Math Honors Thesis - Transmission Dynamics of HA-MRSA and CA-MRSA in the Hospital Setting

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Abstract

Methicillin-resistant Staphylococcus aureus (MRSA) is an antibiotic-resistant, highly virulent bacterium that causes infections in humans. The traditional hospital-acquired strain of MRSA, HA-MRSA, often attacks elderly or otherwise immunocompromised patients who could more readily contract the bacteria and develop bloodstream infections (Nagle, pp. 310). A community-acquired, CA-MRSA, which has been known to affect even young and healthy individuals, has more recently infiltrated the hospital setting (D’Agata, 2009, p. 274). There exist studies that predict CA-MRSA will overtake HA-MRSA in the hospital setting. Thus, this paper endeavors to test these predictions through analysis of a differential equations model developed in 2010 by D’Agata et al. to describe the transmission dynamics of HA-MRSA and CA-MRSA in the hospital setting.

By simplification of the model, we find the critical (equilibrium) points of the system at which the rates of transmission of both CA-MRSA and HA-MRSA are zero. We utilize parameter values estimated by the Beth Deaconess Medical Center (Table 1) to construct a parameter-dependent model of interest. Furthermore, after linearization of the model, we apply the technique of characteristic equations and Jacobian matrices to determine the type and stability of each critical point for the parameter-specific model. The findings for the steady state of the parameter-specific model indicate that CA-MRSA will competitively exclude (drive to extinction) the HA-MRSA strain in accordance with the hypothesis put forth by D’Agata et al. (2010). These results are verified through numerical simulations utilizing the Runge-Kutta method. However, we find that the model is parameter-dependent through uncertainty and sensitivity analyses on the parameters using Latin hypercube sampling structures and partial rank correlation testing. Thus, further research on parameter estimations and distributions is necessary to understand the transmission dynamics and steady state(s) of HA-MRSA and CA-MRSA in the hospital setting.

1 Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) is an antibiotic-resistant and highly virulent bacterium that causes infections in humans. MRSA was first documented in the mid-1980s in the health care setting and has since begun to spread to the general population (Chavez and Decker, 2008, p. 763). The traditional hospital-acquired strain of MRSA, HA-MRSA, has been an issue in hospitals where elderly or otherwise immunocompromised patients could more readily contract
the bacteria and develop bloodstream infections (Nagle et al., 2012, p. 310). The health burden of HA-MRSA on these already debilitated patient groups is severe, as HA-MRSA has commonly been associated with serious infections of the urinary tract, blood stream, surgical wounds, and pneumonia (Chavez and Decker, 2008, p. 764).

More recently, a community-acquired strain of MRSA, CA-MRSA, has been affecting members of the larger community, including young and healthy individuals (D’Agata et al., 2009, p. 274). Often, individuals affected by the CA-MRSA belong to specific groups, such as direct-contact athletes or individuals living in shelters, with risk factors of overcrowding, greater likelihood of skin-to-skin contact, more unhygienic living conditions, or overexposure to antibiotics (Jensen and Skov, 2009, p. 365). Yet, while CA-MRSA is most often associated with skin and soft tissue infections (Chavez and Decker, 2008, p. 764), certain strains of CA-MRSA have been connected to severe infections, including necrotizing skin infections, septic thrombophlebitis, bacteremia, and infective endocarditis (D’Agata et al., 2009, p. 274).

This new strain is being spread into hospitals, and there exist studies that predict CA-MRSA will overtake HA-MRSA in hospitals and likely increase the mortality burden attributed to MRSA (D’Agata et al., 2009, p. 274). The spread of CA-MRSA into the health care setting is inevitable considering the large community reservoir of the bacteria. Also contributing to its infiltration into hospitals is the ability of CA-MRSA to be carried by a host for prolonged periods of time before causing infection, allowing it to be carried undetected into hospitals (Jensen and Skov, 2009, p. 366). The penetration of CA-MRSA into the hospital setting is especially concerning due to the broader reach of CA-MRSA as opposed to HA-MRSA. Additionally, CA-MRSA has the potential to greatly increase the burden of disease on elderly or immunocompromised hospital patients since these individuals are already more at risk for infection than those who typically contract CA-MRSA and due to CA-MRSA’s ability to cause serious infections (D’Agata et al., 2009, p. 274).

There is evidence to suggest infections caused or contributed to by MRSA bacteria cause substantial morbidity and mortality, and mortality rates due to MRSA are estimated to have surpassed those due to HIV infection (D’Agata et al., 2009, p. 274). Thus, due to the immense health implications of MRSA and the changing dynamics of its strains within health care settings, there is sufficient need for further research into the relative disease burden of HA-MRSA and CA-MRSA in the hospital setting. The world-wide crisis of morbidity and mortality increases due to MRSA is in part the consequence of insufficient understanding of its transmission dynamics (D’Agata et al., 2007, p. 287). Differential equations are mathematical models that have been instrumental in adding to the epidemiological studies in understanding the transmission dynamics of MRSA.

One such model developed by Cookson et al. gives precedence for a fixed-capacity hospital model in studying the spread of MRSA. However, this model did not look at the distinction between the two types of MRSA, but was more concerned with the potential influence of community dynamics on transmission within hospitals (Cookson et al., 2004, p. 10223-10224). An expanded version of the Cookson et al. model developed by Jensen and Skov revealed dependence of transmission within the hospital on prevalence of MRSA in the community (Jensen and Skov, 2009, p. 367). This is of particular interest to the question of impact of CA-MRSA in hospital settings due to the increased prevalence of CA-MRSA in the community, though we will not specifically consider the implications of community reservoirs in the scope of this research.

Assumed homogeneity of the patients was listed by the authors as a limitation of the Cookson et al. study, and is often an assumption in differential equation modeling (DEM) (Cookson et al., 2004,
To allow for heterogeneity of patients, one study developed an individual based model (IBM). However, the augmented behavioral detail given by the IBM led to greater computational intensity and difficulty in analyzing significance of parameters in the model (D’Agata et al., 2007, p. 488). Thus, despite the limitations of the homogeneity assumption, we will consider ordinary differential equation modeling in our research.

D’Agata et al. developed a differential equations model in 2009 to ascertain whether there is sufficient evidence to suggest CA-MRSA will overtake HA-MRSA in the hospital setting, as they hypothesized. This model considered a fixed number of patients categorized in five mutually exclusive states of susceptible, colonized with either HA-MRSA or CA-MRSA, or infected with HA-MRSA or CA-MRSA (D’Agata et al., 2009, p. 275). To simplify the model, only transmission due to healthcare workers was considered and homogeneity of patients was assumed (D’Agata et al., 2009, p. 276-277). It was found that even at the baseline model, CA-MRSA was projected to outpace the HA-MRSA and competitively exclude it, driving it to extinction (D’Agata et al., 2009, p. 277-278). Contributing to these results was the CA-MRSA strain’s greater reproductive number (which measures the mean number of secondary cases of MRSA colonization caused by one colonized patient) increased by projected longer lengths of stay of CA-MRSA colonized patients (D’Agata et al., 2009, p. 278). However, it should be noted that at baseline the reproductive numbers of the HA-MRSA and CA-MRSA were only 0.692 and 0.659, respectively (D’Agata et al., 2009, p. 278).

D’Agata and her associates also developed a simplified susceptible-infected-susceptible (SIS) model, i.e. one in which there is no immunity, in March 2010 to further investigate the transmission dynamics of CA-MRSA and HA-MRSA in the hospital setting. Similar to their previous findings, the authors found that with this SIS model, competitive exclusion was dependent on the respective reproduction numbers (D’Agata et al., 2010, p. 647). However, their findings with this particular model did not reveal that CA-MRSA would necessarily competitively exclude HA-MRSA. In this case, D’Agata and her associates ventured to conduct simulations of each generalized case and found that the model was dependent on parameter estimation, though global results were obtained for equilibrium states (D’Agata et al., March 2010, p. 647-648).

The purpose of this paper is to engage with the ordinary differential equation model for the spread of HA-MRSA and CA-MRSA developed D’Agata, E.M.C., Pressley, J., and Webb, G.F. in 2010 and prove their results replicable. We will begin by discussing the model in greater detail.

2 Mathematical Model and its Simplification

Since this is a susceptible-infected-susceptible (SIS) model, at all times the patients in the hospital are classified as in one of three groups:

\[
\begin{align*}
H(t) &= \text{patients colonized with HA-MRSA} \\
C(t) &= \text{patients colonized with CA-MRSA} \\
S(t) &= \text{susceptible patients, those not colonized with either strain}
\end{align*}
\]

Again, because this is a SIS model, once-colonized patients can become susceptible and then colonized again. Essentially, patients are only able to move between the groupings of susceptible, colonized with HA-MRSA, or colonized with CA-MRSA with no overlapping categorizations in time. This is visually demonstrated in Figure 1.
The parameters of the model are defined as follows:

\( \beta_C \) = the rate per day at which CA-MRSA is transmitted between patients

\( \beta_H \) = the rate per day at which HA-MRSA is transmitted between patients

\( \delta_C \) = the rate per day at which patients colonized with CA-MRSA leave the hospital by either death or discharge

\( \delta_H \) = the rate per day at which patients colonized with HA-MRSA leave the hospital by either death or discharge

\( \delta_S \) = the rate per day at which susceptible patients leave the hospital by either death or discharge

\( \alpha_C \) = the rate per day at which patients colonized with CA-MRSA successfully complete decolonization measures

\( \alpha_H \) = the rate per day at which patients colonized with HA-MRSA successfully complete decolonization measures

\( N \) = the total number of patients in the hospital

\( \Lambda \) = the rate per day at which patients enter the hospital

The constructed model, then, is such:

\[
\begin{align*}
\frac{dS}{dt} &= \Lambda - \frac{\beta_H S(t)H(t)}{N} - \frac{\beta_C S(t)C(t)}{N} + \alpha_H H(t) + \alpha_C C(t) - \delta_S S(t), \\
\frac{dH}{dt} &= \frac{\beta_H S(t)H(t)}{N} - \alpha_H H(t) - \delta_H H(t), \\
\frac{dC}{dt} &= \frac{\beta_C S(t)C(t)}{N} - \alpha_C C(t) - \delta_C C(t).
\end{align*}
\]
Now, if we assume that the hospital remains full at all times, we conserve the system (1) by letting 
$\Lambda = \delta_S S(t) + \delta_H H(t) + \delta_C C(t)$. In this scenario, assuming we start with population of size $N$, we have $S(t) + C(t) + H(t) = N$. Thus, we may rewrite this as $S(t) = N(t) - C(t) - H(t)$. This assumption simplifies the system to:

$$
\begin{align*}
\frac{dH}{dt} &= \left(\frac{\beta_H}{N}\right) (N - C(t) - H(t)) H(t) - (\delta_H + \alpha_H) H(t), \\
\frac{dC}{dt} &= \left(\frac{\beta_C}{N}\right) (N - C(t) - H(t)) C(t) - (\delta_C + \alpha_C) C(t).
\end{align*}
$$

where $S$ can be determined by $S(t) = N - H(t) - C(t)$.

### 3 Model Analysis

We will now discuss the process of solving for and analysis of the system’s critical points. Critical points of a differential equation model are equilibrium points at which the derivatives of the functions of interest are all equal to zero and correspond to a constant solution of the model (Nagle et al., 2012, p. 265). In this case, the critical points of the model exist where the rate of spread of both HA-MRSA and CA-MRSA are equal to zero and a constant solution for the system is obtained. Now, it can be quite beneficial to construct the direction field for the system in order to graphically visualize the solution set. The direction field for the system may be obtained by comparing the rate of spread of HA-MRSA with that of CA-MRSA by considering $\frac{dH}{dt}$ and $\frac{dC}{dt}$.

Simplifying, we obtain the following phase plane equation:

$$
\frac{dH}{dC} = \left(\frac{\beta_H}{N}\right) (N - C - H) H - (\delta_H + \alpha_H) H \\
\frac{\beta_C}{N} (N - C - H) C - (\delta_C + \alpha_C) C
$$

The critical, or equilibrium, points for this equation can be found by setting both the equation in the numerator and the equation in the denominator equal to zero. Solving the system of values ro $H$ and $C$,

$$
\left(\frac{\beta_H}{N}\right) (N - C - H) H - (\delta_H + \alpha_H) H = 0
$$

$$
\left(\frac{\beta_C}{N}\right) (N - C - H) C - (\delta_C + \alpha_C) C = 0
$$

we obtain three general solutions for the critical points of $\frac{dH}{dC}$, given in the form $(C_0, H_0)$:

$(0, 0)$

$(0, N - \frac{b_1}{a_1})$, and

$(N - \frac{b_2}{a_2}, 0)$,
where \( a_1 = \frac{\beta_H}{N} \), \( a_2 = \frac{\beta_C}{N} \), \( b_1 = \delta_H + \alpha_H \), and \( b_2 = \delta_C + \alpha_C \).

We may now consider a specific scenario of the simplified system (2) utilizing estimated values for our parameters. Paramenter values estimated by the Beth Deaconess Medical Center (Nagle et al., 2012, p. 312) are given in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Patients</td>
<td>( N )</td>
<td>400</td>
</tr>
<tr>
<td>Length of Stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Susceptible</td>
<td>( \delta_S )</td>
<td>5 days</td>
</tr>
<tr>
<td>— Colonized CA-MRSA</td>
<td>( \delta_C )</td>
<td>7 days</td>
</tr>
<tr>
<td>— Colonized HA-MRSA</td>
<td>( \delta_H )</td>
<td>5 days</td>
</tr>
<tr>
<td>Transmission Rate per Susceptible Patient to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Colonized CA-MRSA per Colonized CA_MRSA</td>
<td>( \beta_C )</td>
<td>0.45 per day</td>
</tr>
<tr>
<td>— Colonized HA-MRSA per Colonized HA_MRSA</td>
<td>( \beta_H )</td>
<td>0.40 per day</td>
</tr>
<tr>
<td>Decolonization Rate per Colonized Patient per Day per Length of Stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— CA-MRSA</td>
<td>( \alpha_C )</td>
<td>0.1 per day</td>
</tr>
<tr>
<td>— HA-MRSA</td>
<td>( \alpha_H )</td>
<td>0.1 per day</td>
</tr>
</tbody>
</table>

Table 1: Parameter Values for the Transmission Dynamics of Community-Aquired and Hospital-Acquired MRSA given by the Beth Deaconness Medical Center

With these estimated parameter values, our specific equation for \( \frac{dH}{dC} \) is as follows:

\[
\frac{dH}{dC} = \frac{0.001(400 - C - H)H - 0.3H}{0.001125(400 - C - H)C - \frac{11}{70}C} \tag{6}
\]

From this specific equation, and utilizing our general solutions for the equilibrium points, we obtain the following values for our three critical points:

(0, 0)

(0, 100), and

\( \left( \frac{11600}{63}, 0 \right) \).

Figure 2 is the constructed direction field for our equation (6) using the parameters estimated by the Beth Deaconess Medical Center. Figures 2 - 5 were generated using the Direction Field Generator tool by Math Scoop (2010).

The type and stability of critical points can give valuable information about the equilibrium state(s) of the system. To determine the type and stability of the critical points we have obtained from substituting the estimated parameter values into our general phase plane equation (3), we apply the method of characteristic equations and eigenvalues. Note, however, that equation (3) is nonlinear.
Figure 2: Direction Field for the specific case using estimated parameters, where the horizontal (x-)axis measures the number of patients colonized by CA-MRSA and the vertical (y-)axis measures the number of patients colonized with HA-MRSA

Equation: $(0.001(400-x-y)y-3y)/(0.001125(400-x-y)x-(17/70)x)$
Thus, our linearizations at the critical point \((C_0, H_0)\) of the equation in the denominator (let us call this \(F\)) and the equation in the numerator (let us call this \(G\)) at each critical point, \((C_0, H_0)\) (Tseng, p. D-2-22). Following the linearization formula \(F(C, H) \approx F(C_0, H_0) + F_C(C_0, H_0)(C - C_0) + F_H(C_0, H_0)(H - H_0) = F_C(C_0, H_0)C + F_H(C_0, H_0)H\), we obtain:

\[
dH = F(C, H) \approx F(C_0, H_0) + F_C(C_0, H_0)(C - C_0) + F_H(C_0, H_0)(H - H_0) = F_C(C_0, H_0)C + F_H(C_0, H_0)H.
\]

Note that we have omitted \(F(C_0, H_0)\) from our resulting formula for the linearization of \(dH\) since we know that at any critical point, \((C_0, H_0)\), we have \(F(C_0, H_0) = 0\) (Tseng, p. D-2-22). Additionally, we have applied the transformations \(H = H - H_0\) and \(C = C - C_0\) in writing our resulting linearization equation because a critical point can be transformed to \((0, 0)\) while still maintaining its stability and type classifications (Tseng, p. D-2-22). Similarly, we may obtain:

\[
dC = G(C, H) \approx G(C_0, H_0) + G_C(C_0, H_0)(C - C_0) + G_H(C_0, H_0)(H - H_0) = G_C(C_0, H_0)C + G_H(C_0, H_0)H.
\]

Now, we obtain the partial derivatives of \(F(C, H)\) and \(G(H, C)\), found in the numerator and denominator of equation (3), respectively, at some critical point \((C_0, H_0)\):

\[
\begin{align*}
F_C(C_0, H_0) &= \left(\frac{-\beta_H}{N}\right)H_0, \\
F_H(C_0, H_0) &= \left(\frac{\beta_H}{N}\right)(N - C_0 - 2H_0) - (\delta_H + \alpha_H), \\
G_C(C_0, H_0) &= \left(\frac{\beta_C}{N}\right)(N - 2C_0 - H_0) - (\delta_C + \alpha_C), \\
G_H(C_0, H_0) &= \left(\frac{-\beta_C}{N}\right)C_0.
\end{align*}
\]

Thus, our linearizations at the critical point \((C_0, H_0)\) become:

\[
\begin{align*}
dH &= F(C, H) \approx \left[\left(\frac{-\beta_H}{N}\right)H_0\right](C_0) + \left[\left(\frac{\beta_H}{N}\right)(N - C_0 - 2H_0) - (\delta_H + \alpha_H)\right](H_0), \\
dC &= G(C, H) \approx \left[\left(\frac{\beta_C}{N}\right)(N - 2C_0 - H_0) - (\delta_C + \alpha_C)\right](C_0) + \left[\left(\frac{-\beta_C}{N}\right)C_0\right](H_0).
\end{align*}
\]

To determine the characteristic equations and obtain eigenvalues for each of the critical points, we construct the Jacobian Matrix, \(J\), for our system of the linearized equations (8). We obtain:

\[
J = \begin{pmatrix}
(\frac{\beta_H}{N})(N - C_0 - 2H_0) - (\delta_H + \alpha_H) & \left(\frac{-\beta_H}{N}\right)H_0 \\
\left(\frac{-\beta_C}{N}\right)C_0 & \left(\frac{\beta_C}{N}\right)(N - 2C_0 - H_0) - (\delta_C + \alpha_C)
\end{pmatrix}.
\]
Since the purpose of this process is to obtain the characteristic equations for each of the specific
critical points we obtained using the given estimated parameters, let us construct our parameters-
specific Jacobian matrix:

\[
J = \begin{pmatrix}
0.001(400 - 2C_0) - 0.003 & -0.001H_0 \\
-0.00125C_0 & 0.00125(400 - 2C_0 - H_0) - \frac{17}{260}
\end{pmatrix}.
\]

To obtain the characteristic polynomial of our eigenvalues, \(\lambda_i, i = 1, 2\), we will calculate \(\det(J - \lambda I)\),
where \(I\) is the identity matrix. We will do so for each specific critical point and its Jacobian matrix.

At the critical point \((0, 0)\) the Jacobian matrix, \(J_1\), is:

\[
J_1 = \begin{pmatrix}
\beta_H - (\alpha_H + \delta_H) & 0 \\
0 & \beta_C - (\alpha_C + \delta_C)
\end{pmatrix}
\]

\[
J_1 = \begin{pmatrix}
0.1 & 0 \\
0 & 0.29 \frac{140}{140}
\end{pmatrix}.
\]

Thus, we calculate:

\[
\det(J_1 - \lambda I) = \det\left(\begin{pmatrix}
0.1 - \lambda & 0 \\
0 & \frac{29}{140} - \lambda
\end{pmatrix}\right) = \lambda^2 - \frac{43}{140} \lambda + \frac{29}{1400}.
\]

Setting this equal to zero, i.e. \(\lambda^2 - \frac{43}{140} \lambda + \frac{29}{1400} = 0\), we obtain the eigenvalues \(\lambda = \frac{43}{280} - 0.5 \sqrt{(\frac{43}{140})^2 - 4(\frac{29}{1400})} \approx 0.2\) and \(\lambda = \frac{43}{280} + 0.5 \sqrt{(\frac{43}{140})^2 - 4(\frac{29}{1400})} \approx 0.41429\). Demonstrated by these
positive real eigenvalues, we may define the classification of the first critical point \((0, 0)\) as an unsta-
ble node (Tseng, 2008, p. D-2-4). Thus, we expect the trajectories of the phase plane to move away
from \((0, 0)\).

We may further examine this graphically. By restricting our window, we may examine more closely
the direction field around each critical point. Figure 3 shows the behavior of the direction field close
to our first critical point of \((0, 0)\).

At the critical point \((0, 100)\) the Jacobian matrix, \(J_2\), is:

\[
J_2 = \begin{pmatrix}
\beta_H(1 - \frac{100}{N}) - (\alpha_H + \delta_H) & -100 \frac{\beta_H}{N} \\
0 & \beta_C(1 - \frac{100}{N}) - (\alpha_C + \delta_C)
\end{pmatrix}.
\]

\[
J_2 = \begin{pmatrix}
-0.1 & -0.1 \\
0 & \frac{53}{560}
\end{pmatrix}.
\]
Figure 3: Direction Field surrounding critical point (0, 0) for the specific case using estimated parameters, where the horizontal (x-)axis measures the number of patients colonized by CA-MRSA and the vertical (y-)axis measures the number of patients colonized with HA-MRSA.

Equation: 
$$(.001(400-x-y)y-.3y)/(0.001125(400-x-y)x-(17/70)x)$$
Thus, we calculate:

\[
 \det(J_2 - \lambda I) = \det \begin{pmatrix}
 -0.1 - \lambda & -0.1 \\
 0 & \frac{53}{560} - \lambda
 \end{pmatrix} = \lambda^2 + \frac{3}{560} \lambda + \frac{53}{560}.
\]

Setting the resulting characteristic equation equal to zero, we obtain the eigenvalues \( \lambda = \frac{-3}{1120} \pm 0.5 \sqrt{(\frac{3}{560})^2 - 4(\frac{53}{5600})}. \) Thus, the eigenvalues are either \( \frac{-3}{1120} \) or \( 0.1 \). Again, because the eigenvalues are both real and positive, we define the classification of the second critical point \((0,100)\) as an unstable node and expect trajectories to move infinitely away from \((0,100)\) (Tseng, 2008, p. D-2-4).

Again, we provide figure 4 for reference to graphically show the behavior of the direction field close to the critical point \((0,100)\).

At the critical point \((\frac{11600}{63},0)\) the Jacobian matrix, \( J_3 \), is:

\[
 J_3 = \begin{pmatrix}
 \beta_H(1 - \frac{11600}{63}N) - (\alpha_H + \delta_H) & 0 \\
 -\beta_C(\frac{11600}{63}) & \beta_C(1 - 2(\frac{11600}{63}N)) - (\alpha_C + \delta_C)
 \end{pmatrix}.
\]

Thus, we calculate:

\[
 \det(J_3 - \lambda I) = \det \begin{pmatrix}
 -\frac{53}{630} - \lambda & 0 \\
 \frac{-29}{140} & \frac{29}{140} - \lambda
 \end{pmatrix} = \lambda^2 - \frac{367}{1260} \lambda + 0.0174263039.
\]

Setting the resulting characteristic equation equal to zero, we obtain the eigenvalues \( \frac{-367}{2520} \pm \frac{31}{504} = \frac{-29}{140}, \frac{-53}{630} \) as an asymptotically stable node (Tseng, 2008, p. D-2-4). Thus, all trajectories should eventually converge to \((\frac{11600}{63},0)\) (Tseng, 2008, p. D-2-4).

Again, we provide figure 5 for reference to graphically show the behavior of the direction field close to our final critical point of \((\frac{11600}{63},0)\).

Given the classifications of our trajectory points, and excluding \((0,0)\) as a trivial solution without real biological meaning, it is apparent that solutions to our parameter-specific model would diverge from \((0,100)\) and converge to \((\frac{11600}{63},0)\). Thus, as time progresses, in the parameter-specific model we would expect the number of cases of HA-MRSA to approach zero and the number of cases of CA-MRSA to approach approximately 184. From this we can conclude that CA-MRSA will overtake HA-MRSA in number of patients colonized with each strain as time progresses. This suggests that with the parameters estimated by the Beth Deaconess Medical Center, CA-MRSA will competitively exclude HA-MRSA, and as the dominant strain become a more common threat to patients’ health.
Figure 4: Direction Field surrounding critical point (0, 100) for the specific case using estimated parameters, where the horizontal (x-)axis measures the number of patients colonized by CA-MRSA and the vertical (y-)axis measures the number of patients colonized with HA-MRSA.

Equation: $0.001(400-x-y)y - 0.3y)/(0.001125(400-x-y)x-(17/70)x)$
Figure 5: Direction Field surrounding critical point \(\left(\frac{11600}{63}, 0\right)\) for the specific case using estimated parameters, where the horizontal (x-)axis measures the number of patients colonized by CA-MRSA and the vertical (y-)axis measures the number of patients colonized with HA-MRSA.

Equation: \(\frac{0.01(400-x-y) - 0.3y}{0.001125(400-x-y)x - (17/70)x}\)
4  Numerical Simulations

In order to validate the findings of the analysis of the model and obtain a better understanding of the time to reach equilibrium, we conduct numerical simulations utilizing the given parameters estimated by Beth Deaconess Medical Center.

One classic method of obtaining approximate numerical solutions for differential equation models is the Euler Method. This method is given by $y_{n+1} = y_n + h \cdot f(x_n, y_n)$, where $h$ is the step size in the procedure (Flannery and Press, 1992, p. 710). However, Euler's method is most accurate only when considering second degree polynomial equations (Butcher, 2007). Additionally, the error generated by the Euler method is only one power of $h$ smaller than the correction, i.e. of the form $O(h^2)$ (Flannery and Press, 1992, p. 710). Given these drawbacks, it is necessary to look elsewhere for a suitable method of obtaining a numerical solution to our model.

We will instead consider the Runge Kutta method, and in particular the fourth-order Runge-Kutta method. The Runge-Kutta method is a set of s-step procedures for numerical approximations of ordinary differential equation solutions. The error in a p-order Runge-Kutta method has order of $p+1$, i.e. is of the form $O(h^{p+1})$ (Butcher, 2007), making this fourth-order method preferable to the Euler method in terms of error. It has been shown that lower order Runge-Kutta methods are more efficient for calculating crude accuracies (Bogacki and Shampine, 1989, p. 321). Furthermore, since Runge-Kutta methods become less stable as order increases (Bogacki and Shampine, 1989, p. 321), we will limit our calculations to the fourth-order method. The two-dimensional fourth-order Runge-Kutta method we utilize in our simulations is given by the following:

$$\begin{align*}
k_1 &= h \cdot f(t_n, C_n, H_n), \\
l_1 &= h \cdot g(t_n, C_n, H_n), \\
k_2 &= h \cdot f(t_n + \frac{h}{2}, C_n + \frac{k_1}{2}, H_n + \frac{l_1}{2}), \\
l_2 &= h \cdot g(t_n + \frac{h}{2}, C_n + \frac{l_1}{2}, H_n + \frac{k_1}{2}), \\
k_3 &= h \cdot f(t_n + \frac{h}{2}, C_n + \frac{l_2}{2}, H_n + \frac{k_2}{2}), \\
l_3 &= h \cdot g(t_n + \frac{h}{2}, C_n + \frac{k_2}{2}, H_n + \frac{l_2}{2}), \\
k_4 &= h \cdot f(x_n + h, C_n + l_3, H_n + k_3), \\
l_4 &= h \cdot g(x_n + h, C_n + l_3, H_n + k_3), \\
C_{n+1} &= C_n + \frac{1}{6}(l_1 + 2l_2 + 2l_3 + l_4) + O(h^5), \\
H_{n+1} &= H_n + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4) + O(h^5)
\end{align*}$$

where $t$ is time that varies by step size, $h$, $f(t, C, H)$ is the rate $\frac{dH}{dt}$, and $g(t, C, H)$ is the rate $\frac{dC}{dt}$.

The following graphs in figures 6 and 7 have been generated to provide further demonstration of the efficiency of the fourth-order Runge-Kutta method. These graphs consider the differential equation...
$dy = -y$ with initial condition $y_0 = 2$ and compare the numerically calculated solution of the Runge-Kutta to the known solution, i.e. $y = 2e^{-x}$, of this equation. Figure 6 shows the comparison of the Runge-Kutta with step size $h=0.1$ and the analytical (true) solutions to this initial value differential equation while Figure 7 is a graph of the difference (analytical - numerical) between the two solutions. The error generated by the Runge-Kutta method clearly varies but stabilizes with time as the actual solution reaches equilibrium. Additionally, note that the Runge-Kutta method overestimates the solution at a magnitude ranging between $1 \times 10^{-7}$ and $7 \times 10^{-7}$, which is an acceptably small error term for our numerical simulations.

Now, utilizing the fourth-order Runge-Kutta method, we ran various simulations on the simplified system (2) applying parameter values given in Table 1 with a step size of $h = 0.1$, varying the initial conditions for $C$ and $H$. Figures 8 through 11 visualize some of these simulations. In particular, figures 8 through 10 record the results of selecting initial conditions for numbers of patients colonized with CA-MRSA and HA-MRSA close to the critical point values to analyze more local behavior. Figure 11 gives the numerical solution of the system when the initial numbers of colonized patients of CA-MRSA and HA-MRSA are equal and approximately equidistant between the results of steady state that we expect from our earlier analysis of the model, i.e. convergence to $(\frac{11600}{63}, 0)$.

As these graphs demonstrate, from the numerical simulations we obtain global results of competitive exclusion by the CA-MRSA and convergence to the critical point of $(\frac{11600}{63}, 0)$ at steady state. Additionally, time to reach steady state varies based on the initial conditions imposed on the model. However, regardless of the selection of number of patients initially colonized with HA-MRSA, as long as there is at least one patient colonized with CA-MRSA and at least one patient colonized with HA-MRSA initially, we determine from these simulations that steady state will be reached in a maximum of approximately 125 days. However, the more likely scenario is that steady state would be reached in 50 to 80 days, since CA-MRSA is more prevalent in the community and true susceptibility to HA-MRSA is likely to exist in a smaller subset of patients.
Uncertainty and Sensitivity Analysis on the Parameters

The steady state competitive exclusionary results we have discussed thus far concern the parameter-dependent model. The next section will be dedicated to discussion of uncertainty and sensitivity analyses on these parameters. Since we obtained global results of competitive exclusion by the CA-MRSA approaching the equilibrium point of \((\frac{11600}{63}, 0)\) at steady state (meaning we obtained this result regardless of initial conditions for H and C), we will not conduct an uncertainty or sensitivity analysis of the initial conditions of the model, but only on the other parameters considered.

Parameters in the field of applied biomathematics often contain a degree of uncertainty due to natural variation, error in measurements, or simply a lack of current techniques to measure them (Hogue et al., 2008, p. 179). The purpose of these uncertainty analyses are to quantify the level of confidence in the theoretical or experimental parameter estimates (Hogue et al., 2008, p. 179), namely those given by the Beth Deaconess Medical Center in Table 1. We utilize the Latin hypercube sampling (LHS) method, the most efficient of the Monte Carlo sampling methods for analyzing uncertainty (Hogue et al., 2008, p. 179). The LHS method gives unbiased estimates for model outputs while requiring fewer samples to achieve the same accuracy as simple random sampling (Hogue et al., 2008, p. 180). Sampling for each parameter is from a specified probability distribution. Because we have little to no \textit{a priori} information for the distributions of the model parameters, we assign a uniform probability distribution to each parameter, which allows the assignment of a reasonable wide range of variation for each parameter (Hogue et al., 2008, p. 180). The range of the uniform distributions applied were designed as a logical range containing the parameter values estimated in Table 1. LHS is a stratified sampling without replacement technique in which the random probability distribution for the given

![Figure 7: Graph of the difference between the analytical and calculated Runge-Kutta solutions to \(dy = -y, y_0 = 2\)](image)
Figure 8: Graph of the Runge-Kutta simulation with initial conditions $H = 2$ (red), $C = 2$ (blue)

Figure 9: Graph of the Runge-Kutta simulation with initial conditions $H = 98$ (red), $C = 2$ (blue)
Figure 10: Graph of the Runge-Kutta simulation with initial conditions $H = 2$ (red), $C = 182$ (blue)

Figure 11: Graph of the Runge-Kutta simulation with initial conditions $H = 90$ (red), $C = 90$ (blue)
Sensitivity analyses generate information vital to parameter estimation, control, and optimization, giving precedence for application of such a technique to this biological model (Li, 2000, pp. 161). Thus, we couple these uncertainty analyses with sensitivity analyses on the parameters to determine the degree to which uncertainty of the parameter impacts model behavior (Hogue et al., 2008, p. 180). We calculate the partial rank correlation coefficients (PRCCs) for each parameter, since PRCC is one of the most efficient and reliable measures for nonlinear monotonic relationships between inputs and outputs utilized in conjunction with Monte Carlo simulations (Hogue et al., 2008, p. 181). Monotonicity between inputs and outputs is a reasonable assumption in this model. Additionally, we may also assume little correlation exists between the inputs, indicating PRCC will be robust (Hogue et al., 2008, p. 181). The PRCC is calculated from a partial correlation on rank-transformed data whereby inputs \( x_j \) and output \( y \) are transformed and then the linear models in equation (10) are built (Hogue et al., 2008, p. 181). The sensitivity analyses will be our main focus in this discussion.

\[
\begin{align*}
\hat{x}_j &= c_0 + \sum_{p=1, p \neq j}^k c_p x_p, \\
\hat{y} &= b_0 + \sum_{p=1, p \neq j}^k b_p x_p
\end{align*}
\]

(10)

Since partial rank correlation is conducted for inputs and a singular output, we perform sensitivity analyses for each parameter of interest and each output, \( H \) and \( C \). Figures 12 through 18 are the scatterplots of variation in the parameters (by their indices) against the variation in \( C \) at the time of 100 days. We choose this time point for demonstration because it is close to steady state for most cases. As demonstrated by the PRCC values of magnitude greater than 0.05, the uncertainty in all of the variables could potentially have impact on the model output. However, the PRCCs for \( \beta_C \) and \( \alpha_C \) have p-values of greater than 0.05 (0.51003 and 0.17409, respectively) and so are not significant at the confidence level of 0.05. All others, that is \( \beta_H, \alpha_H, \delta_C, \delta_H, \) and \( N \), are significant at the 0.05 confidence level. Furthermore, it is apparent that there is significant strong, positive linear association between the number of CA-MRSA colonized patients and the parameters \( N \) and \( \beta_H \). We also detect significant strong, negative linear association between \( C \) and the parameters \( \alpha_H \) and \( \delta_H \). While significant, less can be said for the influence of \( \delta_C \) on the output of \( C \) since the smaller magnitude of its corresponding PRCC denotes a weaker linear association. The results of the sensitivity analysis on the parameter values for the outcomes of \( C \) at day 100 are summarized in Figure 19.

The PRCCs were also calculated at day 100 for the variation in each parameter against variation in \( H \). However, none of the PRCCs were statistically significant at the 0.05 confidence level. Additionally, these results hold even at later times, such as at 200 days when steady state most certainly would have been reached for the parameter-specific model. At this time of 200 days, the results for each of the parameters against HA-MRSA are still insignificant. The results for the variation in parameters against CA-MRSA also hold at 200 days with the previous findings at day 100, with only very minor changes in magnitudes of PRCCs and p-values and no changes in significance. Thus, we can be confident that the number of patients colonized with CA-MRSA at steady state is dependent on the majority of parameters, with positive impacts from \( N \) and \( \beta_H \) and negative influences from \( \alpha_H \) and
\[ \delta_H. \] This suggests that greater focus and resources should be spent on understanding the parameters and transmission of CA-MRSA.

6 Conclusion

The documented health burden of Methicillin-resistant *Staphylococcus aureus* (MRSA) is severe, with some studies estimating that mortality rates due to MRSA have surpassed those due to HIV infection (D’Agata et al., 2009, p. 274). Hospital-acquired (HA-MRSA) is a serious strain of MRSA that tends to target elderly or otherwise immunocompromised patients in the health care setting (Nagle et al., 2012, p. 310). Community-acquired MRSA (CA-MRSA), on the other hand, is prevalent in the general community, affecting even young and healthy individuals (D’Agata et al., 2009, p. 274). More recently, CA-MRSA has been extending its sphere of influence into the hospital setting, which could have significant consequences on the burden of disease attributed to each of these strains (D’Agata et al., 2009, p. 274).

By simplification according to a fixed-capacity assumption of the susceptible-infected-susceptible (SIS) model proposed by D’Agata et al. in 2010, we were able to solve the system of equations for the critical points of the model. We then applied the methods of linearization, characteristic equations, and Jacobian matrices to obtain eigenvalues for each critical point. These eigenvalues were obtained for the model containing parameter values specified in Table 1 and given by the Beth Deaconness Medical Center. Based on these eigenvalues and the critical point classifications, it is clear that equilibrium should be reached at approximately 184 patients colonized with CA-MRSA and 0 patients colonized with HA-MRSA out of the fixed capacity of 400 patients. Through the utilization of fourth-order Runge-Kutta simulations on the parameter-specific model, the results of the model analysis are validated. In concordance with the findings of D’Agata et al., we conclude global competitive exclusion results for the model with CA-MRSA overtaking HA-MRSA in this
Figure 13: Variation in $\beta_C$ by index of $\beta_C$ plotted against variation in $C$.

Figure 14: Variation in $\beta_H$ by index of $\beta_H$ plotted against variation in $C$. 
Figure 15: Variation in $\alpha_C$ by index of $\alpha_C$ plotted against variation in $C$

Figure 16: Variation in $\alpha_H$ by index of $\alpha_H$ plotted against variation in $C$
Figure 17: Variation in $\delta_C$ by index of $\delta_C$ plotted against variation in $C$

Figure 18: Variation in $\delta_H$ by index of $\delta_H$ plotted against variation in $C$
hospital setting. Furthermore, we found that time for steady state to be reached for the parameter-specific model varied according to the numbers of patients colonized initially with HA-MRSA or CA-MRSA, but ranges from 0 to approximately 125 days. The results of the uncertainty and sensitivity analyses on the parameters of the model show that the model outcomes are parameter-dependent, particularly in the case of the CA-MRSA. This is particularly noteworthy as CA-MRSA was seen to competitively exclude the HA-MRSA strain in the parameter-specific model analysis. Thus, this parameter dependence could drastically influence the outcomes of the system. Therefore, further data collection on the parameters is necessary to understand each theoretical probability distribution and obtain estimates of greater confidence for the parameters. This also demonstrates a need for continued research into development of more robust models to study the transmission dynamics of MRSA, and in particular, the CA-MRSA strain in the hospital setting. It should be noted that while monotonicity and independent inputs were reasonably assumed, the need for these assumptions is a drawback to the PRCC technique for analyzing uncertainty. This gives precedence for further research into the uncertainty of the parameters for this model incorporating the use of other techniques.

It should also be noted that similar to other studies of its kind, the assumption of a fixed-capacity model and homogeneity of patients is one limitation of this study. Nevertheless, the results obtained from this study do have notable implications for the medical community, as they reveal global competitive exclusion of the HA-MRSA strain by the CA-MRSA strain in the parameter-specific model obtained using values estimated by the Beth Deaconess Medical Center (in that initial numbers of patients colonized with either strain do not affect this eventual result). This and the greater impact of parameter uncertainty on the behavior of CA-MRSA should suggest to medical professionals that...
greater efforts should be made to identify and quarantine individuals entering the hospital who are already colonized with CA-MRSA, and that increased resources should be allocated for prevention and treatment of the CA-MRSA strain.

7 References


