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# Revised Model for Antibiotic Resistance in a Hospital

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# Revised Model for Antibiotic Resistance in a Hospital

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by

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ABSTRACT

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In this thesis we modify an existing model for the spread of resistant bacteria in a hospital. The existing model does not account for some of the trends seen in the data found in literature. The new model takes some of these trends into account. For the new model, we examine issues relating to identifiability, sensitivity analysis, parameter estimation, uncertainty analysis, and equilibrium stability.

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# 1 INTRODUCTION

Antibiotic resistance occurs when an antibiotic has lost its effectiveness against the bacteria it is trying to kill. Normally, the bacteria is killed by an antibiotic, but in some situations, like the overuse of antibiotics, development of bacterial resistance of an antibiotic can occur. Drugs can lose their ability to kill bacteria and thus cure patients. It happens frequently in various hospital settings. [26] Patients will not get better immediately because of antibiotic resistance. This resistance, in turn, makes it harder for medical staff to treat patients effectively for their illnesses. The development and occurrence of antibiotic resistance cannot be eliminated completely, but there may be ways to reduce its occurrence. Joyner et al. [1]. introduced a model to simulate the spread of antibiotic resistant bacteria to two drugs in a hospital setting. Patients were categorized as colonized with either resistant bacteria or uncolonized. The colonized patients were separated into four groups. It was assumed that four types of colonized patients could influence each other, and colonized and uncolonized patients could also affect each other. The simulation of the model in Joyner et al. [1] shows that the proportion of patients colonized with dual antibiotic resistant bacteria are higher than other proportions of patients. It was explained that this was possibly due to the assumption that there was no treatment for those patients. This is unrealistic.The majority of patients are likely to be colonized with bacteria sensitive to antibiotics [2]. In this thesis, we focused on revising the model by Joyner et al. [1] to try to more accurately represent the trend in a hospital.

We illustrate how we changed the previous model to get the new model in Section 2. In Section 3 we analyze the identifiability of the parameters in the new model and

the sensitivity of the variables to the parameter values. In Section 4, we focused on parameter estimation. In section 5, we address uncertainty in the model. In Section 6, we focus on the existence and stability of a resistant-free equilibrium. We end the thesis with some final conclusions and remarks about future work.

## 2 MODEL DEVELOPMENT

In this section, we discuss the specific modifications to an existing model for the spread of antibiotic resistance in a hospital setting. The original model by Joyner et al. [1] is a compartmental model in which patients are classified in one of five categories based on their bacterial colonization. It is assumed there are only two drugs and patients can be resistant to one, two or none of the antibiotics. Resistance may then be transmitted to patients who are uncolonized or colonized with a type of resistance which spreads faster. Patients can become uncolonized either through treatment or through their immune system fighting off the bacteria. The simulation of the original model is shown in Figure 1.

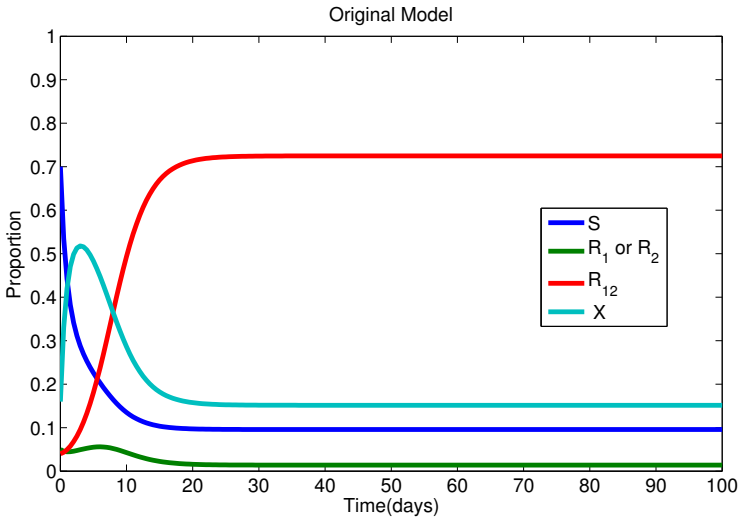


Figure 1: Simulation of Original Model developed by Joyner et al. [1]

Figure 1 shows that after approximately 20 days of treatment, the proportion of patients in the hospital colonized with dual resistance is approximately 72%. The

proportion of patients uncolonized and colonized with sensitive bacteria are approximately 16% and 10%, respectively. The proportion of patients with single resistance is only around 2%. The simulation is not what is expected based on observed hospital data [2]. The proportion of the hospital colonized with dual resistance should be lower than the proportion of the hospital colonized with single resistance as shown in the data by Takesque et al. [2]. In our model, we focus on new assumptions which might more accurately show what occurs in a hospital setting.

The first change in the model is a change in the model variables. We let $S$ be the proportion of patients with bacteria sensitive to all drugs in the hospital. We let $R$ be the proportion of patients colonized with bacteria resistant to only a single antibiotic. We let $M$ be the proportion of patients colonized with bacteria resistant to multiple antibiotics, and $X$ represents the proportion of patients who are uncolonized. We assume a constant population in the hospital, so $S + R + M + X = 1$. Analyzing the simulation from the original model, we made three major changes. First, we assumed there is treatment available for patients colonized with multiple-resistant bacteria [3]. The previous model assumed there was no antibiotic available to treat dual resistance (thus the proportion of people colonized with dual resistance was much higher than what is typically seen in the hospital). Therefore, we instead chose to assume a variable which included all patients colonized with bacteria resistant to more than one drug, but instead of assuming there are no antibiotics to treat them, we instead assume they can be treated at a rate $\tau_M$, a slower rate than treatment of patients colonized with either bacteria resistant to a single antibiotic or colonized with sensitive bacteria. Second, we assume that resistance can develop during treatment [9]. We

assume resistance can develop during treatment at a rate $e_\tau$, reducing the effective treatment rate from $\tau$ to $(1-e_\tau)\tau$ where $0 < e_\tau < 1$. The third major change is that we assume there can be transfer of resistant mechanisms from bacteria to bacteria [4, 5]. When two bacteria are close to each other, conjugation can occur in which one bacteria can transfer the mechanism for antibiotic resistance to the other bacteria causing both bacteria to be resistant to the antibiotic. We assume that conjugation can only occur through either direct or indirect contact. A plasmid transfer rate $\beta p_T$ is assumed in the new model. For example, $\beta p_T RM$ is the development of multiple resistant bacteria due to the transfer of a second resistant mechanism to a single resistant bacteria. The schematic for the new model is given in Figure 2 with the parameters in Table 1. The model is given by the set of differential equations

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \lambda m_S - S\mu_S + \beta S[X - p_T R] - (\tau + \gamma)S, \qquad (1)\\
\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \lambda m_R - R\mu_R + \beta R[(1-c_R)X + p_T(S - R - M)] - (\tau_R + \gamma)R\\
&\quad + e_\tau \tau S,\\
\\
\frac{\mathrm{d}M}{\mathrm{d}t} &= \lambda m_M - M\mu_M + \beta M[(1-c_M)X + p_T R] + \beta p_T R^2 + e_\tau \tau_R R\\
&\quad - M[\tau_m(1-e_\tau) + \gamma].
\end{aligned}$$

Since we assume a constant hospital population, the differential equation for $X$ is defined by the relationship

$$\frac{\mathrm{d}X}{\mathrm{d}t} = 1 - \frac{\mathrm{d}S}{\mathrm{d}t} - \frac{\mathrm{d}R}{\mathrm{d}t} - \frac{\mathrm{d}M}{\mathrm{d}t}.$$

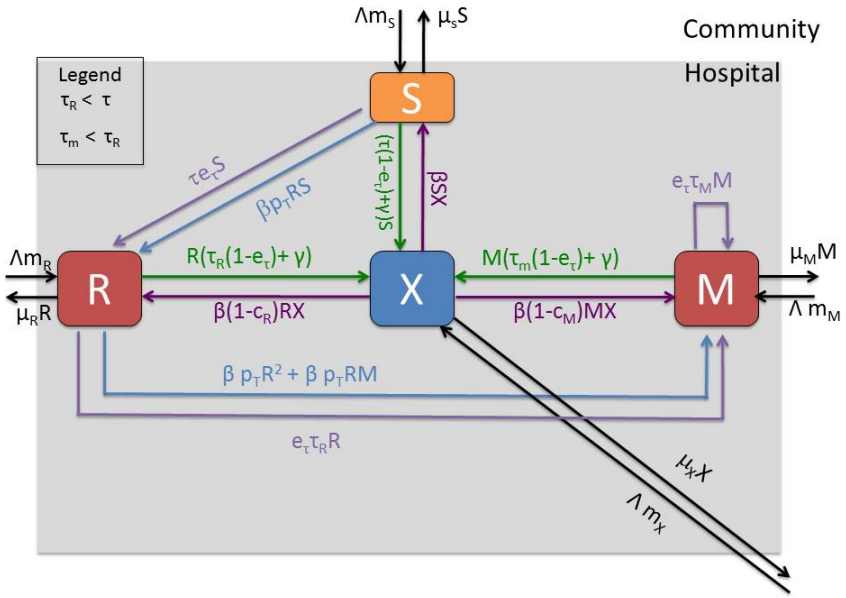


Figure 2: Schematic for the revised model after making the revisions discussed in Section 2

Table 1: Definitions of Parameters

| Parameters | Description | value | ref. |
|---|---|---|---|
| $\beta$ | colonization rate | 1/day | [21, 24] |
| $p_T$ | probability of plasmid transfer upon contact | $10^{-6}$/day | [4, 5] |
| $c_R$ | fitness cost of bacteria resistant to single drug | 0.05/day | [21] |
| $c_M$ | fitness cost of bacteria resistant to multiple drugs | 0.15/day | [21] |
| $\tau$ | per capita treatment rate of sensitive bacteria ($\sim$ 31 hours) | 0.78/day | [9] |
| $\tau_R$ | per capita treatment rate of resistance to a single drug ($\sim$ 1/2 day longer than sensitive) | 0.56/day | [12] |
| $\tau_M$ | per capita treatment rate of resistance to multiple drugs. ($\sim$ 2x as long as sensitive) | 0.39/day | [3] |
| $e_\tau$ | rate of resistance developing during treatment | $10^{-7}$/day | [20, 22, 23] |
| $\gamma$ | per capita clearance rate of bacteria due to immune response | 0.03/day | [21, 24, 25] |
| $\mu_S$ | patients discharge rate for $S$ | 0.7/day | [11] |
| $\mu_R$ | patients discharge rate for $R$ | 0.05/day | estimated |
| $\mu_M$ | patients discharge rate for $M$ | 0.005/day | estimated |
| $\mu_X$ | patients discharge rate for $X$ | 0.245/day | [10] |

The simulation of the new model is shown in Figure 3. By comparing the difference between the new simulation (Figure 3) and the previous simulations (Figure 1), the proportion of patients with bacteria of multiple antibiotic resistances is lower than the proportion of patients with bacteria of single antibiotic resistance as hoped. The simulation also shows that the majority of patients are either uncolonized or colonized with bacteria sensitive to antibiotics which is more in line with what is expected. However, the proportion of uncolonized is expected to be lower than the proportion

of patients with colonized bacteria sensitive to all antibiotics. One possible reason is that the parameters value in Table 1 may not be ideal for modeling a particular hospital. In order to identify the combination of parameters ideal to mimic the trends seen in the data, one needs to take the data from a particular hospital and use it to estimate the parameters. Therefore, the parameters must be identifiable, and, if so, an inverse problem can be formulated to estimate the parameters. In the next section we focus on identifiability of parameters in the model.

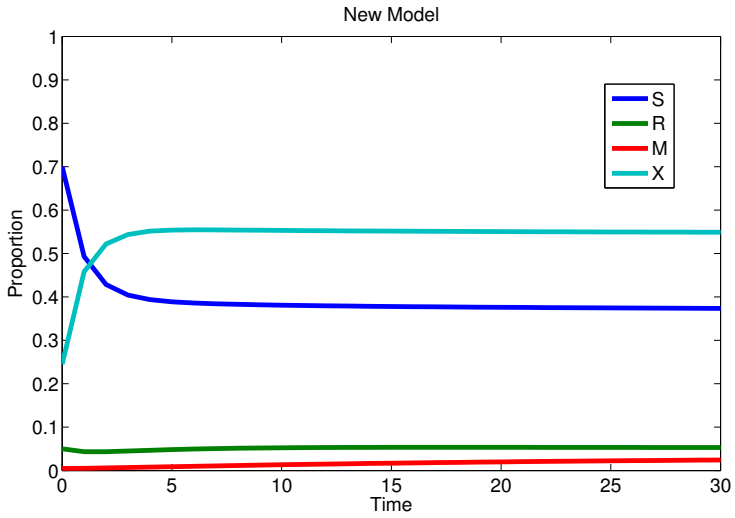


Figure 3: Simulation for the new model given by Eq. (1)

# 3 IDENTIFIABILITY AND SENSITIVITY ANALYSIS

In the previous section, we discussed that the choice of parameters may need to be examined further in order for simulations to better represent the data found in the literature. Therefore, in this section we examine the identifiability of the model, so that in the future, this model can be adapted to a specific hospital. There are many approaches in which one can examine identifiability. Eisenberg [13] uses a differential algebra approach which involves reducing the system of differential equations to an input-output equation to determine identifiable parameters. This process was attempted with our model; however, the resulting input-output equations were quite messy and therefore hard to use to determine the identifiable parameters.

Another approach for determining a subset of identifiable parameters is given in the paper by Cintron-Arias et al. [8]. The Fisher Information Matrix (FIM) associated with the model helps to determine the number of identifiable parameters in the given subset of parameters. The Fisher Information Matrix is given by

$$\text{FIM} = \chi^T \chi \tag{2}$$

where $\chi$ is the sensitivity matrix of the system discussed below. The rank of the FIM gives the number of identifiable parameters from the given subset. All possible parameter combinations can be tested until the Fisher Information Matrix has full rank. Therefore, for identifiability, we need the FIM to have full rank.

Output for our model can be denoted by

$$z(t_i, q_0) = (S(t_i, q_0), R(t_i, q_0), M(t_i, q_0))$$

where $t_i$ is a time point and $q_0$ is a given parameter value. If the model is a good

model for the spread of resistant bacteria, the output of the model should match data from a hospital fairly well. But, normally patients aren't tested for resistant bacteria while in a hospital unless treatment fails. Therefore, in our model, we assume the only measurable output from the model would be the number of patients in the hospital colonized with bacteria of multiple antibiotic resistance which can be obtained from $z(t_i, q_0) = NM(t_i, q_0)$ where $N$ is the population of the hospital and $M(t_i, q_0)$ is the proportion of the patients colonized with bacteria of multiple antibiotic resistance.

We needed the sensitivity matrix to calculate the Fisher Information Matrix; therefore, we describe the sensitivity analysis for the given model and then use this analysis to aid in identifiability. The sensitivity matrix $\chi = \frac{\partial M}{\partial q_i}$ is given below, where

$$q = [m_S \;\; \mu_S \;\; \beta \;\; p_T \;\; \tau \;\; \gamma \;\; m_R \;\; \mu_R \;\; c_R \;\; \tau_R \;\; e_\tau \;\; m_M \;\; c_M \;\; \tau_M \;\; ]$$

is the vector of parameters in the model and

$$\chi = \begin{bmatrix} \frac{\partial M(t_1)}{\partial m_S} & \cdots & \frac{\partial M(t_1)}{\partial \tau_M} \\ \frac{\partial M(t_2)}{\partial m_S} & \cdots & \frac{\partial M(t_2)}{\partial \tau_M} \\ \vdots & \ddots & \vdots \\ \frac{\partial M(t_n)}{\partial m_S} & \cdots & \frac{\partial M(t_n)}{\partial \tau_M} \end{bmatrix}. \tag{3}$$

Traditional sensitivity analysis, as defined by Hamby [14], uses the modified $L_2$ norm

$$\left\| \frac{\partial M}{\partial q} \right\|_2 = \frac{1}{\max\limits_{t_0 \le t \le t_f} (M(t))} \left[ \frac{1}{t_f - t_0} \int_{t_0}^{t_f} \left( \frac{\partial M}{\partial q} q \right)^2 \mathrm{d}t \right]^{\frac{1}{2}} \tag{4}$$

to determine the relative ranking of the sensitivity of $M$ to the various parameters where $t_f = 30(days)$ is the finishing time and $t_0 = 0$. The result from the sensitivity analysis is shown in Figure 4. Based on what is shown in this analysis, we can conclude that the model is most sensitive to the parameters $m_S$, $\beta$, $\tau_M$. When changed, those parameters result in the most change in $M$.

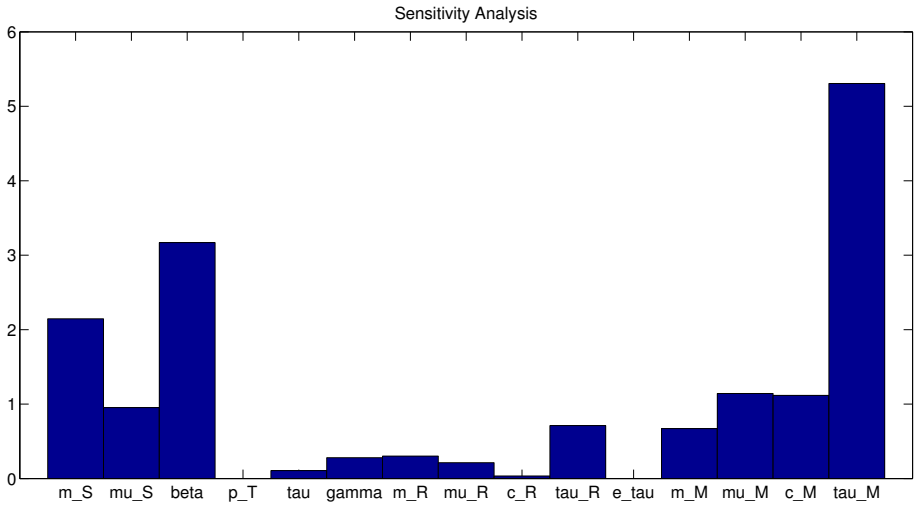


Figure 4: Sensitivity analysis for the model given by Eq (1)

Back to the concept of identifiability, the size of the FIM is $15 \times 15$, but the rank of the FIM is 11. So it is not full rank and the full set of parameters is not identifiable. It is possible to choose subsets of parameters, but instead we first analyze the system and reparameterize it to remove all sums and products which we know cannot be identified separately. For instance consider the product, $e_\tau \tau$ in the differential equation. When $e_\tau$ is increased and $\tau$ is decreased by the same proportion, the product is the same. We reparameterize the model; the new parameters are given in Table 2. The schematic for the reparameterized model is given in Figure 5 with the associated

ordinary differential equation system given by Eq. (5).

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \lambda m_S - S\mu_S + \beta SX - (\tau+\gamma)S - \beta_T RS, \qquad (5)\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \lambda m_R - R\mu_R + \tilde{\tau}_S S + \beta_T(RS - R^2 - RM) - (\tau_R+\gamma)R + \beta_{RX}RX,\\
\frac{\mathrm{d}M}{\mathrm{d}t} &= \lambda m_M - M\mu_M + \beta_{MX}MX + \beta_T(R^2 + RM) + \tilde{\tau}_R R - M(\alpha+\gamma).
\end{aligned}$$

Table 2: New parameter values for identifiability

| New Parameter | Original Parameter |
|---|---|
| $\widetilde{\tau}_S$ | $\tau e_\tau$ |
| $\widetilde{\tau}_R$ | $\tau_R e_\tau$ |
| $\widetilde{\tau}_M$ | $\tau_M e_\tau$ |
| $\beta_T$ | $\beta P_T$ |
| $\beta_{RX}$ | $\beta(1-c_R)$ |
| $\beta_{MX}$ | $\beta(1-c_M)$ |
| $\alpha$ | $\tau_M(1-e_\tau)$ |

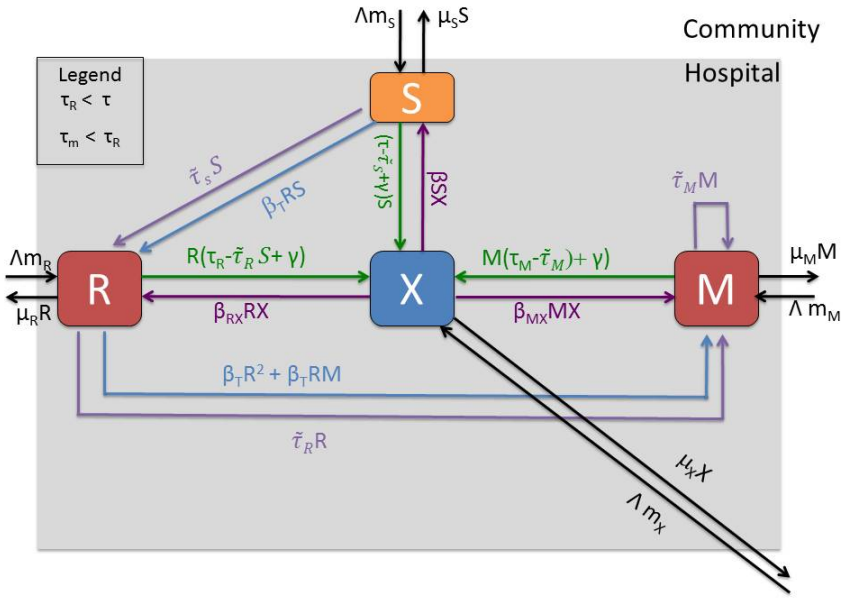


Figure 5: Schematic for the reparameterized model

Recalculating the Fisher Information Matrix using the reparameterized system with 16 new parameters, we have a rank of 15. It is still not full rank. The parameter $\gamma$ represents the ability of the immune system to kill off the bacteria. It is more likely to find data on how long it would take for a person's immune system to fight off something like antibiotic resistance. After removing $\gamma$ from the parameter list, FIM is full rank. Thus the remaining parameters,

$$q = [m_S \ \mu_S \ m_R \ \mu_R \ m_M \ \mu_M \ \beta \ \beta_T \ \beta_{RX} \ \beta_{MX} \ \tau \ \tau_R \ \widetilde{\tau}_S \ \widetilde{\tau}_R \ \alpha \ ]$$

are structurally identifiable. We will consider this reparameterized model for the remainder of this thesis.

# 4 PARAMETER ESTIMATION

The forward problem assumes that given a parameter $q = q_0$, the solution of the model in

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = f(t, Z(t), q_0) \tag{6}$$

can be calculated where $Z$ is the vector of variables $Z = [S, R, M, X]$. The inverse problem assumes some observable data from which the parameter $q_0$ can then be estimated. As mentioned previously, we assume the number of patients colonized with multiple resistant bacteria, $Y = NM$, are likely the only population which can be measured in a hospital setting. Therefore, even though we are still unlikely to be able to identify every patient with multiple resistance, we are going to assume that is possible in this thesis to establish the ability to estimate parameters in the best possible case. We assume the data, $y_i$, is one realization for the statistical model

$$Y_i = M(t_i, q_0) + \varepsilon_i \tag{7}$$

where $Y_i$ is a random variable , and $M(t_i, q_0)$ is the solution of Eq. (5) where $q_0$ is assumed to be some true parameter corresponding to the data. It shows the observation is equal to the model output, which is the solution to the forward problem given the true parameter $q_0$, plus any measurement error. The terms $\varepsilon_i, i = 1, 2, \ldots$ are independent and identically distributed random variables satisfying a normal distribution with mean 0 and variance $\mathrm{var}(\varepsilon_i) = \sigma_0^2 < \infty$ i.e. $\varepsilon_i \approx N(0, \sigma_0^2)$.

Given the assumption for the statistical model, we use ordinary least squares for the parameter estimation in which we estimate parameter $\hat{q}$. The cost function is

shown as follows

$$\hat{q} = \underset{q}{\operatorname{argmin}} \sum_{i}^{n} ([y_i - M(t_i, q)]^2) \tag{8}$$

where $y_i$ is the data assumed to be a realization of the model in Eq. (7) and $M(t_i, q)$ is the solution of Eq. (5) for a given parameter $q$.

We use the package *fminsearchcon* developed for Matlab in this minimization problem [15]. This algorithm is adapted from the built-in minimization routine *fminsearch*. Both of them are used to find the minimum of a given cost function. We chose *fminsearchcon* because it allows one to input parameter constraints. The lower bound and upper bound are two of the constraints. We let all of the parameters have lower bound 0. Since some of the parameters $m_S$, $\mu_S$, $m_R$, $\mu_R$, $m_M$, $\mu_M$, $\tau$, $\tau_R$, $\widetilde{\tau}_S$, $\widetilde{\tau}_R$, $\alpha$ are proportions, they should less than 1. The incoming patient constraints are $m_S > m_R > m_M$. This occurs because most of the patients who are admitted to the hospital are sensitive to most of the drugs. There are barely any patients resistant to multiple drugs. The departure rate constraints are $\mu_S > \mu_R > \mu_M$. Patients who are sensitive to most of the drugs would be cured quicker than patients who are resistant to drug treatment. The treatment rate constraints are $\tau > \tau_R > \tilde{\tau}_S > \tilde{\tau}_R$. The treatment rate of patients who are drug sensitive should be quicker than the treatment rate of patients who are drug resistant. A few patients will develop resistance to a drug during treatment. The colonization rate constraints are $\beta > \beta_{RX} > \beta_{MX} > \beta_T$. When patients contact each other, we assume the uncolonized transfer to colonized with multiple drug resistance is more difficult than becoming colonized with singleton drug resistance. The transfer by conjugation is least likely to happen.

In this thesis, we generate simulated data in order to determine the ability to

estimate parameters. To generate the data, we use Eq. (7) where we use the command *randn* in Matlab to generate the term $\varepsilon_i$ with mean 0. Using an initial guess close to the actual parameters, we obtain the estimates given in Table 3. The absolute and relative error give an idea of the accuracy of our estimates error, where absolute error is given by

$$\text{Absolute error} = |q_0 - \hat{q}|,$$

and relative error can be calculated as

$$\text{Relative error} = \frac{|q_0 - \hat{q}|}{|q_0|}.$$

The data together with the solution using the estimated parameters is shown in Figure 6. These are estimated parameter values; the confidence intervals will be given in the next section when we discuss uncertainty analysis.

Table 3: Estimated Parameter Values and Calculated Error

| Parameter | True value $q_0$ | Estimated value $\hat{q}$ | Absolute error | Relative error % |
|---|---|---|---|---|
| $m_S$ | 7.0000e-01 | 6.5302e-01 | 4.6977e-02 | 6.7110e+00 |
| $\mu_S$ | 2.0833e-01 | 1.3407e-01 | 7.4268e-02 | 3.5649e+01 |
| $m_R$ | 5.0000e-02 | 3.5278e-02 | 1.4722e-02 | 2.9445e+01 |
| $\mu_R$ | 1.6801e-01 | 9.9447e-02 | 6.8564e-02 | 4.0809e+01 |
| $m_M$ | 5.0000e-03 | 5.0366e-03 | 3.6638e-05 | 7.3275e-01 |
| $\mu_M$ | 8.4005e-02 | 9.9444e-02 | 1.5439e-02 | 1.8378e+01 |
| $\beta$ | 1.0000e+00 | 8.9694e-01 | 1.0306e-01 | 1.0306e+01 |
| $\beta_T$ | 1.0000e-06 | 1.1738e-06 | 1.7376e-07 | 1.7376e+01 |
| $\beta_{RX}$ | 9.5000e-01 | 8.7521e-01 | 7.4795e-02 | 7.8731e+00 |
| $\beta_{MX}$ | 8.5000e-01 | 8.7520e-01 | 2.5200e-02 | 2.9647e+00 |
| $\tau$ | 7.8000e-01 | 7.1135e-01 | 6.8653e-02 | 8.8017e+00 |
| $\tau_R$ | 5.6000e-01 | 5.4764e-01 | 1.2360e-02 | 2.2071e+00 |
| $\widetilde{\tau}_S$ | 7.8000e-08 | 1.7073e-02 | 1.7073e-02 | 2.1889e+07 |
| $\widetilde{\tau}_R$ | 5.6000e-08 | 1.3684e-03 | 1.3684e-03 | 2.4435e+06 |
| $\alpha$ | 3.9000e-01 | 3.7749e-01 | 1.2508e-02 | 3.2071e+00 |

Table 3 shows that the relative error of $\widetilde{\tau}_S$ and $\widetilde{\tau}_R$ are much larger than the others. These large relative errors indicate it is not possible to accurately estimate these parameter values. There is also significant error in the estimated values for $\mu_R$, $m_R$, and $\mu_S$; therefore, although these parameters are structurally identifiable, it may be difficult to identify these parameters in the presence of noise. We examine the error in these values further in the next section where we calculate confidence intervals for these parameters. However, we note that although there is large relative error in several parameters, Figure 6 shows that the simulation for the model using the estimated parameters is an extremely good estimate for the model using the exact parameters.

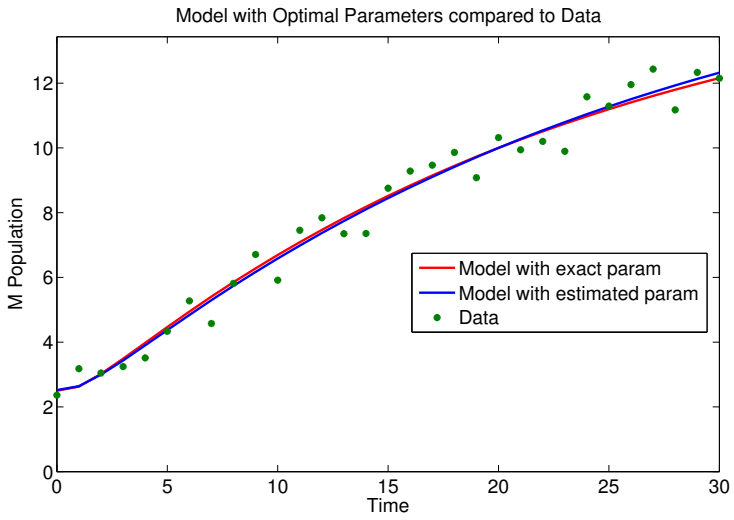


Figure 6: Solution to Eq (5) with both exact parameters and estimated parameters given in Table 3 together with simulated data

# 5 UNCERTAINTY ANALYSIS

Uncertainty analysis is an important part of a modeling process because there is variability in the data which effect parameter estimations. Similarly, uncertainty in the parameter estimations propagate throughout the model. In this section we look at both uncertainties in the parameter estimations by calculating confidence intervals as well how this uncertainty propagates through the model. The method used in this thesis is a bootstrapping method [16, 8]. The following algorithm can be used to compute the bootstrapping estimate $\hat{q}_{BOOT}$ of $q_0$.

1. First estimate $\hat{q}^0$ from the entire sample $Y_i^N$ using OLS, where $\hat{q}^0$ is a first parameter estimated from Eq. (8).

2. Using this estimate, we define the standardized residuals

$$\bar{r}_i = \sqrt{(\frac{N}{N-k_0})(Y_i - M(t_i;\hat{q}^0))} \quad for \quad i = 1,\ldots,N$$

   where $N = 30$ is the number of data points and $k_0$ is the number of parameters, $k_0 = 15$.

3. Create a bootstrapping sample of size $N$ using random sampling with replacement from the data (realizations) $\{\bar{r}_1,\ldots,\bar{r}_N\}$ to form a bootstrapping sample $\{\bar{r}_1^m,\ldots,\bar{r}_N^m\}$. We randomly shuffle each individual of the residual set and give new ordered residual set which is the bootstrapping sample.

4. Create bootstrap sample points

$$Y_i^m = M(t_i;\hat{q}^0) + r_i^m, \quad \text{where} \quad i = 1,\ldots,30.$$

In this step, we let the bootstrapping sample replace the measurement error to get the new sample $Y_i^m$,

5. Obtain a new estimate $\hat{q}^m$ from the bootstrapping sample $\{Y_i^m\}$ using OLS. We use same way as step 1 to get new estimate $\hat{q}^m$.

6. Set $m = m + 1$ and repeat steps 3-5 until $m \geq 1000$.

We let $m = 1000$ and obtain $\{\hat{q}^m\}$, $m = 1, ..., 1000$. The confidence intervals for the parameter values at the $100(1-\alpha)\%$ level are given by

$$C = [\hat{q}_{BOOT} - t_{1-\alpha/2}\mathrm{SE}_k(\hat{q}^m), \hat{q}_{BOOT} - t_{1-\alpha/2}\mathrm{SE}_k(\hat{q}^m)] \quad k = 1, \ldots, 15, \tag{9}$$

where $\hat{q}_{BOOT}$ is the mean value of $\{\hat{q}^m\}$. Let $\alpha = 0.05$ for 95% confidence intervals. The critical value $t_{1-\alpha/2} = 1.745884$ is computed from the students t distribution with $k_0 = 15$ degrees of freedom. Standard error is calculated by

$$\mathrm{SE}_k(\hat{q}^m) = \sqrt{\mathrm{Var}(q_{BOOT})_{kk}}$$

where

$$\mathrm{Var}(q_{BOOT}) = \frac{1}{1000-1}\sum_{m=1}^{1000}(\hat{q}^m - \hat{q}_{BOOT})^T(\hat{q}^m - \hat{q}_{BOOT}).$$

Confidence intervals are shown in Table 4 providing more information on the extent of uncertainty involved in estimating $q_0$. The solutions, $M(t, \hat{q}_m)$, $m = 1, ..., 1000$, are shown in Figure 7.

Table 4: Confidence Interval for Parameter Estimates

| Parameters | True value | $\hat{q}_{BOOT}$ | $C$ |
|---|---|---|---|
| $m_S$ | 7.0000e-01 | 6.6946e-01 | [ 4.0212e-01 , 9.3679e-01] |
| $\mu_S$ | 2.0833e-01 | 2.3849e-01 | [1.3286e-02 , 4.6369e-01] |
| $m_R$ | 5.0000e-02 | 6.4878e-02 | [-7.7942e-02 , 2.0770e-01] |
| $\mu_R$ | 1.6801e-01 | 1.5298e-01 | [7.8344e-03 , 2.9813e-01] |
| $m_M$ | 5.0000e-03 | 4.1250e-03 | [2.1650e-03 , 6.0850e-03] |
| $\mu_M$ | 8.4005e-02 | 7.9443e-02 | [2.0312e-02 , 1.3857e-01] |
| $\beta$ | 1.0000e+00 | 1.0432e+00 | [7.3260e-01 , 1.3537e+00] |
| $\beta_T$ | 1.0000e-06 | 1.0582e-06 | [5.4029e-07 , 1.5761e-06] |
| $\beta_{RX}$ | 9.5000e-01 | 9.4735e-01 | [7.3691e-01 , 1.1578e+00] |
| $\beta_{MX}$ | 8.5000e-01 | 8.6234e-01 | [7.6018e-01 , 9.6450e-01] |
| $\tau$ | 7.8000e-01 | 7.8803e-01 | [6.3728e-01 , 9.3879e-01] |
| $\tau_R$ | 5.6000e-01 | 5.9233e-01 | [3.5408e-01 , 8.3058e-01] |
| $\widetilde{\tau}_S$ | 7.8000e-08 | 2.1096e-02 | [-8.4058e-02 , 1.2625e-01] |
| $\widetilde{\tau}_R$ | 5.6000e-08 | 1.7241e-03 | [-3.5549e-03 , 7.0030e-03] |
| $\alpha$ | 3.9000e-01 | 3.8284e-01 | [2.9463e-01 , 4.7106e-01] |

The left confidence interval of $m_R$, $\widetilde{\tau}_S$, and $\widetilde{\tau}_R$ are negative. As defined, these parameters should not be negative. Recall that these parameter values are also the ones which gave the largest initial relative error (see Table 3). This is more indication that we cannot accurately estimate these parameters. The mean estimated parameter value for all other parameters had less than 18% relative error with all but two parameter values resulting in less than 10% relative error.

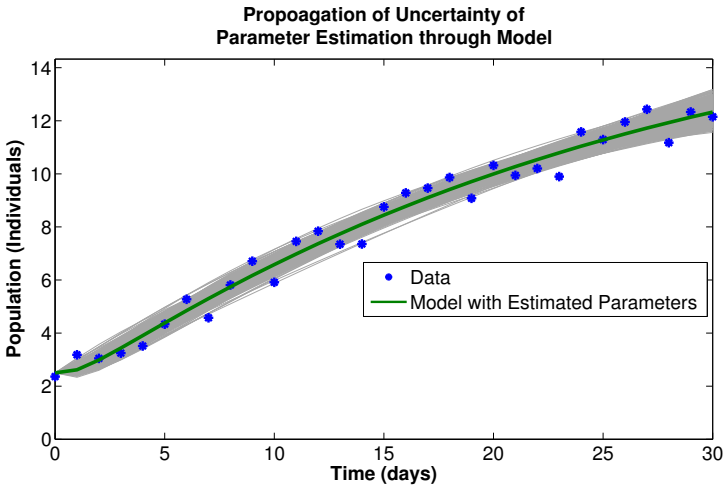


Figure 7: Variation in the solution $M(t, \hat{q}^m)$ in Eq. (5) given the variability in parameter values seen in Table 4

## 6 EQUILIBRIUM AND STABILITY ANALYSIS

In this section, we analyze the potential of a stable resistance-free equilibrium. The disease-free equilibrium is not a realistic possibility, since patients will continuously enter the hospital colonized with bacteria; therefore, we consider a resistant-free equilibrium (RFE) given by $\mathrm{E}_R = (S, R, M, X) = (S^*, 0, 0, X^*)$. As discussed in Section 2, $S + R + M + X = 1$; therefore, $X = 1 - (S + R + M)$ and thus $X^* = 1 - S^*$. $S^*$ can be calculated by the equation $S^* = \frac{\mathrm{d}S}{\mathrm{d}t}|_{E_R} = 0$, where $\frac{\mathrm{d}S}{\mathrm{d}t}$ is given in Eq. (5). This gives

$$S^* = \frac{\beta - \mu_S - \tau - \gamma \pm \sqrt{(\beta - \mu_S - \tau - \gamma)^2 + 4\beta\lambda m_S}}{2\beta}.$$

We first reorder the system with the resistant variables as given by

$$\begin{aligned}
\frac{\mathrm{d}R}{\mathrm{d}t} &= \lambda m_R - R\mu_R + \tilde{\tau}_S S + \beta_T(RS - R^2 - RM) - (\tau_R + \gamma)R + \\
&\quad \beta_{RX} R(1 - S - R - M), \\
\frac{\mathrm{d}M}{\mathrm{d}t} &= \lambda m_M - M\mu_M + \beta_{MX} M(1 - S - R - M) + \beta_T(R^2 + RM) + \\
&\quad \tilde{\tau}_R R - M(\alpha + \gamma), \\
\frac{\mathrm{d}S}{\mathrm{d}t} &= \lambda m_S - S\mu_S + \beta S(1 - S - R - M) - (\tau + \gamma)S - \beta_T RS.
\end{aligned}$$

The stability of the RFE can be computed by using the next generation approach [17]. We then linearize the reordered system about the RFE. The Jacobian Matrix evaluated at the RFE is given by

$$J = \left[\begin{array}{cc|c} J_{11} & 0 & \tilde{\tau}_S \\ \tilde{\tau}_R & J_{22} & 0 \\ \hline S^*(-\beta - \beta_T) & -\beta S^* & J_{33} \end{array}\right]$$

where

$$\begin{aligned} J_{11} &= -(\mu_R + \tau_R + \gamma) + \beta_T S^* + \beta_{RX}(1 - S^*) \\ J_{22} &= -(\mu_M + \alpha + \gamma) + \beta_{MX} \\ J_{33} &= -(\mu_S + \tau + \gamma) + \beta(1 - 2S^*) \end{aligned}$$

The terms in the Jacobian matrix can be separated as new colonizations with resistant bacteria and all other transitions. The new colonizations are given by

$$F = \begin{bmatrix} F_{11} & 0 \\ 0 & F_{22} \end{bmatrix}$$

where

$$\begin{aligned} F_{11} &= \beta_T S^* + \beta_{RX}(1 - S^*) \\ F_{22} &= \beta_{MX} \end{aligned}$$

and all the other transitions are given by

$$V = \begin{bmatrix} \mu_R + \tau_R + \gamma & 0 \\ -\widetilde{\tau}_R & \mu_M + \alpha + \gamma \end{bmatrix}.$$

V is a non-singular matrix. The matrix product $FV^{-1}$ is called the next generation matrix where $V^{-1}$ is given as:

$$V^{-1} = \begin{bmatrix} \dfrac{1}{\mu_R + \tau_R + \gamma} & 0 \\ \dfrac{\widetilde{\tau}_R}{(\mu_M + \alpha + \gamma)(\mu_R + \tau_R + \gamma)} & \dfrac{1}{\mu_M + \alpha + \gamma} \end{bmatrix}.$$

The terms $V_{jk}$ represent the average length of time that a patient stays in compartment $j$. Then the spectral radius $\rho$ of the matrix $FV^{-1}$ is defined as follows:

$$R_s = \rho(FV^{-1}) = \max\left\{ \frac{\beta_T S^* + \beta_{RX}(1 - S^*)}{\mu_R + \tau_R + \gamma}, \frac{\beta_{MX}}{\mu_M + \alpha + \gamma} \right\}. \tag{10}$$

Based on theory developed by Hadeler [17] and using the approach from Snyder [26] on our spectral radius, $R_s$, we have the following theorem concerning the model in Eq. (5).

**Theorem 6.1** *The resistant-free equilibrium for the model in Eq. (5),* $RFE = (S^*, 0, 0, X^*)$*, is locally asymptotically stable if and only if* $R_s$ *given in Eq. (10) satisfies* $R_s < 1$.

# 7 CONCLUTIONS AND FUTURE WORK

In this thesis, a new model was built by modifying a previous model given in the paper by Joyner et al. [1]. We then considered the reparameterization of the model to enable identifiability and then considered parameter estimation. The result of the simulation of our new model shows that it follows the trend seen in the data more than the previous model. The parameter estimation resulted in close estimates to the true parameters. The future work should focus on looking for real data. We need a real data record from the hospital to support that our model captures the relationships in an actual hospital. Future work may also include examining if all the important relationships are considered in our model. Another potential idea for future work could be using the model to test strategies for reducing antibiotic resistance in the hospital.

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