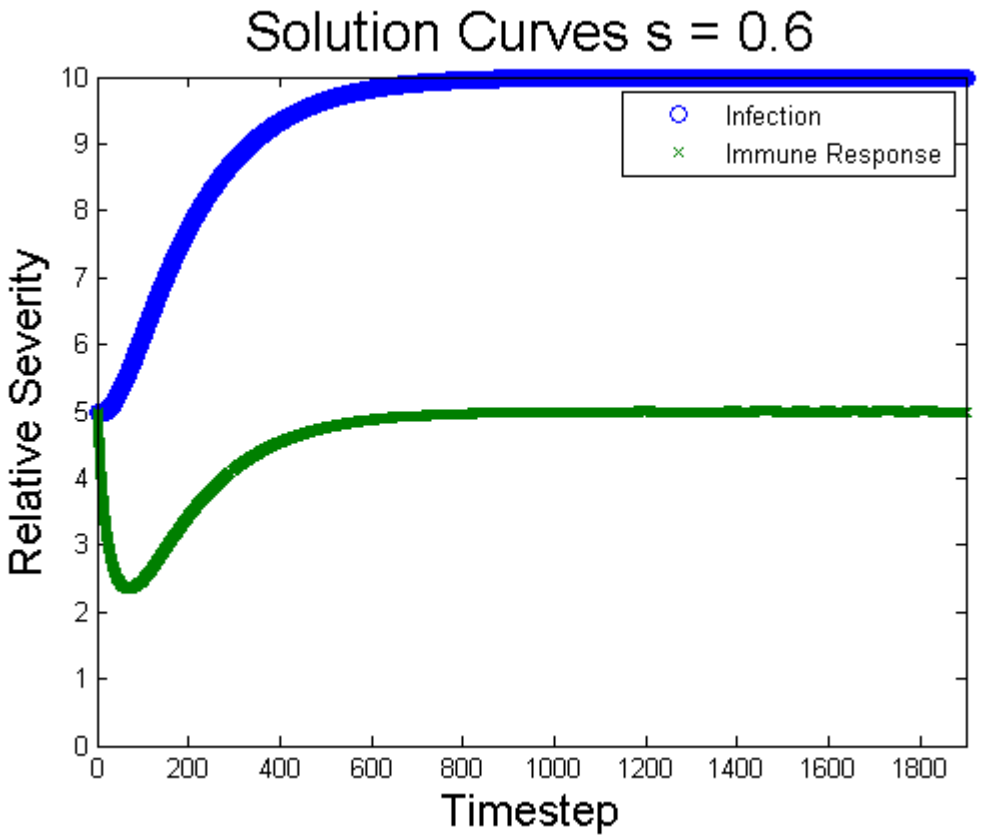
The last equilibrium point is dependent on s and occurs at (10, -1 + 10s) at s = .1 and s = 1.1 the system is subject to transcritical bifurications as the moving equilibrium point passes through the equilibra at (10,10) and (10,0) respectively. At s = .1 (10, -1+10s) = (10,0) and similarly at s = 1.1, (10, -1+10s) = (10,10). When the sensitivity parameter is between 0.1 and 1.1 the equilibrium at (10, -1 + 10s) is a stable node. Clinically this corresponds to a situation where the immune response is insufficient to counter against the infection and the infection endures indefinitely. From a modeling perspective such situations might result in either patient mortality or situations where the infection cannot be cured and the only option is palliative care.

At s = 1 the model undergoes a degenerate bifurication resulting in a manifold of equilibria occuring on the line y = 1 + w. This represents a patient's immune response being equal to the infection. The infection will stabilize based on the initial conditions.

Of most interest is what happens at s = 1.1. At s = 1.1 (10 , -1 + 10s) = (10,10) causing an exchange of stability. For s greater than 1.1, (10,10) stays a saddle point. This means that the only equilibrium solutions in the system for s greater than 1.1 are (0,0) and (1,0) implying that for s greater than 1.1 a patient can never die. The patient therefore must always revert back to a mildly healthy state either perfectly healthy (0,0) or retaining a non-infective but persistent cold (1,0).



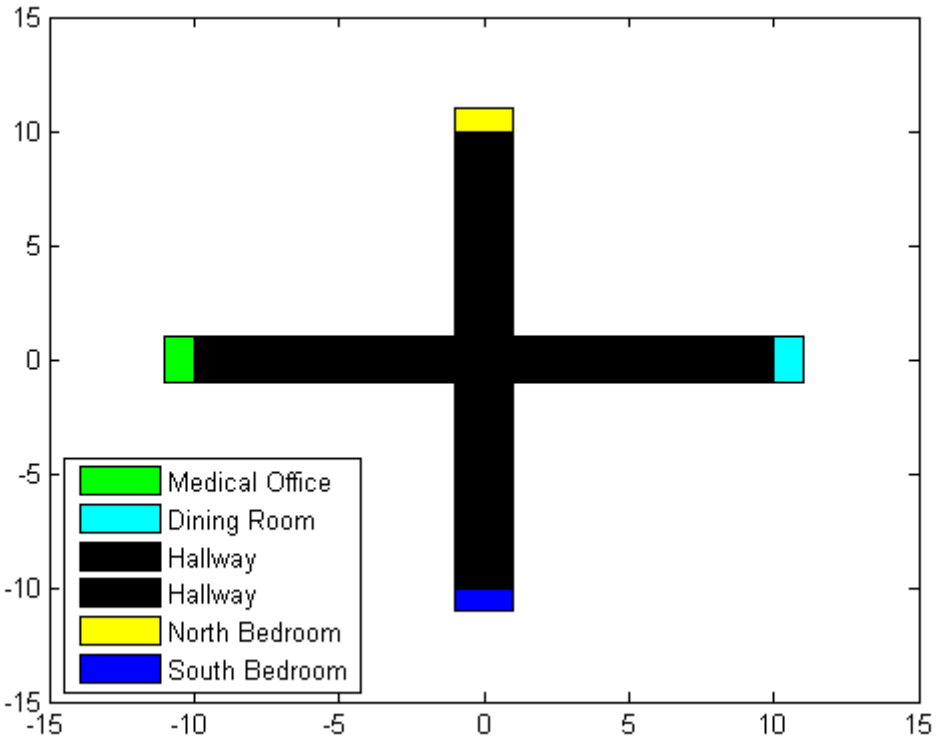
When s = 1.6, the model's dynamics force the patient to return to a mildly healthy state. The infection level monotonically decreases to zero, while the immune response first heightens to fight off the infection, then decreases down to zero. The patient in question returns to a perfect healthy state.



For s = .6, (10,-1+10s) is a stable equilibrium. The patient's infection is fast moving and does not allow the patient's immune response enough time to successfully combat the infection. The infection increases towards ten while the immune response approaches five. Physically this can be interpreted as a patient death or an incurable infection.

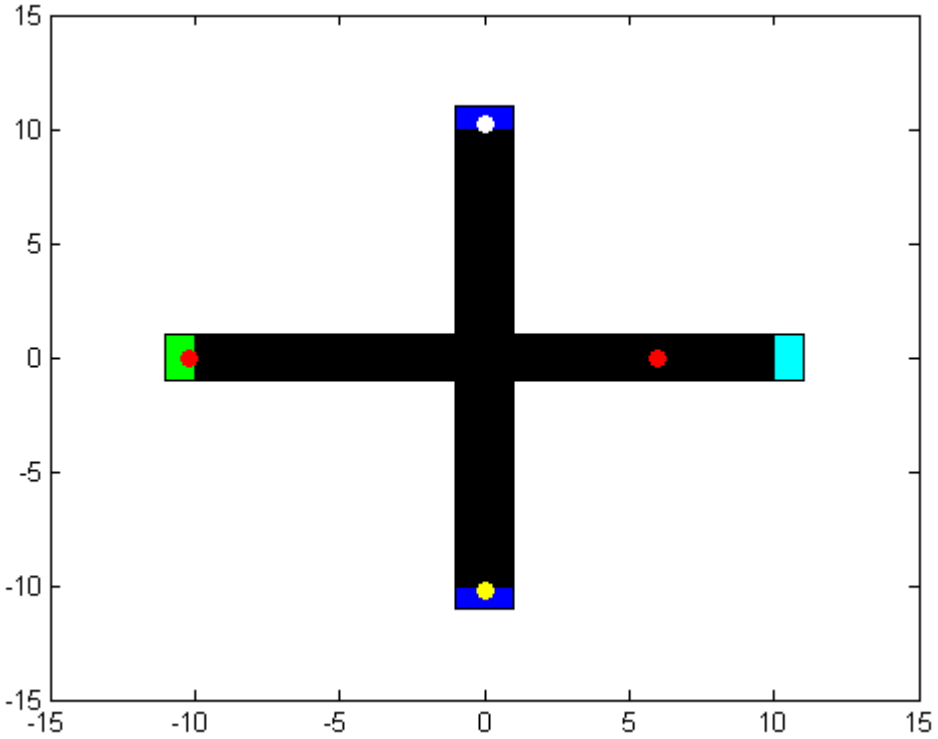
1.1.4 Description of the Ward, Agents Classes, and the Associated Partially Randomized Schedules

A single simulation follows a cohort of 10 patients and 2 nurses each given a partially random, partially deterministic route through the ward. The infection level, the immune response, and location of each agent was tracked independently throughout the simulation. One simulation represents one day in the ward. The hospital ward is represented by an 11 by 11 grid containing two bedrooms each housing two groups of five patients (denoted North Patients and South Patients), a medical office, and a dining/recreation room.



The patients are broken into two subclasses depending on the bedroom they are housed in: North and South. The North Patients begin and end all simulations in the North Bedroom, while the South Patients begin and end all simulations in South Bedroom.

The partially randomized schedule for each agent within the system dictates their (x,y) coordinates at every time step. Due to the layout of the ward, one of the coordinates is always 0. The schedule assigned to each agent is only partially randomized due to the fact that each patient eats breakfast, lunch, and dinner at the same time. For all other times during the simulation, all



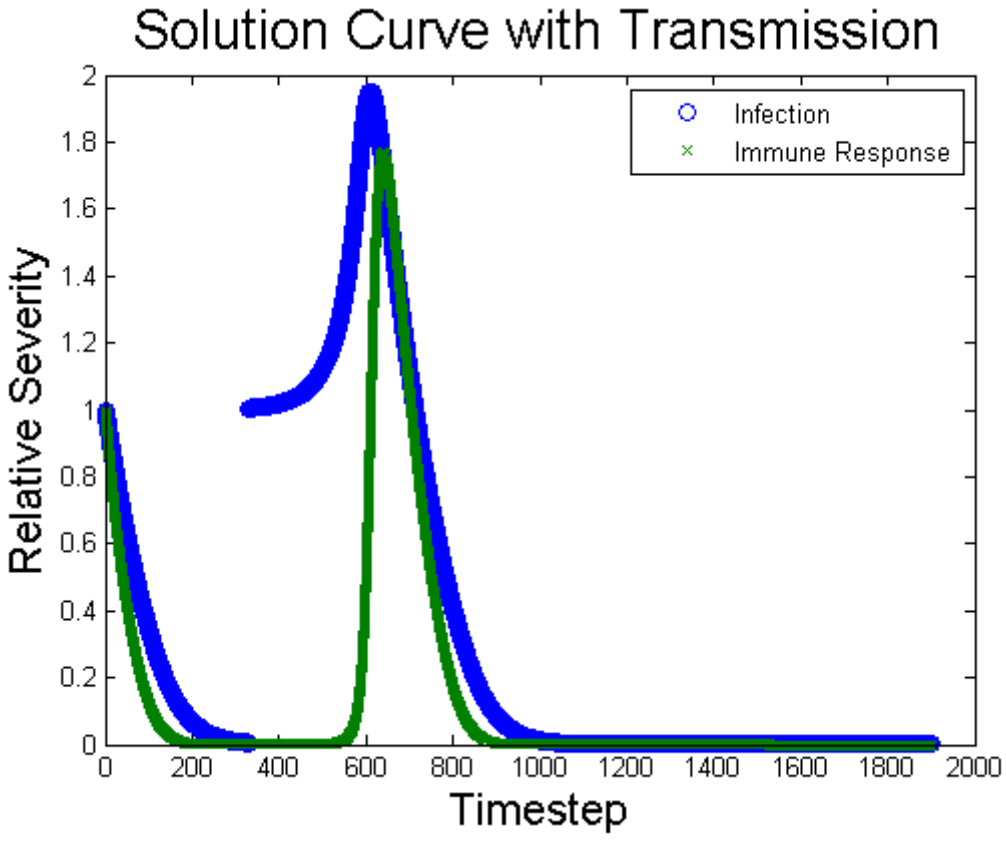
patients are proscribed one of five behaviors to complete: walking to the medical office and back, walking to the opposite bedroom and back, walking to the dining room and back, walking to and from the center of the ward twice, or resting in their respective bedroom. The nurses have a set walk through the ward that is predetermined. Starting at the medical office, the nurses first walk to the south bedroom, then to the dining room, then to the north bedroom, and back once again to the medical office. This action is completed by both nurses twice during a simulation separated by a randomized piece. The nurse's randomized piece is a binary choice between staying in the medical office and walking to and from the dining room. For visual purposes the North Patients are represented by white dots, the South Patients are represented by yellow dots, and the Nurses are represented by red dots. The figure above displays all patients resting while one nurse holds down the medical office and the other patrols the ward.

1.1.5 Transmission Dynamics

At the start of each simulation one patient ("patient zero") begins with initial conditions of (9,3), while all other agents start at (1,1), a relatively healthy state. All agents are assigned an s value greater than 1.1. Given the stable equilibrium solutions for the associated nonlinear coupled ODE, all agents must eventually get better in one of two ways: revert back to a perfectly healthy state (0,0) or end the simulation with a slight non-infective cough (1,0).

The infection is spread solely by agents coughing. Patients have a 7% probability of coughing if their infection level is greater than five. This allows for occasional coughing opposed to continual coughing throughout the simulation. For an agent to be infected by a cough, they must be in the "splash-zone" of a coughing agent. The splash zone is defined as a 1 unit radius around a coughing agent's position. For each agent, the transmission probability is held constant at 5%. No agent can infect themselves, but each agent can infect every other agent in the simulation.

If an agent is infected by a cough, their infection severity is incremented by 1. Successful transmission events are easy to detect during simulations by the one unit jumps in the infection equation.



At the end of 1900 time steps one of two things can happen: if the all agents have infection levels less than five (no agents are coughing at t = 1900), the simulation ends. If one or more agent(s) has an infection level greater than five, the simulation is elongated by 1900 steps. In rare cases an agent can be infected multiple times in a row, forcing the infection and immune response level towards (10,10). To stop an agent from becoming "stuck" exactly at (10,10), before the elongation of the simulation all agents' infection level are accessed. If a specific agent's infection is greater than nine it is reduced by 2 units. This is justified because the model is applied to non-terminal outbreaks that all patients are expected to recover from.

Chapter 2

Results

2.1 Simulation Results

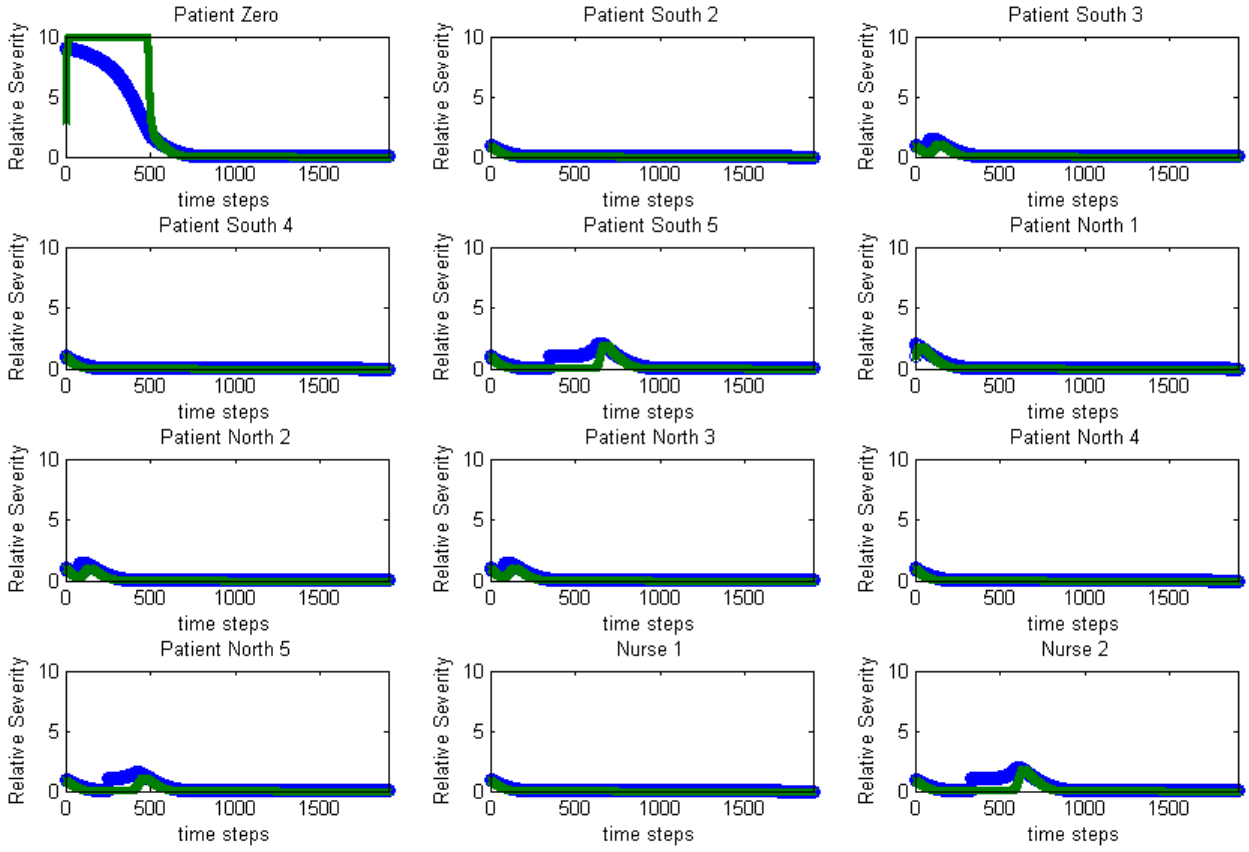
100 simulations were run that included two Nurses, five North Patients, and five South Patients. Each of which were assigned a partially randomized schedule and an s-parameter equal to 1.6. In each of the simulations, South Patient One started with initial conditions equal to (9,3). All other agents in the simulation started with the initial conditions equal to (1,1). Transmission dynamics between agents were as previously described. Each simulation ran initially for 1900 time steps. If all agents' infection level was less than five after 1900 time steps the simulation was deemed over. If not, the simulation continues iteratively as previously described until the outbreak is over. For each of the simulations, λ_1 was equal to 500 and λ_2 was held constant at 200.

The average number of transmission events per simulation was 6.7, with a minimum of 1 transmission event and a maximum of 14 transmission events. The average length of the outbreak was 393.48 time steps, with a minimum of 389 time steps and a maximum of 551 time steps. No control group simulation went beyond 1900 time steps.

2.1.1 Experimental Comparison

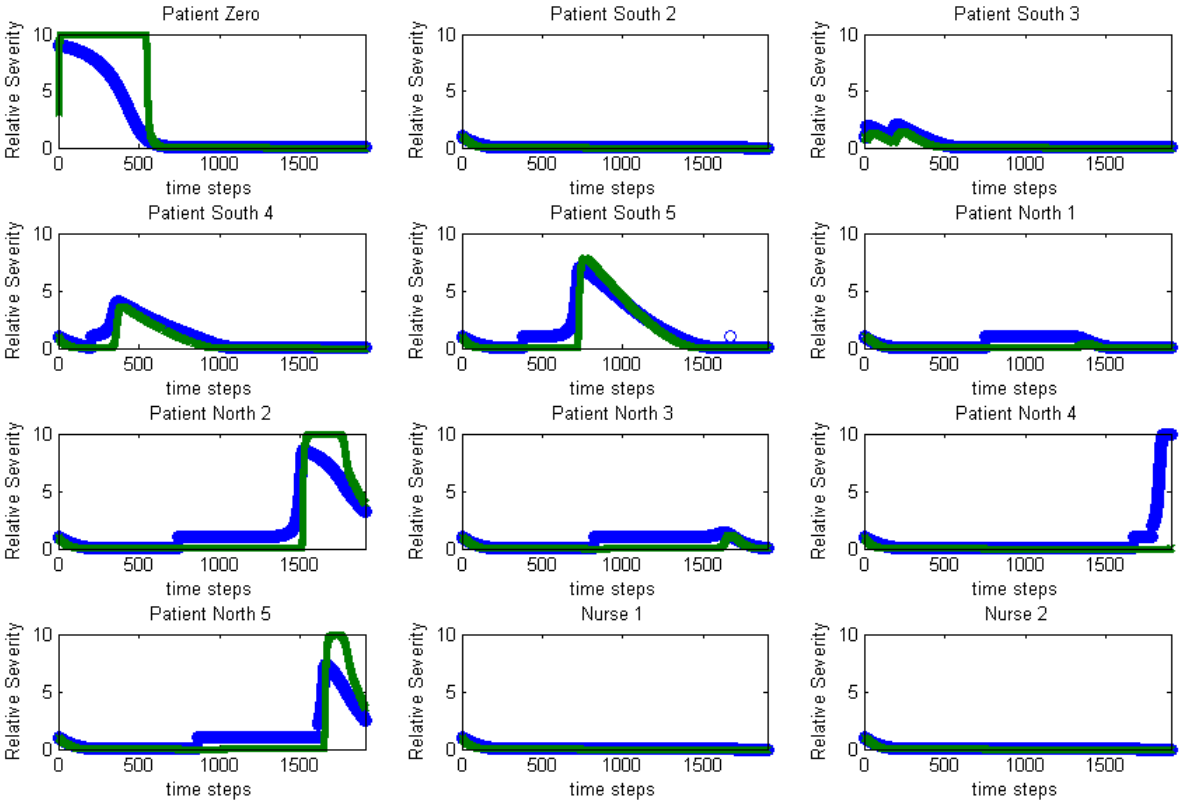
Another round of 100 simulations were run on an experimental group. All conditions, dynamics, and modeling assumptions were held constant except for the s-parameter. In the experimental group, each agent's s-parameter was drawn from a uniform random distribution between 1.1 to 2.1.

In the experimental group both the average number of transmission events per simulation and the average length of the outbreak increased. The average number of transmission events per simulation was 15, with a minimum of 3 and a maximum of 115. The average length of the outbreak was 618.19 time steps, with a minimum of 380 time steps and a maximum of 4071 time steps. Seven out of 100 simulations went beyond 1900 time steps indicating a multi-day outbreak. The difference between the length of the infection and the number of transmission events between the experimental and control group is significant at an alpha value of .01 ($p = .0007$ and $p = .00000335$, respectively).



Above are the associated plots for a single control group simulation (when s = 1.6 for all agents). About half of the agents experience one to two transmission events while the all other agents experience no transmission events whatsoever. None of the agents besides Patient Zero experienced an infection level greater than five during the entire simulation. This particular

simulation ended before 400 time steps.



Above are the associated plots for a single experimental group simulation (s is drawn from a uniform random distribution between 1.1 to 2.1). The behavior in general is more erratic and exciting. Patient North Four ends the first day with an infection level that exceeds five indicating a multi-day outbreak. Four out of 12 agents exceeded an infection level of five at some point during the first 1900 time steps.

Number of Transmission	S = 1.6	S Varied
Min	1	3
Max	14	115
Average	6.7	15

Length of Infections	S = 1.6	S Varied
Min	389	380
Max	551	4071
Average	393.48	618.19

2.1.2 Discussion

There is a clear difference between both the length of an infection and number of infections when s in drawn from a uniform random distribution between 1.1 and 2.1 and when s = 1.6 for all agents in the simulation. These results have clear implications for the mathematical modeling community.

A few things are clear. For infections that all patients are expected to recover from, variation in the individual strength of the immune response lengthens the time for an entire ward to recover from an infection. This is not necessarily intuitive as both the control group and experimental group had an average immune response hovering around s = 1.6. For the mathematical epidemiological modeling community, these results imply the need for more specificity when making models and modeling assumptions for immune responses at both the individual and communal level. The individual pieces do not necessarily act as the average (or whole) does. It also emphasizes the need for more non-traditional modeling techniques such as agent based-modeling to help increase variability between individuals in the study. Traditional mathematical epidemiological modeling techniques rely on differential equations techniques (SIS,SIR, and SEIR modeling) alone. This type of modeling assumes homogeneity in each subclass making meaningful variability impossible to include in a way that evolves as the infection progresses.

2.1.3 Future Work

Though this study showed that variation within a population's immune response caused the duration of the outbreak to last longer than the same outbreak in a completely homogeneous

population with respect to immune response, it did not tackle questions regarding what part of the heterogeneity in the group caused the reduced resiliency. The next experiment should involve quarantining agents with the weakest immune responses (i.e. s less than 1.6) and monitoring the length of the outbreak for quarantined agents and the general population (agents with an average to high functioning immune response s less than or equal to 1.6).

If this experiment was shown to be effective in reducing the length of time until an outbreak was over, it would be a meaningful result. The result would have direct implications into hospital design and outbreak protocol. It would also have implications for densely populated housing design where influenza and other sicknesses can easily spread. Examples include military and university housing. Similar systems are used in intensive care units, but are commonly used for infections and diseases with higher mortality rates, though the concept would be beneficial in a multitude of housing scenarios for non-life-threatening illnesses.

Identifying biomarkers corresponding to the strength of a patient's immune response with respect to a certain infection would be helpful for not only understanding the population's collective and individual immune response, but also to help set an immune response threshold. The biomarkers would generate a quantitative measure of a patient's immune resiliency to the infection. Given this information, it would be easy to partition the population into two groups: the general population consisting of members with average to high functioning immune systems, and individuals with a weak immune system that would be isolated.

Other future directions include small changes to the existing model. In some hospitals, health care workers are now wearing location tracking devices making route data available. Given this information, the schedule that nurses and other health care workers take through the simulation could be more realistic. Similarly, if route data was available for patients, their associated simulation paths would also be more accurate.

During hospital stays patients often receive visitors in the form of friends, family members, and medical specialists other than general nurses and physicians. Visitors can often bring in new pathogens on their clothing or infect patients through direct transmission. Including outsider visitation is just one way of making the model more realistic, others include: increasing the size and complexity of the hospital ward. This might be accomplished by including more beds in the

ward, creating more rooms for the patient and health care workers to assess, or even creating a multi-floor ward. In addition, numerous other distributions could be sampled to generate individual agent's s parameter to understand the distribution's affect on the length of the outbreak within the ward. Transmission dynamics could also be adapted to include indirect transmission from fomite vectors or time-delayed transmission. An example of fomite transmission might include an agent sneezing on a piece of furniture, then another agent sitting on the piece of furniture and becoming infected. Time-delayed transmission might include an agent's cough (or other effluvia) lingering in the splash zone for n time steps opposed to a single time step.

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Modeling Nosocomial Disease Outbreaks using Differential Equations and an Agent Based-Modeling Approach

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ABSTRACT

A nosocomial infection is an infection that a patient develops while in a hospital or healthcare related setting, also known as a hospital acquired infection (HAI). According to the CDC in 2011, of the patients that developed HAIs nearly 10% eventually died. This project has two foci: firstly to model the progress of a HAI within an individual, then secondly to understand community-level propagation effects of the infection within a hospital ward. An analysis of a novel system of coupled nonlinear ODE's (representing the HAI attack and immune response within an individual) was first completed. After, the dynamic behaviors of these models were fully characterized, an agent based-modeling approach was used to understand community level dynamics in a small hospital ward including the effectiveness of masks to limit successful disease transmission.

THE MODEL

$$\frac{dy}{dt} = \frac{1}{\lambda_1} y(10-y)\left(\frac{y}{1+w} - 1\right)$$

$$\frac{dw}{dt} = \frac{1}{\lambda_2} w(10-w)(-1+sy-w)$$

- Equilibria are dependent on s

Parameter	Meaning
y	Infection
w	Immune response
s	sensitivity parameter (with regard to the infection)
λ_1	scaling parameter for infection
λ_2	scaling parameter for immune response

METHODS

- The system includes 10 patients, 2 nurses, a healthcare worker office, a dining/recreation center, and two bedroom units each housing five patients
- Each individual is assigned a randomized schedule and a coupled nonlinear ODE with a sensitivity parameter.

- A day is simulated exposing the agents to transmission events without any mask
- Another day is simulated with all agents wearing masks to limit transmission events.

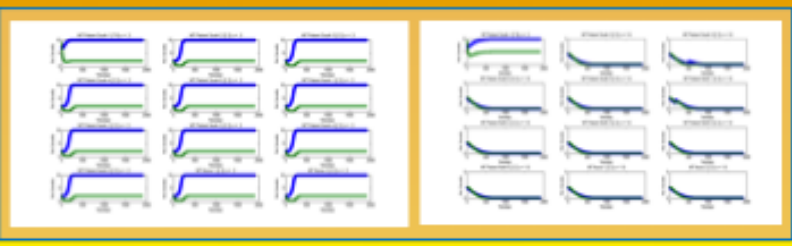
TRANSMISSION MECHANICS

- There exists one 'patient zero' in the system coughing on a schedule .
- For a given cough position (x,y), a rectangular "splash-zone" is created.
- The "splash-zone" is a unit rectangle centered at the cough location.
- If another agent is in the "splash-zone" during a cough, there an associated transmission probability
- Transmission probability without masks = 10%
- Transmission probability with masks = 1%
- If the transmission event is successful, the model changes slightly:

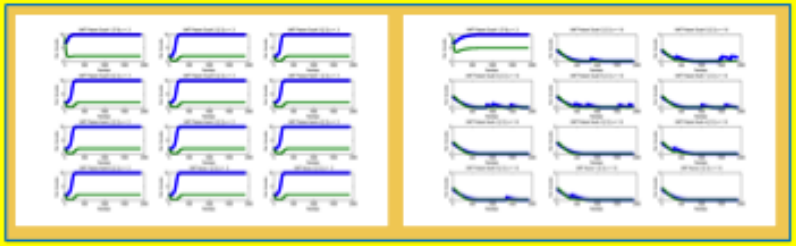
$$\frac{dy}{dt} = \frac{1}{\lambda_1} y(10-y)\left(\frac{y}{1+w} - 1\right) + \frac{1}{2}$$

$$\frac{dw}{dt} = \frac{1}{\lambda_2} w(10-w)(-1+sy-w)$$

MASKED TRANSMISSION DYNAMICS RESULTS



UNMASKED TRANSMISSION DYNAMICS RESULTS



MASKED VS. UNMASKED TRANSMISSION

FUTURE DIRECTIONS

- Vary the value of s depending on agent classes.
- Randomize the value of s.
- Run the simulation over a longer period of time.
- Create more complex multi-agent transmission dynamics.
- Adjust the intensity of the "penalty" associated with a transmission event.

AKNOWLEDGEMENTS

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