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MODELING ANTIBIOTIC RESISTANCE WHEN ADDING A NEW ANTIBIOTIC TO A HOSPITAL SETTING

A Thesis

Presented to

The Faculty of the Department of Mathematics & Statistics

And the Honors College

East Tennessee State University

In Partial Fulfillment

of the Requirements for the Degree

Bachelors of Science/Honors College

by

Brandi N. Canter

May 2012

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The Designated Thesis Committee Approves the Thesis Titled

MODELING ANTIBIOTIC RESISTANCE WHEN ADDING A NEW ANTIBIOTIC TO A HOSPITAL SETTING

by

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APPROVED FOR THE DEPARTMENT OF MATHEMATICS & STATISTICS

EAST TENNESSEE STATE UNIVERSITY

May 2012

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ABSTRACT

MODELING ANTIBIOTIC RESISTANCE WHEN ADDING A NEW ANTIBIOTIC TO A HOSPITAL SETTING

by Brandi N. Canter

As of now, not many pharmaceutical companies are producing new categories of antibiotics to fight bacterial infections [10]. Therefore, bacteria are building up a resistance to the medications commonly used. Often, antibiotic resistance begins within a hospital. To combat resistance, researchers completed several studies using cycling of the medications that are already in place, but they found either no improvement or the resistance increased with this type of setting [3, 8, 16, 12, 21, 22]. In addition, although preventative infection control measures have been shown to decrease antibiotic resistance for some antibiotics, the level of antibiotic resistance found in hospitals is still extremely high [9, 14]. This motivates the main goal of this thesis: to quantify how much the overall resistance can be lowered by simply adding one new drug to the regimen.

The process of adding a new antibiotic can be quantified using mathematical models that show the flow of patients colonized with various types of bacteria into, out of, and within the hospital. Deterministic models can be used to model the spread of resistant bacteria in hospitals with a relatively large number of beds. However, not all hospitals are large enough to accurately determine the effects using a deterministic model; thus, we must use stochastic models, where mathematical formulations include probability in ways that describe intrinsic random fluctuations, typical of infection processes at smaller scales [2, 20].

In examining the addition of a new antibiotic within a hospital, we consider different administration protocols, either assuming that physicians are equally likely to prescribe the new antibiotic as they are to prescribe existing antibiotics or that

physicians prescribe the new antibiotic to only a targeted population of patients. We will examine the variation in the expected level of overall resistance in a hospital depending on the administration procedure as well as the whether the hospital is large (deterministic model) or small (stochastic model). We will conclude with initial results for fitting these models to simulated data using common inverse problem methodology.

DEDICATION

To My Family. I love you!

ACKNOWLEDGEMENTS

Thanks to God for giving me the ability to write this thesis. Thanks to Dr. Michele Joyner of East Tennessee State University for assisting me in this process. Also, thanks to my family and friends for being so patient.

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INTRODUCTION

Public health is a major concern to all and when something as serious as antibiotic resistance threatens the traditional way of medicine, we need to be concerned. We need to pay close attention to antibiotic resistance; the goal should be to effectively treat patients by using current antibiotics wisely and focus on the manufacture of new antibiotics. As of now, "...[it] is estimated that each year, antibiotic resistance in the United States alone results in $20 billion of excess health care costs. ... Furthermore, the CDC estimates that resistant infections result in a total of 8 million additional days that people spend in the hospital each year" [12]. Joyner [12] states that "[today], we attribute longer survival of severely ill patients and longer life expectancy in the elderly to increase use of antibiotics". Some scientists have found the following practices are ...

> risk factors for the development of antibiotic resistance: excessive and irrational over-utilization of antibiotics in outpatient practice and in hospitalized patients, either therapeutically or prophylactically, use of antibiotics in agricultural industry, particularly in the production of food, longer survival of severely ill patients, longer life expectancy with increased use of antibiotics in the elderly, advances in medical science have resulted in the survival of many patients with severe illness and at risk for infections: Critically ill patients, Immunosuppression, Congenital diseases (i.e. cystic fibrosis), lack of use of proven and effective preventive infection control measure such as hand washing, antibiotic usage restrictions and proper isolation of patients with resistant infections, increased use of invasive procedures, and increased use of prosthetic devices and foreign bodies amenable to super infection with resistant bacteria [1].

Although antibiotics have cured many life threatening diseases, the increased use of antibiotics comes with side effects. It has been shown by the World Heath

Organization [18] that increased use of antibiotics can lead bacteria to form defenses and become resistant to the prescription drugs which is called antibiotic resistance. These resistant bacteria can become a catastrophic problem causing normal infections to become harder and sometimes impossible to treat. Once an individual is colonized with bacteria resistant to a particular antibiotic, that individual can spread the resistant bacteria either by direct contact or indirect contact through a secondary source such as a healthcare worker in a hospital. Hospital stays could become a problem for both the patient and the healthcare provider resulting in costlier stays [17]. This situation can be improved if we can determine how the resistant strains spread and then how to limit this spread. Mathematical models can aid in describing the spread of resistant bacteria.

Once a mathematical model is developed with an accurate description of the process involved in the transfer of resistant bacteria within an environment, it can be used as a tool to measure the quantitative effects of various protocols on the reduction of the prevalence of resistant bacteria. Lipsitch and Samore [15] state, "... [mathematical models] can be particularly valuable in at least four ways: 1) generating hypotheses about the relationship between antibiotic use and resistance that can be used in designing and prioritizing empirical studies; 2) defining the conditions under which a particular intervention is likely to work, thereby suggesting how empirical results can (and cannot) be extrapolated to other settings; 3) providing explanations for phenomena that have been observed but whose causes were uncertain; and 4) identifying biological mechanisms that, while important, remain poorly understood".

Many mathematical models can be found in literature describing various aspects of antibiotic resistance. A few of the models have tested protocols involving current antibiotics such as mixing versus cycling, a process which takes a limited

number of antibiotics, normally two, and uses one for a specific amount of time and then switches to the other medication [14, 15]. Another protocol is isolation where patients isolated from the general population, such as to another wing of the hospital [6, 9]. Bergstrom et. al. [6] consider a scenario in which two antibiotics were used in a cycling protocol, considering only the presence of resistance to only a single antibiotic. Dual resistance, i.e. resistance to two antibiotics, was assumed to be negligible. In this scenario, mixing (using two antibiotics in a random manner) appeared to be a better administration protocol than cycling the antibiotics. Chow et. al. [9] include the effects of the dual resistance and the competition between the spread of bacteria resistant to a singular antibiotic versus resistance to two antibiotics. In this scenario, simulations indicated cycling reduced the spread of dual resistant bacteria while increasing the spread of single resistant bacteria. Therefore, they concluded that neither cycling nor mixing caused much impact on the overall proportion of the hospital colonized with a resistant strain of bacteria. Although isolation reduced the spread of resistant bacteria slightly, simulations suggest there would still be a significant proportion of the patients colonized with resistant bacteria even when isolation practices are implemented.

Therefore, the goal of this thesis is to determine the effect of the introduction of a new antibiotic on the proportion of patients colonized with resistant bacteria and how to effectively introduce these new drugs when they are produced. If one can determine how to utilize the new drugs most effectively then it might be possible to reduce the widespread incidence of resistance.

In Chapter 2, we will develop deterministic models which depict the introduction of a new antibiotic under various administration procedures within a hospital setting. Although deterministic models can be accurately used to describe the spread of antibiotic resistance when there is a large number of patients in a

hospital, we must use stochastic models for small hospitals or single units of a large hospital such as an intensive care unit. Therefore, Chapter 3 will focus on the corresponding stochastic models. In Chapter 4, we will examine the inverse problem which can be used to determine a subset of parameters found in the models developed in Chapters 2 and 3. Finally, in Chapter 5 we conclude with some closing remarks and directions for future work.

CHAPTER 2

DETERMINISTIC MODELING OF ANTIBIOTIC RESISTANCE

In this chapter we will develop three deterministic models which describe the spread of resistant bacteria in a hospital and quantify the effects of introducing a new drug on this spread. Since the goal of this thesis is to determine how introducing a new antibiotic in the hospital effects the overall level of patients colonized with resistant bacteria, a base model is used as a comparison which is established based on the model developed by Chow et. al. [9]. The Base Model illustrates the spread of the resistant bacteria with no prevention protocols. Two additional models are developed, the Random Drug Model and the Targeted Drug Model which both illustrate adding a new drug under different administration protocols; all the patients are equally likely to receive the antibiotic (Random Drug Model) or a targeted population only receives the new antibiotic (Targeted Drug Model).

We are focusing "...on the introduction of an entirely new antibiotic as opposed to simply an upgrade of an antibiotic within the same class as the drugs already employed in the hospital. Due to chromosomal mutations or acquisition of new genetic material leading to the development of resistant bacteria, if a new antibiotic is introduced which is an upgrade of a current antibiotic, the use of the new antibiotic on patients already colonized with bacteria resistant to the older antibiotic could lead to a new high-level resistant strain" [13]. A comparison between a next-generation antibiotic and a new class of antibiotic can be found in [12]. In addition, since we are considering an entirely new class of antibiotics, resistance to the new antibiotic is neglected since the initial mutation rate is

presumed to be on the order of 10^{-6} [7, 16, 19]. Given this rate and the fact that resistance to the new antibiotic could be treated with either of the two existing antibiotics, we assume resistance to the new antibiotic would be minimal compared to other resistant populations within the system.

2.1 The Base Model

First, we examine in detail the Base Model from which both the Random Drug Model and Targeted Drug Models are derived. This model incorporates patients who are colonized with bacteria resistant to both one and two drugs, denoted "single" or "dual" resistant, respectively. We are assuming here that there are only two antibiotics in the model and that some of the patients may be colonized with bacteria resistant to either one drug or both drugs or neither. It is assumed there is no antibiotic present to treat the patients resistant to both drugs, other than their own body's ability to fight off the infection, a process known as "spontaneous clearance". Figure 2.1 gives a schematic for the Base Model.

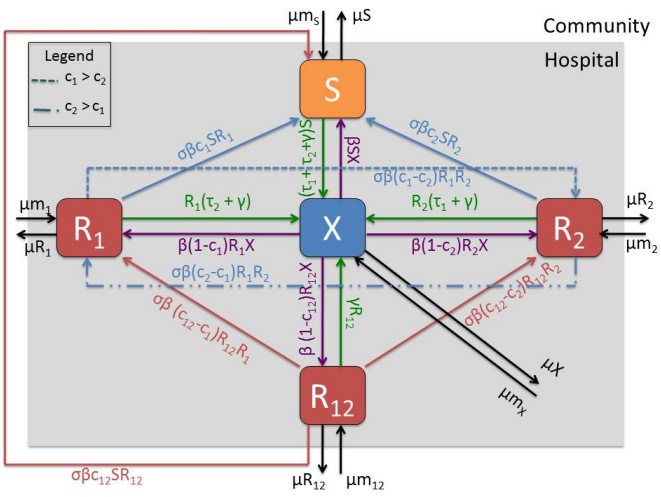

Figure 2.1: Schematic of the Base Model

The overall model, the grey box in Figure 2.1, represents a hospital with a fixed population size N, where N represents 100% of the total hospital population. Proportions of patients can be categorized in one of five possible compartments, S, R_1, R_2, R_{12}, and X. The state variable S represents the proportion of patients in the hospital who are colonized with bacteria sensitive to both drugs in the model. Therefore, S is the *number* of patients colonized with sensitive bacteria divided by the total population. Sensitive patients can be effectively treated and cleared with either drug 1 or drug 2. The uncolonized group, X, represents the proportion of patients in the hospital who are not colonized with bacteria (other than natural bacteria). The compartments R_1 and R_2 represent the proportion of patients colonized with single resistant bacteria, either bacteria resistant to drug 1, R_1, or resistant to drug 2, R_2. The main difference between these groups is the type of drug which will effectively treat the patients. Patients in compartment R_1 can only be effectively treated with drug 2, and patients in R_2 can only be effectively treated with drug 1. the compartment R_{12} is the proportion of "dual resistant" patients in the hospital, because they cannot be effectively treated with either drug 1 or drug 2. In other words, they are colonized with bacteria resistant to both drugs. A summary of the state variables can be found in Table 2.1. As all the state variables are considered as proportions of patients within the hospital, we have conservation of mass

$$1 = S + X + R_1 + R_2 + R_{12}. \tag{2.1}$$

Only a fixed proportion of the total population is assumed to be treated with antibiotics which is consistent with data found in literature [13]. Physicians prescribe either drug 1 or drug 2. The rate at which the doctors prescribe drug 1 is denoted by τ_1 and, similarly, τ_2 is the rate at which doctors prescribe drug 2.

Although doctors freely prescribe either of the drugs; patients colonized with bacteria resistant to a single antibiotic, R_1 or R_2, will only be effectively treated with one of the two antibiotics. Patients colonized with bacteria resistant to both drugs, R_{12}, will be unaffected by the prescription of either antibiotic; whereas, patients colonized with bacteria sensitive to either drug will be effectively treated by both.

Table 2.1: The Definition of Model Variables

Variables	Description
S	Proportion of patients colonized with bacteria sensitive to both drugs
R_i	Proportion of patients colonized with bacteria resistant to drug i, $i = 1, 2$
R_{12}	Proportion of patients colonized with bacteria resistant to both drugs
X	Proportion of patients uncolonized

As mentioned previously, it is assumed the total number of patients within the hospital remain fixed 2.1. Therefore, for every one person entering the hospital, there must be exactly one person who is discharged. We assume patients enter and leave the hospital at a constant rate, μ, which is given by the reciprocal of the average number of days of stay in the hospital. Furthermore, it is assumed patients can enter the hospital in any of the given compartments. The proportion of patients entering the hospital with bacteria susceptible to both drugs is given by m_S. The proportion of patients entering colonized with a single resistant bacteria is given by m_1 and m_2 for single resistance to drug 1 and single resistance to drug 2, respectively. The proportion of patients entering the hospital colonized with dual resistant bacteria is given by m_{12}. Therefore, the proportion of patients admitted to the hospital uncolonized, m_X, can be given by $m_X = 1 - (m_s + m_1 + m_2 + m_{12})$.

The total admission rate is then given by

$$\mu m_S + \mu m_1 + \mu m_2 + \mu_{12} + \mu m_X.$$

Substituting for m_X, we get the total admission rate

$$\mu m_S + \mu m_1 + \mu m_2 + \mu_{12} + \mu[1 - (m_s + m_1 + m_2 + m_{12})] = \mu.$$

Similarly, it is assumed patients can be discharged from any compartment where the proportion of patients discharged per day from a particular compartment is μ times the total proportion in that compartment at time t. For example, μS is the proportion of patients colonized with susceptible bacteria discharged per day. The proportion discharged in each compartment is computed in a similar manner. Therefore, μX is the proportion of uncolonized patients discharged per day. μR_1 and μR_2 represent the proportion of single resistant patients discharged per day and lastly, μR_{12} is the proportion of the dual resistant patients discharged from the hospital per day. So, the total discharge rate from the hospital is given by

$$\mu S + \mu X + \mu R_1 + \mu R_2 + \mu R_{12} = \mu(S + R_1 + R_2 + R_{12} + X) = \mu(1) = \mu.$$

As stated the admission and discharge rates are both given by μ.

We assume that interactions between the different groups, S, X, R_1, R_2, and R_{12}, can take place either directly or indirectly through healthcare workers. For example, suppose a nurse checks on a patient colonized with bacteria resistant to drug 1 and does not strictly follow the hand-hygiene rules. Then that nurse may act as an indirect vector in the colonization of patients when checking on other patients. It is assumed that an average patient in the hospital makes βN effective contacts with other patients per unit time through either direct contact or similar indirect contact. This assumption of a rate of contact per infective proportional to the

population size N is called the mass action incidence [11]. The probability that a random contact is made by a patient colonized with sensitive bacteria with an uncolonized patient is given by the number of uncolonized patients divided by the total population. Therefore, the proportion of the patients in the hospital gained by new colonizations in a unit time by contact is βX. Thus, the rate of transfer from compartment X to compartment S is given by βXS. In a similar manner, uncolonized patients, X, may become colonized with bacteria resistant to drug 1, drug 2, or both and hence move from X to either R_1, R_2, or R_{12}, respectively. The terms representing these movements are similar to the movement from X to S except the probability of becoming colonized with resistant bacteria is offset by the fitness cost of the resistant bacteria represented by the parameters c_1, c_2, and c_{12}. The fitness cost of bacteria resistant to drug 1 is c_1, c_2 is the fitness cost of bacteria resistant to drug 2, and, likewise, c_{12} is the fitness cost of the dual resistant bacteria.

> Fitness cost is a parameter which describes the rate at which resistant bacteria revert back to being susceptible in the absence of antibiotic treatment. Resistant bacteria thrive in the presence of antibiotics; however, in an antibiotic-free environment, the resistant bacteria are at a disadvantage and less able to reproduce, thus providing an advantage to the susceptible bacteria. When the fitness cost is high, the ability to reproduce is much lower and thus more difficult to spread. On the other hand, the lower the fitness cost of the resistant bacteria, the easier it is for the bacteria to spread. ...we assume ... that the dual resistant strain is harder to spread and, therefore, has a higher fitness cost than the single resistant bacteria [13].

In other words, if c_1 is reduced then the term $(1 - c_1)$ is increased taking into account that bacteria spreads at a faster rate. The same is true for c_2 and c_{12}.

Patients may also move from S to X by being effectively treated with either drug 1 or drug 2, or through the process of spontaneous clearance, represented by the terms $\tau_1 S$, $\tau_2 S$, and γS respectively. Combining these together, we obtain the

rate at which patients colonized with sensitive bacteria move from S to X, $(\tau_1 + \tau_2 + \gamma)S$.

Similarly patients may transfer from either R_1, R_2, or R_{12} to X. However, in each of these instances either only one antibiotic will work (R_1, R_2) or none (R_{12}). We are again assuming that physicians are unaware of the type of bacteria present. Hence, if patients are colonized with bacteria resistant to drug 1, they will not be cleared until treated with drug 2, represented by the term $\tau_2 R_1$, or by spontaneous clearance, γR_1. Terms for R_2 and R_{12} can be found in the schematic in Figure 2.1.

It is assumed that patients cannot be colonized with more than one strain of bacteria at a given time. Furthermore, the bacteria with the lowest fitness, thus the quickest rate of reproduction will "win" out over any competing bacteria. It is assumed that bacteria resistant to multiple antibiotics has a more difficult time reproducing [9], thus the dual resistant bacteria will never "out-compete" the single resistant bacteria nor the susceptible bacteria. Therefore, we assume patients colonized with dual resistant bacteria may move from R_{12} to either R_1, R_2, or S; however, patients in R_1, R_2, or S are never assumed to move to R_{12} simply through interactions. (We are neglecting the possibility of conjugation in this paper.) If the fitness cost of drug 1 (c_1) is larger than the fitness cost of drug 2 (c_2), bacteria resistant to drug 2 out-competes bacteria resistant to drug 1. This process of one type of bacteria out-competing another type is considered secondary colonization and is represented by the term σ. Combining all these terms, we have a system of nonlinear ordinary differential equations describing the Base Model as follows where the definitions for the parameters are given in Table 2.2.

$$
\begin{aligned}
\tfrac{dS}{dt} &= (m_S - S)\mu - (\tau_1 + \tau_2 + \gamma)S + \beta XS + \beta\sigma(c_1R_1 + c_2R_2 + c_{12}R_{12})S \\
\tfrac{dR_1}{dt} &= (m_1 - R_1)\mu - (\tau_2 + \gamma)R_1 + \beta(1 - c_1)XR_1 \\
&\quad +\sigma\beta[(c_{12} - c_1)R_{12} + (c_2 - c_1)R_2 - c_1S]R_1 \\
\tfrac{dR_2}{dt} &= (m_2 - R_2)\mu - (\tau_1 + \gamma)R_2 + \beta(1 - c_2)XR_2 \\
&\quad +\sigma\beta[(c_{12} - c_2)R_{12} + (c_1 - c_2)R_1 - c_2S]R_2 \\
\tfrac{dR_{12}}{dt} &= (m_{12} - R_{12})\mu - \gamma R_{12} + \beta(1 - c_{12})XR_{12} \\
&\quad -\sigma\beta[c_{12}S + (c_{12} - c_1)R_1 + (c_{12} - c_2)R_2]R_{12} \\
\tfrac{dX}{dt} &= (m_X - X)\mu + (\tau_1 + \tau_2 + \gamma)S + (\tau_2 + \gamma)R_1 + (\tau_1 + \gamma)R_2 + \gamma R_{12} \\
&\quad -\beta X(S + (1 - c_1)R_1 + (1 - c_2)R_2 + (1 - c_{12})R_{12}).
\end{aligned}
\tag{2.2}
$$

Table 2.2: The Definition of Parameters

Parameters	Description	Units
β	Per capita primary transmission rate (colonization rate)	1/day
σ	Relative rate of secondary colonization to that of primary colonization	Dimensionless
c_i	Fitness cost of bacteria resistant to drug i, $i = 1, 2$	Dimensionless
c_{12}	Fitness cost of bacteria resistant to both drugs	Dimensionless
τ_i	Per capita treatment rate of drug i, $i = 1, 2$	1/day
γ	Per capita clearance rate of bacteria due to immune response	1/day
μ	Per capita patient turnover rate in hospital	1/day
m_S	Proportion of admitted patients colonized with sensitive bacteria	Dimensionless
m_i	Proportion of admitted patients colonized with bacteria resistant to drug i, $i = 1, 2$	Dimensionless
m_{12}	Proportion of admitted patients colonized with bacteria resistant to both drugs	Dimensionless

2.2 The Random Drug Model

The objective of this thesis is to determine what happens to the total level of patients colonized with resistant bacteria within the hospital when a completely new

drug is added to the prescription regimen. In both the Random Drug and Targeted Drug Models, we are adding a new antibiotic, referred to as drug 3, to the regimen to see if the overall total proportion of patients colonized with resistant bacteria is lowered. The difference between these models is in the population that receives the new medication. In the Random Drug Model, we are assuming that the doctors can give any of the three drugs to all patients. In other words, we are assuming there is an equal likelihood the doctors will choose drug 1, drug 2, or drug 3. The per capita treatment rates of drugs 1, 2, and 3 are given by τ_1, τ_2, and τ_3, respectively, where it is assumed $\tau_1 = \tau_2 = \tau_3$.

Although a new antibiotic is added to the regimen, we assume that the total population being treated per day, T, remains the same as the Base Model. Thus, $T = \tau_1 + \tau_2 + \tau_3$ where $\tau_i = \frac{T}{3}$ for $i = 1, 2, 3$. This inherently means that when we add the third drug, we are lowering the per capita treatment rates of drug 1 and 2. Although we still assume physicians do not know what type of bacteria each patient has contracted, two drugs are now effective for patients colonized with single resistant bacteria. Furthermore, patients colonized with dual resistant bacteria now have a mechanism for clearance other than their own immune system. As with the Base Model, there is a possibility that patients will initially be given a medication that does not work. For example, if a patient is in the R_1 compartment and given drug 1, the patient will not be cleared. However, if they are given drug 2 or drug 3 in the Random Drug Model, they will become uncolonized. Figure 2.2 shows a schematic fro the Random Drug Model.

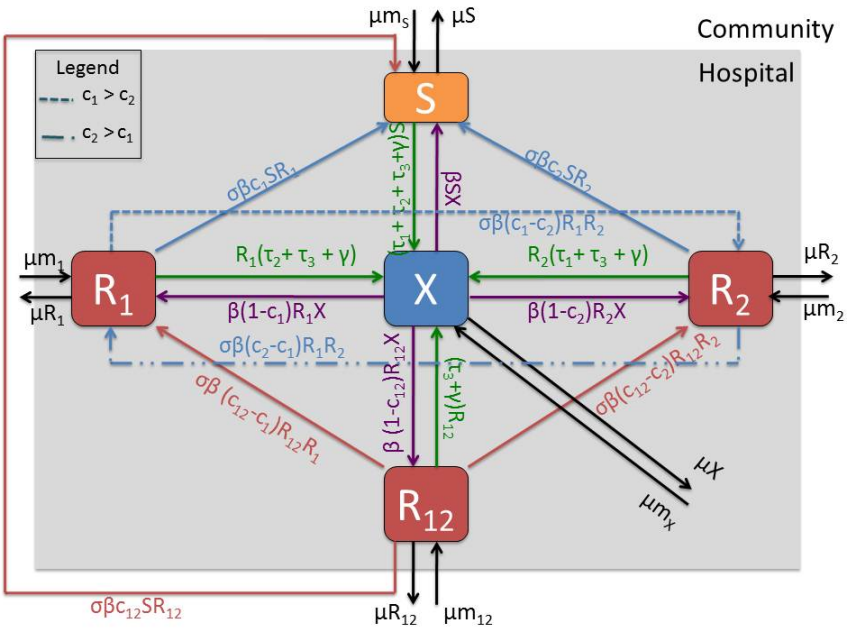

Figure 2.2: Schematic of the Random Drug Model

The set of differential equations representing the model are as follows:

$$
\begin{aligned}
\tfrac{dS}{dt} &= (m_S - S)\mu - (\tau_1+\tau_2+\tau_3+\gamma)S + \beta XS \\
&\quad +\beta\sigma(c_1R_1 + c_2R_2 + c_{12}R_{12})S \\
\tfrac{dR_1}{dt} &= (m_1 - R_1)\mu - (\tau_2+\tau_3+\gamma)R_1 + \beta(1-c_1)XR_1 \\
&\quad +\sigma\beta[(c_{12}-c_1)R_{12} + (c_2-c_1)R_2 - c_1S]R_1 \\
\tfrac{dR_2}{dt} &= (m_2 - R_2)\mu - (\tau_1+\tau_3+\gamma)R_2 + \beta(1-c_2)XR_2 \\
&\quad +\sigma\beta[(c_{12}-c_2)R_{12} + (c_1-c_2)R_1 - c_2S]R_2 \\
\tfrac{dR_{12}}{dt} &= (m_{12} - R_{12})\mu - (\tau_3+\gamma)R_{12} + \beta(1-c_{12})XR_{12} \\
&\quad -\sigma\beta[c_{12}S + (c_{12}-c_1)R_1 + (c_{12}-c_2)R_2]R_{12} \\
\tfrac{dX}{dt} &= (m_X - X)\mu + (\tau_1+\tau_2+\tau_3+\gamma)S \\
&\quad +(\tau_2+\tau_3+\gamma)R_1 + (\tau_1+\tau_3+\gamma)R_2 + (\tau_3+\gamma)R_{12} \\
&\quad -\beta X[S + (1-c_1)R_1 + (1-c_2)R_2 + (1-c_{12})R_{12}].
\end{aligned}
\tag{2.3}
$$

2.3 The Targeted Drug Model

In the previous model, the Random Drug Model, we assumed that everyone within the hospital could receive the third drug, because it was readily available to physicians for prescription. The Targeted Drug Model assumes the new drug is only used to target one group of patients, namely patients colonized with bacteria resistant to both drugs 1 and 2. As with both of the previous models, the Targeted Drug Model keeps the total proportion of patients being treated, T, fixed with $T = \tau_1 + \tau_2 + \tau_3$; however, within the Targeted Drug Model, we are not making the assumption that the three drugs are given at the same rate. In this model, we are assuming that $\tau_1 = \tau_2$, therefore, drug 1 and drug 2 are given at the same rate per day. However, the rate at which drug 3 is given, τ_3, depends on the proportion, p, we assume can be identified, by either testing or through treatment failure of drugs 1 and 2, as carrying the dual resistant strain. All those identified can then be treated with the new antibiotic. Thus, $\tau_3 = pR_{12}$ is a function of time, because R_{12} changes across time. It is intuitive that if the proportion of patients we can identify increases, the treatment rate of drug 3 will also increase. Figure 2.3 depicts the schematic for the Targeted Drug Model "... where the parameter $\delta = 1/\text{day}$ is introduced only to help distinguish between the proportion of patients colonized with dual resistance who are identified and treated, $R^T = pR_{12}$ (dimensionless quantity), and the actual treatment rate with drug 3, $\tau_3 = \delta pR_{12}$ (units 1/day)" [13].

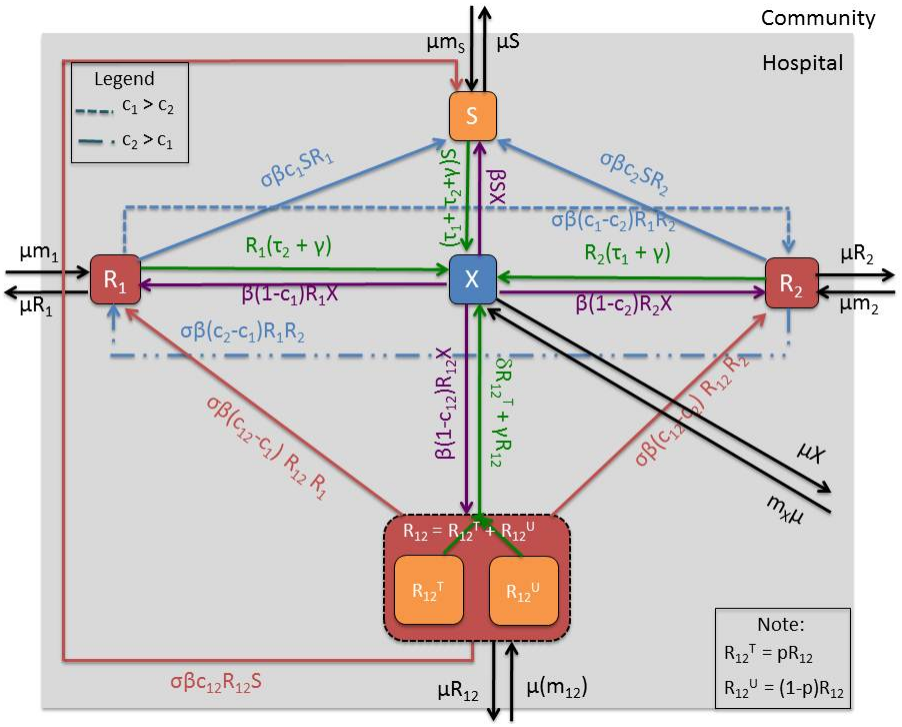

Figure 2.3: Schematic of the Targeted Drug Model

The system of differential equations describing the Targeted Drug Model are as follows:

$$
\begin{aligned}
\frac{dS}{dt} &= (m_S - S)\mu - (\tau_1 + \tau_2 + \gamma)S + \beta X S + \beta\sigma(c_1 R_1 + c_2 R_2 + c_{12} R_{12})S \\
\frac{dR_1}{dt} &= (m_1 - R_1)\mu - (\tau_2 + \gamma)R_1 + \beta(1 - c_1)X R_1 + \sigma\beta[(c_{12} - c_1)R_{12} + (c_2 - c_1)R_2 - c_1 S]R_1 \\
\frac{dR_2}{dt} &= (m_2 - R_2)\mu - (\tau_1 + \gamma)R_2 + \beta(1 - c_2)X R_2 + \sigma\beta[(c_{12} - c_2)R_{12} + (c_1 - c_2)R_1 - c_2 S]R_2 \\
\frac{dR_{12}}{dt} &= (m_{12} - R_{12})\mu - (\delta p + \gamma)R_{12} + \beta(1 - c_{12})X R_{12} \\
&\quad -\sigma\beta[c_{12} S + (c_{12} - c_1)R_1 + (c_{12} - c_2)R_2]R_{12} \\
\frac{dX}{dt} &= (m_X - X)\mu + (\tau_1 + \tau_2 + \gamma)S + (\tau_2 + \gamma)R_1 + (\tau_1 + \gamma)R_2 + (\delta p + \gamma)R_{12} \\
&\quad -\beta X[S + (1 - c_1)R_1 + (1 - c_2)R_2 + (1 - c_{12})R_{12}].
\end{aligned}
\tag{2.4}
$$

2.4 Numerical Simulation Results

Results of numerical simulations are given in Figure 2.4 for each of the three the models given parameter values in Table 2.3. Figure 2.4 also shows simulated

results for a model not explained in this paper, namely the Isolation Model. This model is shown for comparison purposes and was first introduced by Chow et. al., [9] and then further discussed by the author in [12]. In this model, patients colonized with the dual resistant bacteria are isolated from the other patients at a rate η. The theory is that patients will be less likely to spread the dual resistant strain when isolated.

The simulations indicate that if there are no protocols for treatment of the patients colonized with dual resistance, i.e. the Base Model, then on average across 100 days approximately 70% of the hospital population will become colonized with a resistant strain. This proportion is only slightly reduced when isolation is practiced. On the other hand, for the Random Drug Model, i.e., when a new antibiotic is used at the same rate as the existing antibiotics and each patient is equally as likely to receive drug 3 as drugs 1 or 2, the total proportion of the hospital colonized with a resistant strain drops to 35%. This is a significant reduction from the 70% level for the Base Model. The last plot in Figure 2.4 shows the state variables for the Targeted Drug Model, using a value of $p = .30$. Recall, the value p is the percentage we assume are able to be identified as being colonized with bacteria resistant to drugs 1 and 2. Therefore, if one were able to identify and treat 30% of those patients in the hospital who are colonized with bacteria resistant to both drugs, we could lower the total proportion of patients colonized with any type of resistant bacteria by an additional 3% over the Random Drug Model.

Figure 2.5 shows a comparison of the total resistance for each model while varying p in the Targeted Drug Model. Since the Targeted Drug Model depends on the proportion of patients carrying the dual resistant strain who can be identified, it is necessary to analyze how varying the parameter p effects the total proportion of patients colonized with a resistant strain in the hospital. If we cannot identify any

Table 2.3: Values of Model Parameters for the Deterministic Models [13]

Parameters	Base Model	Random Drug	Targeted Drug
β	1/day	1/day	1/day
σ	0.25	0.25	0.25
γ	0.03/day	0.03/day	0.03/day
μ	0.10/day	0.10/day	0.10/day
m_S	0.70	0.70	0.70
m_1	0.05	0.05	0.05
m_2	0.05	0.05	0.05
m_{12}	0.04	0.04	0.04
m_X	0.16	0.16	0.16
c_1	0.05	0.05	0.05
c_2	0.05	0.05	0.05
c_{12}	0.15	0.15	0.15
τ_1	0.39/day	0.26/day	$\frac{1}{2}(T-\tau_3)/day$
τ_2	0.39/day	0.26/day	$\frac{1}{2}(T-\tau_3)/day$
τ_3	-	0.26/day	pR_{12}/day
T	-	-	0.78/day

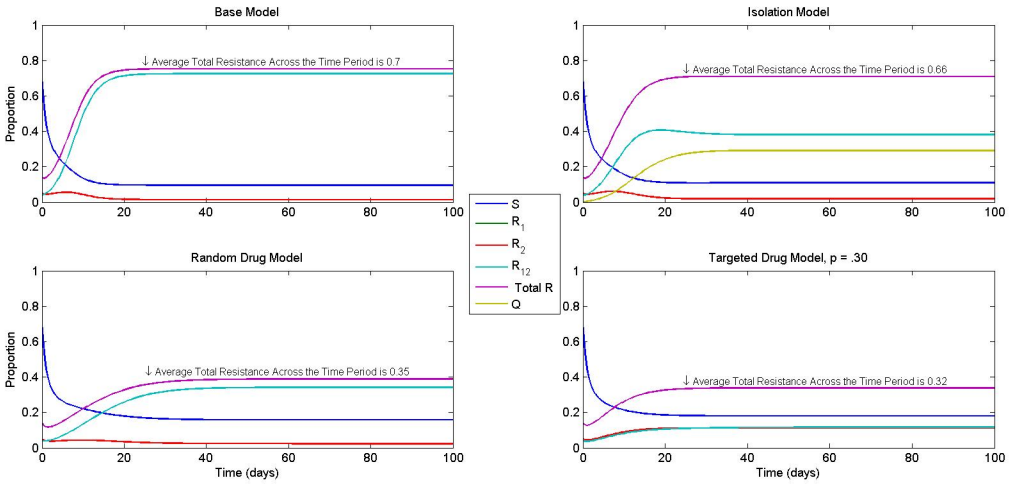

Figure 2.4: Comparison of All of the State Variables for Each Model

of the patients colonized with resistant bacteria ($p = 0$), the model is equivalent to the Base Model. On the other hand, if $p = 1$, we assume we are able to identify and treat *all* of the patients colonized with dual resistance. This scenario is unrealistic

since hospitals do not test for resistance upon admittance. However, if we can identify and treat approximately 25% or more of the patients colonized with the dual resistant bacteria, the Targeted Drug Model is the best way to administer the new drug. This method of administration could result in a reduction of total resistance by approximately 40% over the Base Model!

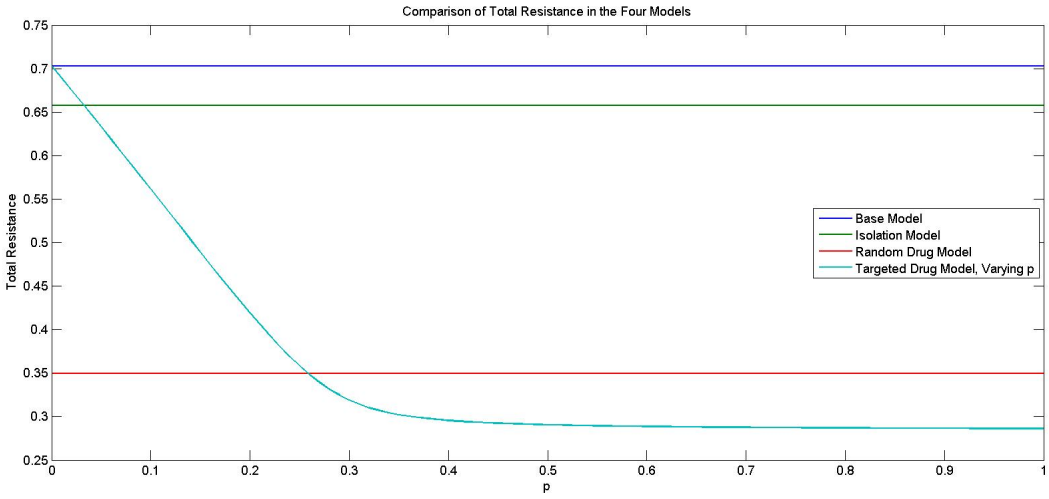

Figure 2.5: Comparison of the Total Resistance for Each Model

CHAPTER 3

STOCHASTIC MODELING OF ANTIBIOTIC RESISTANCE

In the previous chapter, we focused on deterministic models for the spread of resistant bacteria within a hospital. In general, "deterministic models predict an outcome with absolute certainty, whereas stochastic models provide only the probability of an outcome" [2]. Stochastic models incorporate randomness into the model. Each time a solution for a stochastic model is simulated, called a realization, it is slightly different than another realization. However, as the population size of our system becomes large, the mean of all the realizations of the stochastic model approach the solution of the deterministic model. There are a variety of methods and techniques used to formulate stochastic models based on the specific application. In this paper, we will develop stochastic models which are based on stochastic processes continuous in time with discrete state space in $\mathbb{Z}^5$. These are called continuous-time Markov chain (CTMC) models [2]. Therefore, we can assume that colonization occurs in units of whole individuals (discrete state space) but the occurrence of events is a probabilistic process. The formal definition for a stochastic process is given by Definition 3.0.1 [2].

Definition 3.0.1. *A* stochastic process *is a collection of random variables* $\{X_t(s) : t \in T, s \in S\}$*, where* T *is some index set and* S *is the common* same space *of the random variables. For each fixed* t*,* $X_t(s)$ *denotes a single random variable defined on* S*. For each fixed* $s \in S, X_t(s)$ *corresponds to a function defined on* T *that is called a* sample path *or a* stochastic realization *of the process* [2].

CTMC models are governed by the Markov property

$$Prob\{X(t_{t+1}) = i_{n+1} | X(t_0) = i_0, X(t_1) = i_1, \ldots, X(t_n) = i_n\} =$$

$$Prob\{X(t_{n+1}) = i_{n+1} | X(t_n) = i_n\}$$

which simply indicates a "memoryless property", i.e., the probability of an event occurring depends only on the previous time step.

3.1 The Stochastic Base Model

To derive the Stochastic Base Model, which can be modified to obtain the Stochastic Random Drug Model and the Stochastic Targeted Drug Model, we consider the state variables to be the *number* of patients in a given compartment as opposed to the *proportion* of the total population in that compartment as consider in the deterministic models. We denote the new state variable as

$$\mathbf{X}^N = (X_1^N, X_2^N, X_3^N, X_4^N, X_5^N)^T,$$

where N denotes the total population and the random variables $i = 1, 2, \ldots, 5$ are described in Table 3.1.

Table 3.1: The Modified Definitions of Model Variables

Variables	Description
$X_1^N(t)$	Number of patients colonized with bacteria sensitive to both drugs
$X_2^N(t)$	Number of patients colonized with bacteria resistant to drug i, $i = 1$
$X_3^N(t)$	Number of patients colonized with bacteria resistant to drug i, $i = 2$
$X_4^N(t)$	Number of patients colonized with bacteria resistant to both drugs
$X_5^N(t)$	Number of patients uncolonized

For the stochastic model, some of the parameters need to be modified from the deterministic models in order to represent the *number* of patients accurately. For example, β is replaced with $\beta^N = \frac{\beta}{N}$. In general it is assumed that an average patient makes $\beta = \beta^N N$ adequate contacts with an infective per unit time, that is,

contacts sufficient to lead to colonization [23]. For example, the probability that a random contact with an uncolonized patient leads to a *new* colonization in unit time is given by the proportion of patients uncolonized. Thus the number of *new* colonizations is given by

$$\beta X = \beta^N N X = \beta^N N \frac{X_5^N}{N} = \beta^N X_5^N.$$

Thus, the rate of new colonizations with sensitive bacteria is now given by $\beta^N X_5^N X_1^N$. See Table 3.2 for the other modified parameters; all other parameters are left unchanged and are described in Table 2.2.

Table 3.2: The Definition of Modified Parameters

Parameters	Description	Units
β^N	Per capita primary transmission rate = 1/N times the colonization rate	$\frac{1}{individuals \cdot day}$
m_S^N	Number of admitted patients colonized with sensitive bacteria	Individuals
m_i^N	Number of admitted patients colonized with bacteria resistant to drug i, $i = 1, 2$	Individuals
m_{12}^N	Number of admitted patients colonized with bacteria resistant to both drugs	Individuals

For small time intervals of length Δt, we assume $\{\mathbf{X}^N(t), t \geq 0\}$ jumps from the state $\mathbf{x}^N$ to $\mathbf{x}^N + \mathbf{v}_j$ with probability $\lambda_j(\mathbf{x}^N)\Delta t + o(\Delta t)$, i.e.,

$$Prob\{\mathbf{X}^N(t + \Delta t) = \mathbf{x}^N + \mathbf{v}_j | \mathbf{X}^N(t) = \mathbf{x}^N\} = \lambda_j(\mathbf{x}^N)\Delta t + o(\Delta t), \qquad j = 1, 2, \ldots, l,$$

$\mathbf{x}^N = (x_1^N, x_2^N, x_3^N, x_4^N, x_5^N)^T \in \mathbb{Z}^5$ and λ_j is the transition rate for reaction j, where l denotes the number of transitions [5]. The probability of transitioning from one state to another state during a small time interval $\Delta t = dt$ is described by the equations (3.1) to (3.20) where the variables S^N, R_1^N, R_2^N, R_{12}^N, and X^N are given by

$$S^N = x_1^N = N \cdot S,$$

$$R_1^N = x_2^N = N \cdot R_1,$$

$$R_2^N = x_3^N = N \cdot R_2,$$

$$R_{12}^N = x_4^N = N \cdot R_{12},$$

$$X^N = x_5^N = N \cdot X$$

where S, R_1, R_2, R_{12}, and X are the variables from the deterministic model. For example, (3.1) describes the probability that in time dt, one individual will enter the sensitive compartment while one individual leaves the "resistant to drug 1" compartment. Recall that we assume a constant population, thus if an individual is added to one compartment, an individual must also be subtracted from a different compartment. In Figure 2.1, we notice it is not possible to have a direct transition from R_1 compartment to the S compartment. Thus, the only way for one individual to enter S while an individual leaves R_1 is if one is discharged from the hospital from the R_1 compartment, and at the same time one is admitted to the hospital. We further note that to simplify the stochastic models, we do not consider the effect of secondary colonization in these models. Hence, transitions involving σ in Figure 2.1 are neglected.

$$\begin{aligned} &P\{S^N(t+dt) = i+1, R_1^N(t+dt) = j-1, R_2^N(t+dt) = k, R_{12}^N(t+dt) = l, \\ &X^N(t+dt) = m | S^N(t) = i, R_1^N(t) = j, R_2^N(t) = k, R_{12}^N(t) = l, X^N(t) = m\} \\ &= \mu R_1^N m_S^N dt + o(dt), \end{aligned} \tag{3.1}$$

$$\begin{aligned} &P\{S^N(t+dt) = i+1, R_1^N(t+dt) = j, R_2^N(t+dt) = k-1, R_{12}^N(t+dt) = l, \\ &X^N(t+dt) = m | S^N(t) = i, R_1^N(t) = j, R_2^N(t) = k, R_{12}^N(t) = l, X^N(t) = m\} \\ &= \mu R_2^N m_S^N dt + o(dt), \end{aligned} \tag{3.2}$$

$$P\{S^N(t+dt)=i+1, R_1^N(t+dt)=j, R_2^N(t+dt)=k, R_{12}^N(t+dt)=l-1,$$
$$X^N(t+dt)=m|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu R_{12}^N m_S^N dt+o(dt), \tag{3.3}$$

$$P\{S^N(t+dt)=i+1, R_1^N(t+dt)=j, R_2^N(t+dt)=k, R_{12}^N(t+dt)=l,$$
$$X^N(t+dt)=m-1|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu X^N m_S^N dt+\beta^N S^N X^N dt+o(dt), \tag{3.4}$$

$$P\{S^N(t+dt)=i-1, R_1^N(t+dt)=j+1, R_2^N(t+dt)=k, R_{12}^N(t+dt)=l,$$
$$X^N(t+dt)=m|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu S^N m_1^N dt+o(dt), \tag{3.5}$$

$$P\{S^N(t+dt)=i, R_1^N(t+dt)=j+1, R_2^N(t+dt)=k-1, R_{12}^N(t+dt)=l,$$
$$X^N(t+dt)=m|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu R_2^N m_1^N dt+o(dt), \tag{3.6}$$

$$P\{S^N(t+dt)=i, R_1^N(t+dt)=j+1, R_2^N(t+dt)=k, R_{12}^N(t+dt)=l-1,$$
$$X^N(t+dt)=m|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu R_{12}^N m_1^N dt+o(dt), \tag{3.7}$$

$$P\{S^N(t+dt)=i, R_1^N(t+dt)=j+1, R_2^N(t+dt)=k, R_{12}^N(t+dt)=l,$$
$$X^N(t+dt)=m-1|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu X^N m_1^N dt+\beta^N(1-c_1)R_1^N X^N dt+o(dt), \tag{3.8}$$

$$P\{S^N(t+dt)=i-1, R_1^N(t+dt)=j, R_2^N(t+dt)=k+1, R_{12}^N(t+dt)=l,$$
$$X^N(t+dt)=m|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu S^N m_2^N dt+o(dt), \tag{3.9}$$

$$P\{S^N(t+dt)=i, R_1^N(t+dt)=j-1, R_2^N(t+dt)=k+1, R_{12}^N(t+dt)=l,$$
$$X^N(t+dt)=m|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu R_1^N m_2^N dt+o(dt), \tag{3.10}$$

$$P\{S^N(t+dt)=i, R_1^N(t+dt)=j, R_2^N(t+dt)=k+1, R_{12}^N(t+dt)=l-1,$$
$$X^N(t+dt)=m|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu R_{12}^N m_2^N dt+o(dt), \tag{3.11}$$

$$P\{S^N(t+dt)=i, R_1^N(t+dt)=j, R_2^N(t+dt)=k+1, R_{12}^N(t+dt)=l,$$
$$X^N(t+dt)=m-1|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu X^N m_2^N dt+\beta^N(1-c_2)R_2^N X^N dt+o(dt), \tag{3.12}$$

$$P\{S^N(t+dt)=i-1, R_1^N(t+dt)=j, R_2^N(t+dt)=k, R_{12}^N(t+dt)=l+1,$$
$$X^N(t+dt)=m|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu S^N m_{12}^N dt+o(dt), \tag{3.13}$$

$$P\{S^N(t+dt)=i, R_1^N(t+dt)=j-1, R_2^N(t+dt)=k, R_{12}^N(t+dt)=l+1,$$
$$X^N(t+dt)=m|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu R_1^N m_{12}^N dt+o(dt), \tag{3.14}$$

$$P\{S^N(t+dt)=i, R_1^N(t+dt)=j, R_2^N(t+dt)=k-1, R_{12}^N(t+dt)=l+1,$$
$$X^N(t+dt)=m|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu R_2^N m_{12}^N dt+o(dt), \tag{3.15}$$

$$P\{S^N(t+dt)=i, R_1^N(t+dt)=j, R_2^N(t+dt)=k, R_{12}^N(t+dt)=l+1,$$
$$X^N(t+dt)=m-1|S^N(t)=i, R_1^N(t)=j, R_2^N(t)=k, R_{12}^N(t)=l, X^N(t)=m\}$$
$$=\mu X^N m_{12}^N dt+\beta^N(1-c_{12})R_{12}^N X^N dt+o(dt), \tag{3.16}$$

$$P\{S^N(t+dt) = i-1, R_1^N(t+dt) = j, R_2^N(t+dt) = k, R_{12}^N(t+dt) = l,$$
$$X^N(t+dt) = m+1 | S^N(t) = i, R_1^N(t) = j, R_2^N(t) = k, R_{12}^N(t) = l, X^N(t) = m\}$$
$$= \mu S^N m_X^N dt + (\tau_1 + \tau_2 + \gamma) S^N dt + o(dt), \tag{3.17}$$

$$P\{S^N(t+dt) = i, R_1^N(t+dt) = j-1, R_2^N(t+dt) = k, R_{12}^N(t+dt) = l,$$
$$X^N(t+dt) = m+1 | S^N(t) = i, R_1^N(t) = j, R_2^N(t) = k, R_{12}^N(t) = l, X^N(t) = m\}$$
$$= \mu R_1^N m_X^N dt + (\tau_2 + \gamma) R_1^N dt + o(dt), \tag{3.18}$$

$$P\{S^N(t+dt) = i, R_1^N(t+dt) = j, R_2^N(t+dt) = k-1, R_{12}^N(t+dt) = l,$$
$$X^N(t+dt) = m+1 | S^N(t) = i, R_1^N(t) = j, R_2^N(t) = k, R_{12}^N(t) = l, X^N(t) = m\}$$
$$= \mu R_2^N m_X^N dt + (\tau_1 + \gamma) R_2^N dt + o(dt), \tag{3.19}$$

$$P\{S^N(t+dt) = i, R_1^N(t+dt) = j, R_2^N(t+dt) = k, R_{12}^N(t+dt) = l-1,$$
$$X^N(t+dt) = m+1 | S^N(t) = i, R_1^N(t) = j, R_2^N(t) = k, R_{12}^N(t) = l, X^N(t) = m\}$$
$$= \mu R_{12}^N m_X^N dt + \gamma R_{12}^N dt + o(dt). \tag{3.20}$$

The transition rates and reactions are summarized in Table 3.3 where

$$e_i(j) = \begin{cases} 1 & j = i \\ 0 & j \neq i, \end{cases}$$

and where $\downarrow$ is the decrease of an individual out of a given compartment and $\uparrow$ means an increase of an individual to a given compartment. The increase $\uparrow$ and decrease $\downarrow$ may be by direct transfer from one compartment to another (such as colonization of an individual previously uncolonized, i.e., from $X \to S$) or by a discharge and corresponding admittance of a patient to two separate compartments.

In order to simulate a single realization of the stochastic model, the standard Gillespie algorithm [5] (referred to the Stochastic Simulation Algorithm (SSA)) was used; however, we wanted to determine the effect of the population size, N, on the

Table 3.3: Transition rates $\lambda_j(\mathbf{x}^N)$ as well as the corresponding state changes $\mathbf{v}_j$ for the Stochastic Base Model, $j = 1, 2, \ldots, 5$.

Event	Transition Rate	$\mathbf{v}_j$
$\downarrow X_2^N \uparrow X_1^N$	$\lambda_1 = \mu x_2^N m_S^N$	$e_1 - e_2$
$\downarrow X_3^N \uparrow X_1^N$	$\lambda_2 = \mu x_3^N m_S^N$	$e_1 - e_3$
$\downarrow X_4^N \uparrow X_1^N$	$\lambda_3 = \mu x_4^N m_S^N$	$e_1 - e_4$
$\downarrow X_5^N \uparrow X_1^N$	$\lambda_4 = \mu x_5^N m_S^N + \beta^N x_1^N x_5^N$	$e_1 - e_5$
$\downarrow X_1^N \uparrow X_2^N$	$\lambda_5 = \mu x_1^N m_1^N$	$-e_1 + e_2$
$\downarrow X_3^N \uparrow X_2^N$	$\lambda_6 = \mu x_3^N m_1^N$	$e_2 - e_3$
$\downarrow X_4^N \uparrow X_2^N$	$\lambda_7 = \mu x_4^N m_1^N$	$e_2 - e_4$
$\downarrow X_5^N \uparrow X_2^N$	$\lambda_8 = \mu x_5^N m_1^N + \beta^N (1 - c_1) x_2^N x_5^N$	$e_2 - e_5$
$\downarrow X_1^N \uparrow X_3^N$	$\lambda_9 = \mu x_1^N m_2^N$	$-e_1 + e_3$
$\downarrow X_2^N \uparrow X_3^N$	$\lambda_{10} = \mu x_2^N m_2^N$	$-e_2 + e_3$
$\downarrow X_4^N \uparrow X_3^N$	$\lambda_{11} = \mu x_4^N m_2^N$	$e_3 - e_4$
$\downarrow X_5^N \uparrow X_3^N$	$\lambda_{12} = \mu x_5^N m_2^N + \beta^N (1 - c_2) x_3^N x_5^N$	$e_3 - e_5$
$\downarrow X_1^N \uparrow X_4^N$	$\lambda_{13} = \mu x_1^N m_{12}^N$	$-e_1 + e_4$
$\downarrow X_2^N \uparrow X_4^N$	$\lambda_{14} = \mu x_2^N m_{12}^N$	$-e_1 + e_4$
$\downarrow X_3^N \uparrow X_4^N$	$\lambda_{15} = \mu x_3^N m_{12}^N$	$-e_3 + e_4$
$\downarrow X_5^N \uparrow X_4^N$	$\lambda_{16} = \mu x_5^N m_{12}^N + \beta^N (1 - c_{12}) x_4^N x_5^N$	$e_4 - e_5$
$\downarrow X_1^N \uparrow X_5^N$	$\lambda_{17} = \mu x_1^N m_X^N + (\tau_1 + \tau_2 + \gamma) x_1^N$	$-e_1 + e_5$
$\downarrow X_2^N \uparrow X_5^N$	$\lambda_{18} = \mu x_2^N m_X^N + (\tau_2 + \gamma) x_2^N$	$-e_2 + e_5$
$\downarrow X_3^N \uparrow X_5^N$	$\lambda_{19} = \mu x_3^N m_X^N + (\tau_1 + \gamma) x_3^N$	$-e_3 + e_5$
$\downarrow X_4^N \uparrow X_5^N$	$\lambda_{20} = \mu x_4^N m_X^N + \gamma x_4^N$	$-e_4 + e_5$

total resistance across several realizations to obtain an average of the expected outcome. The value of N effects the computational time required [5]; therefore, as done in [5], we implemented the modified explicit tau-leaping method summarized next (full details on implementation of this method can be found in [5] and the references therein). The main difference between the standard Gillespie Algorithm (SSA) and the explicit tau-leaping method is in the time step taken. In the SSA Algorithm, incremental steps are taken in time, keeping track of $\mathbf{X}(t)$ at each step; whereas the explicit tau-leaping method leaps from one interval to the next by a value of τ. Thus it is necessary to approximate the number of times a transition λ_j occurs within the time interval $[t, t + \tau]$. The choice of the leap value τ is

determined by requiring relative changes in X_i to be bounded. As explained by the author in a previous paper [5],

> Let $\Delta X_i = X_i(t+\tau) - x_i$ with x_i being the ith component of $\mathbf{x}$, $i = 1, 2, \ldots, n$ and ϵ be an error control parameter with $0 < \epsilon \ll 1$. In the given τ-selection procedure, τ is chosen such that
>
> $$\Delta X_i \leq \min\left\{\frac{\epsilon}{g_i}x_i, 1\right\}, i = 1, \ldots, n,$$
>
> which evidently requires the relative change in X_i to be bounded by $\frac{\epsilon}{g_i}$ except that X_i will never be required to change by an amount less than 1. The value of g_i is chosen such that the relative changes in all the transitions rates will be bounded by ϵ. For example, if the transitions rate λ_j has the form $\lambda_j(\mathbf{x}) = c_j x_i$ with c_j being a constant, then the reaction j is said to be first order and the absolute change in $\lambda_j(\mathbf{x})$ is given by
>
> $$\Delta\lambda_j(\mathbf{x}) = \lambda_j(\mathbf{x} + \mathbf{\Delta x}) - \lambda_j(\mathbf{x}) = c_j(x_i + \Delta x_i) - c_j x_i = c_j \Delta x_i.$$
>
> Hence, the relative change in $\lambda_i(\mathbf{x})$ is related to the relative change in X_i by $\frac{\Delta\lambda_j(\mathbf{x})}{\lambda_j(\mathbf{x})} = \frac{\Delta x_i}{x_i}$, which implies that if we set the relative change in X_i by ϵ (i.e., $g_i = 1$), then the relative change in λ_j is bounded by ϵ. If the transition rate λ_j has the form $\lambda_j(\mathbf{x}) = c_j x_i x_r$ with c_j bein a constant, then the reaction j is said to be second order and the absolution change in $\lambda_j(\mathbf{x})$ is given by
>
> $$\Delta\lambda_j(\mathbf{x}) = c_j(x_i+\Delta x_i)(x_r+\Delta x_r) - c_j x_i x_r = c_j x_r \Delta x_i + c_j x_i \Delta x_r + c_j \Delta x_i \Delta x_r.$$
>
> Hence, the relative change in $\lambda_j(\mathbf{x})$ is related to the relative change in X_i by
>
> $$\frac{\Delta\lambda_j(\mathbf{x})}{\lambda_j(\mathbf{x})} = \frac{\Delta x_i}{x_i} + \frac{\Delta x_r}{x_r} + \frac{\Delta x_i}{x_i}\frac{\Delta x_r}{x_r}$$
>
> which implies that if we set the relative change in X_i by $\frac{\epsilon}{2}$ and the relative change in X_r by $\frac{\epsilon}{2}$ (i.e., $g_i = 2$, $g_r = 2$), then the relative change in λ_j is bounded by ϵ to the first order approximation [5].

For our model, it is necessary to determine g_i for each state variable $X_i, i = 1, \ldots, 5$. Let $\Delta\lambda_i(\mathbf{x}) = \lambda_i(\mathbf{x} + \Delta x) - \lambda_i(\mathbf{x})$ with Δx being the absolute changes in the state variables, $i = 1, 2, \ldots, 20$. We can see that several transitions

are first order, because the transition only takes into account one of the state variables. However, we must examine transitions λ_4, λ_8, λ_{12}, λ_{16}, λ_{17}, λ_{18}, λ_{19}, and λ_{20} because they depend on more than one state variable. Recall from Table 3.3 that transition λ_4 is given by

$$\lambda_4 = \mu x_5 m_S + \beta x_1 x_5.$$

Therefore,

$$\Delta\lambda_4 = \mu(x_5 + \Delta x_5)m_S + \beta(x_1 + \Delta x_1)(x_5 + \Delta x_5) - \mu x_5 m_S - \beta x_1 x_5$$

$$= \mu\Delta x_5 m_S + \beta x_1 \Delta x_5 + \beta\Delta x_1 x_5 + \beta\Delta x_1 \Delta x_5$$

which implies that

$$\frac{\Delta\lambda_4}{\lambda_4} = \frac{\mu\Delta x_5 m_S + \beta x_1 \Delta x_5 + \beta\Delta x_1 x_5 + \beta\Delta x_1 \Delta x_5}{\mu x_5 m_S + \beta x_1 x_5}.$$

Using the triangle inequality and the positiveness of the state variables, we have the following inequality

$$\frac{|\Delta\lambda_4|}{\lambda_4} \leq \frac{|\Delta x_5|}{x_5} + \frac{|\Delta x_5|}{x_5} + \frac{|\Delta x_1|}{x_1} + \frac{|\Delta x_1 \Delta x_5|}{x_1 x_5} \leq \frac{|\Delta\lambda_4|}{\lambda_4} \leq \frac{2|\Delta x_5|}{x_5} + \frac{|\Delta x_1|}{x_1}.$$

If we choose

$$|\Delta x_1| < \frac{\epsilon}{2} x_1 \quad \text{and} \quad |\Delta x_4| < \frac{\epsilon}{4} x_5,$$

then the absolute relative change in λ_4 is given by

$$\frac{|\Delta\lambda_4|}{\lambda_4} < 2\left(\frac{\epsilon}{4}\right) + \frac{\epsilon}{2} = \epsilon.$$

If, in addition, we choose

$$|\Delta x_2| < \frac{\epsilon}{2} x_2, \quad |\Delta x_3| < \frac{\epsilon}{2} x_3 \quad \text{and} \quad |\Delta x_4| < \frac{\epsilon}{2} x_4,$$

we also have the following reactions will all be bounded by ϵ:

$$\text{Reaction 17:} \quad \frac{|\Delta\lambda_{17}|}{\lambda_{17}} \leq \frac{|\Delta x_1|}{x_1} + \frac{|\Delta x_1|}{x_1} < \epsilon$$

$$\text{Reaction 18:} \quad \frac{|\Delta\lambda_{18}|}{\lambda_{18}} \leq \frac{|\Delta x_2|}{x_2} + \frac{|\Delta x_2|}{x_2} < \epsilon$$

$$\text{Reaction 19:} \quad \frac{|\Delta\lambda_{19}|}{\lambda_{19}} \leq \frac{|\Delta x_3|}{x_3} + \frac{|\Delta x_3|}{x_3} < \epsilon$$

$$\text{Reaction 20:} \quad \frac{|\Delta\lambda_{20}|}{\lambda_{20}} \leq \frac{|\Delta x_4|}{x_4} + \frac{|\Delta x_4|}{x_4} < \epsilon.$$

Given these bounds on each transition, we need to set $g_i = 2, i = 1, \ldots, 4$ and $g_5 = 4$. Using these values of g_i and the parameter values in Table 3.4, we have plotted one realization for six different population sizes (N = 10, 25, 50, 100, 200, and 300 patients) in Figure 3.1 using the Explicit Tau-Leaping algorithm for the Stochastic Base Model. On each graph we have also plotted the corresponding solution for the deterministic model. For each population size, we notice that the majority of patients are colonized with the dual resistance (in red) similar to the results for the deterministic model.

Table 3.4: The Values of Model Parameters for the Stochastic Base Model

Parameters	Values for SSA & Explicit Tau-Leaping
β^N	$\frac{1}{N}$
σ	0
γ	0.03
μ	0.10
m_S^N	0.70*N
m_1^N	0.05*N
m_2^N	0.05*N
m_{12}^N	0.04*N
m_X^N	0.16*N
c_1	0.05
c_2	0.05
c_{12}	0.15
τ_1	0.39
τ_2	0.39

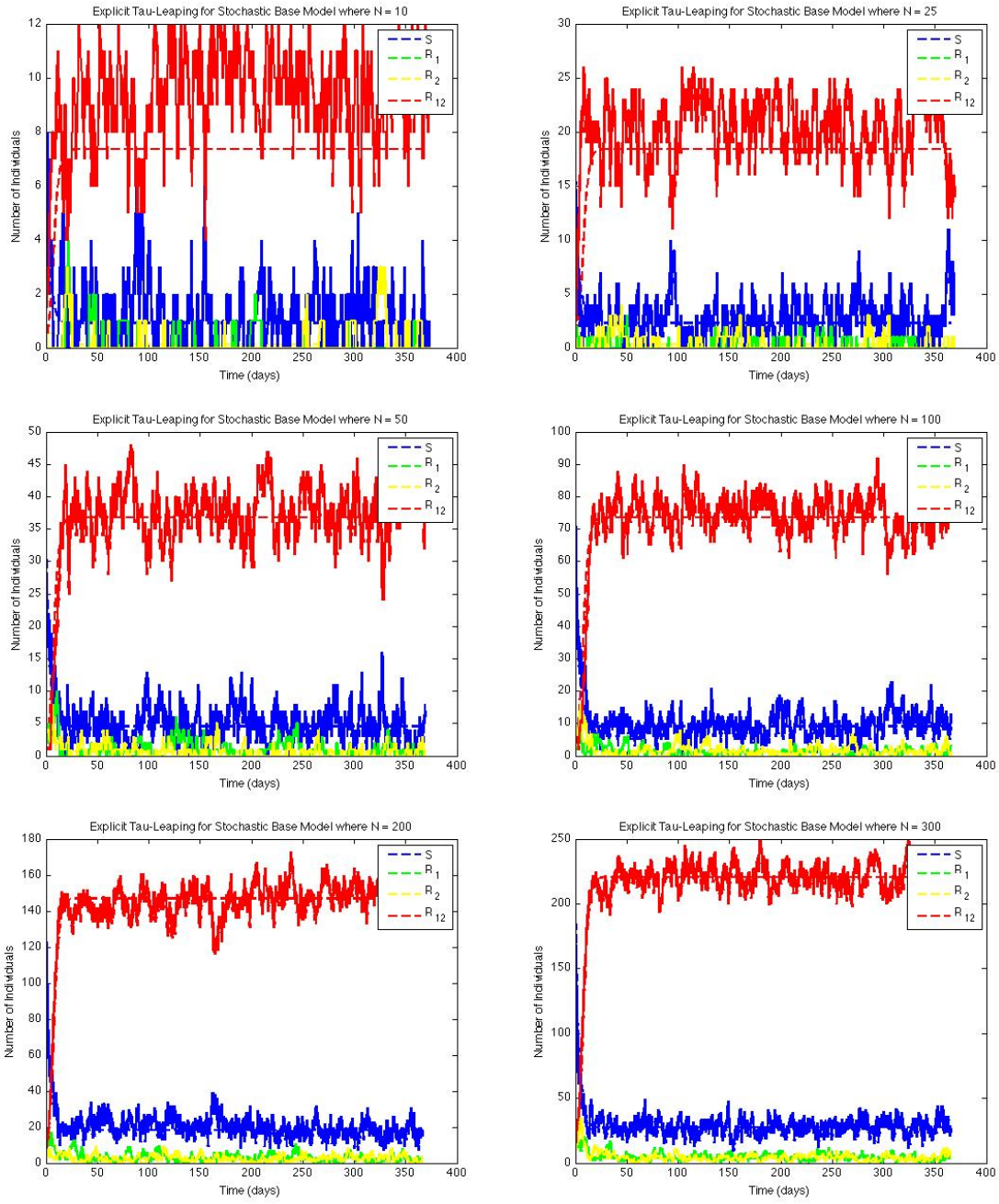

Figure 3.1: Results for the Stochastic Base Model where N = 10, 25, 50, 100, 200, 300 compared to the corresponding deterministic results (the straight lines)

To obtain an average result across numerous realizations (as each realization is different), we ran 500 realizations for each of the following populations: 10, 25, 50, 100, 200, and 300 patients and compared these averages to the deterministic model. Table 3.5 gives the average proportion of the population colonized with resistant bacteria over one year, $t_f = 365$ days, across the m=500 realizations, calculated using Equations (3.21) and (3.22).

$$\frac{1}{m}\left[\sum_{i=1}^{m}\left(\frac{1}{t_f N}\int_0^{t_f}\left[X_4^N(t)_i\right]\mathrm{d}t\right)\right] \tag{3.21}$$

$$\frac{1}{m}\left[\sum_{i=1}^{m}\left(\frac{1}{t_f N}\int_0^{t_f}\left[X_2^N(t)_i + X_3^N(t)_i + X_4^N(t)_i\right]\mathrm{d}t\right)\right] \tag{3.22}$$

Table 3.5: Average Proportion of Population Colonized with Resistant Bacteria over 1 Year with varying Population sizes for the Stochastic Base Model vs. Deterministic Base Model

Base Model Population	10	25	50	100	200	300	Deterministic
Proportion - Dual Resistance	.89	.78	.74	.72	.72	.72	.72
Proportion - Total Resistance	.93	.82	.77	.75	.75	.75	.75

Table 3.5 shows that the proportion of patients colonized with the dual resistant strain is .89 when $N = 10$ compared to .72 for the deterministic model. (Note that when we increase a resistant group by one patient when $N = 10$, we increase the proportion by 10% whereas when we increase the resistant group by one patient when the population size is 100, we only increase the proportion by 1%.) Hence, for the deterministic model, it is estimated that on average across one year, approximately 75% of the hospital population will be colonized with bacteria resistant to both drugs. We note that the results of the deterministic model is not dependent on the total population size, as we only consider proportions in the deterministic model. This is an under approximation of what is simulated to occur in a unit of a hospital where $N = 10$. In this case it is estimated that 89% of the

population will be colonized with resistant bacteria. This can be seen in Figure 3.1. When $N = 10$ the deterministic solution for R_{12} is consistently below the stochastic model realization for R_{12}. This results in a change in the total resistance as well. The stochastic model indicates that on average the total proportion of patients colonized with some type of resistant bacteria when $N = 10$ is approximately .93; however, the deterministic model significantly underestimates this proportion at .75. Once the value for N reaches approximately 100 patients or more, the two models being to look similar. This is further evidenced in Figure 3.1 where the results of the deterministic model are close to the realization for the stochastic model; it appears neither below or above the stochastic model for the given realization.

3.2 Stochastic Random Drug Model

Most of the terminology used in deriving the Stochastic Base Model is the same for the Stochastic Random Drug Model with the exception of the addition of the third drug to this model. The term representing the addition of the new antibiotic is found in transitions λ_{17}, λ_{18}, λ_{19}, and λ_{20}, where τ_3 is the per capita treatment rate of drug 3. Using similar probabilities of transitioning from one state to another state as in (3.1) - (3.20), we obtain the corresponding transitions in Table 3.6.

As done in the Stochastic Base Model, we need to calculate appropriate values of g_i for this system. All of the transitions are the same as the Stochastic Base Model except λ_{17}, λ_{18}, λ_{19}, and λ_{20}. However, calculations (not shown here) show values of g_i can be chosen the same.

The parameter values for the Stochastic Random Drug Model are the same as in Table 3.4 with the exception of τ_1, τ_2, and τ_3 which are all set to 0.26. One realization for the Stochastic Random Drug Model with population sizes of $N = 10$,

Table 3.6: Transition rates $\lambda_j(\mathbf{x}^N)$ as well as the corresponding state changes $\mathbf{v}_j$ for the Stochastic Random Drug Model, $j = 1, 2, \ldots, 5$.

Event	Transition Rate	$\mathbf{v}_j$
$\downarrow X_2^N \uparrow X_1^N$	$\lambda_1 = \mu x_2^N m_S^N$	$e_1 - e_2$
$\downarrow X_3^N \uparrow X_1^N$	$\lambda_2 = \mu x_3^N m_S^N$	$e_1 - e_3$
$\downarrow X_4^N \uparrow X_1^N$	$\lambda_3 = \mu x_4^N m_S^N$	$e_1 - e_4$
$\downarrow X_5^N \uparrow X_1^N$	$\lambda_4 = \mu x_5^N m_S^N + \beta^N x_1^N x_5^N$	$e_1 - e_5$
$\downarrow X_1^N \uparrow X_2^N$	$\lambda_5 = \mu x_1^N m_1^N$	$-e_1 + e_2$
$\downarrow X_3^N \uparrow X_2^N$	$\lambda_6 = \mu x_3^N m_1^N$	$e_2 - e_3$
$\downarrow X_4^N \uparrow X_2^N$	$\lambda_7 = \mu x_4^N m_1^N$	$e_2 - e_4$
$\downarrow X_5^N \uparrow X_2^N$	$\lambda_8 = \mu x_5^N m_1^N + \beta^N (1 - c_1) x_2^N x_5^N$	$e_2 - e_5$
$\downarrow X_1^N \uparrow X_3^N$	$\lambda_9 = \mu x_1^N m_2^N$	$-e_1 + e_3$
$\downarrow X_2^N \uparrow X_3^N$	$\lambda_{10} = \mu x_2^N m_2^N$	$-e_2 + e_3$
$\downarrow X_4^N \uparrow X_3^N$	$\lambda_{11} = \mu x_4^N m_2^N$	$e_3 - e_4$
$\downarrow X_5^N \uparrow X_3^N$	$\lambda_{12} = \mu x_5^N m_2^N + \beta^N (1 - c_2) x_3^N x_5^N$	$e_3 - e_5$
$\downarrow X_1^N \uparrow X_4^N$	$\lambda_{13} = \mu x_1^N m_{12}^N$	$-e_1 + e_4$
$\downarrow X_2^N \uparrow X_4^N$	$\lambda_{14} = \mu x_2^N m_{12}^N$	$-e_1 + e_4$
$\downarrow X_3^N \uparrow X_4^N$	$\lambda_{15} = \mu x_3^N m_{12}^N$	$-e_3 + e_4$
$\downarrow X_5^N \uparrow X_4^N$	$\lambda_{16} = \mu x_5^N m_{12}^N + \beta^N (1 - c_{12}) x_4^N x_5^N$	$e_4 - e_5$
$\downarrow X_1^N \uparrow X_5^N$	$\lambda_{17} = \mu x_1^N m_X^N + (\tau_1 + \tau_2 + \tau_3 + \gamma) x_1^N$	$-e_1 + e_5$
$\downarrow X_2^N \uparrow X_5^N$	$\lambda_{18} = \mu x_2^N m_X^N + (\tau_2 + \tau_3 + \gamma) x_2^N$	$-e_2 + e_5$
$\downarrow X_3^N \uparrow X_5^N$	$\lambda_{19} = \mu x_3^N m_X^N + (\tau_1 + \tau_3 + \gamma) x_3^N$	$-e_3 + e_5$
$\downarrow X_4^N \uparrow X_5^N$	$\lambda_{20} = \mu x_4^N m_X^N + (\tau_3 + \gamma) x_4^N$	$-e_4 + e_5$

25, 50, 100, 200, and 300 patients is given in Figure 3.2.

As with the Stochastic Base Model, 500 realizations for each of the following populations: 10, 25, 50, 100, 200, and 300 patients were averaged and compared to the deterministic model. The results are given in Table 3.7.

Table 3.7: Average Proportion of Population Colonized with Resistant Bacteria over 1 Year with varying Population sizes for the Stochastic Random Drug Model vs. Deterministic Random Drug Model

Random Drug Model Population	10	25	50	100	200	300	Deterministic
Proportion - Dual Resistance	.21	.28	.31	.33	.34	.34	.35
Proportion - Total Resistance	.30	.35	.37	.38	.39	.39	.39

Table 3.7 shows that the average proportion of patients colonized with the dual resistant strain will be approximately .21 when $N = 10$ compared to the

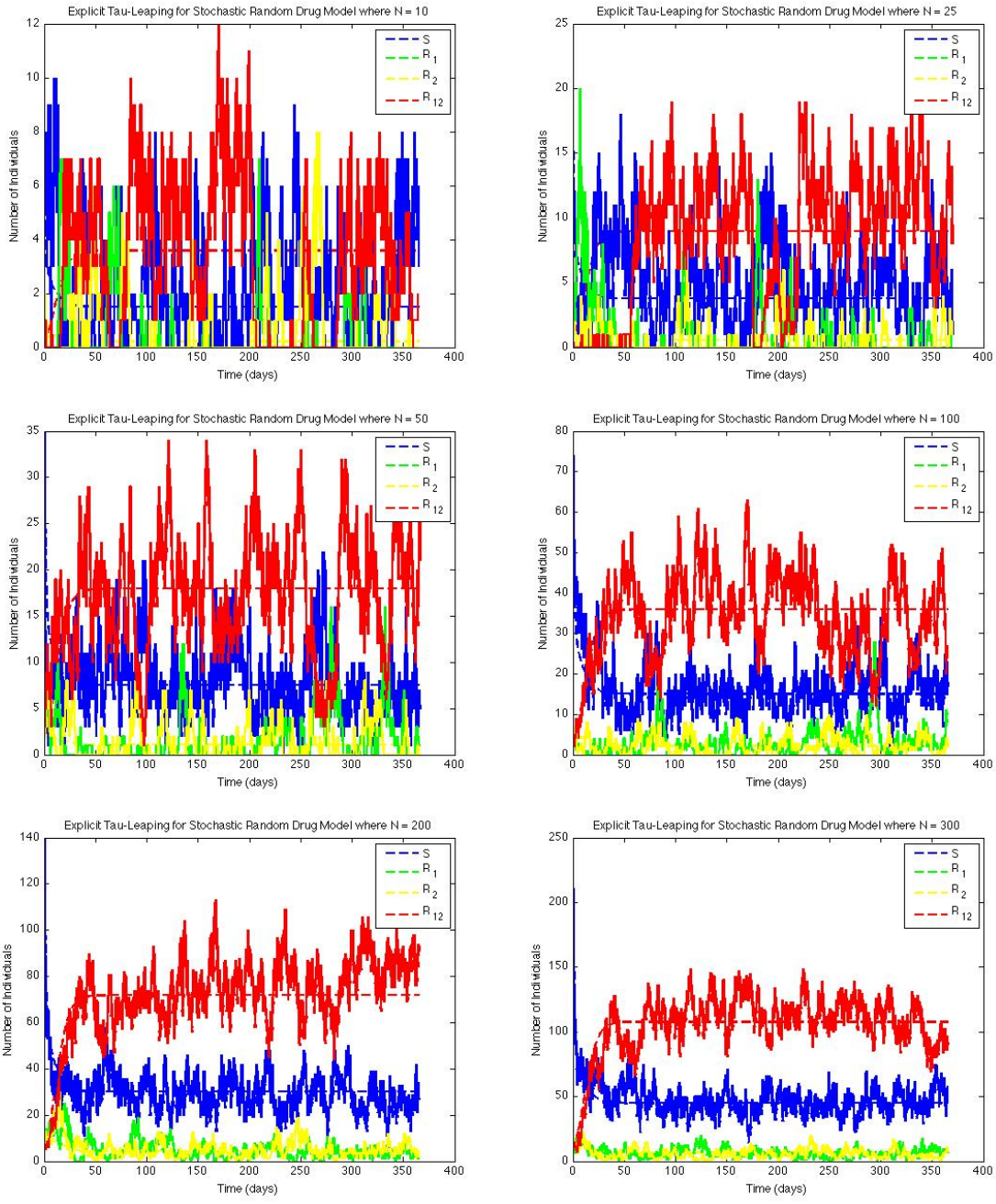

Figure 3.2: Results for Stochastic Random Drug Model where N = 10, 25, 50, 100, 200, 300 compared to the corresponding deterministic results (the straight lines)

estimated value of .35 given by the deterministic model. Hence, the deterministic model estimates that on average across one year approximately 35% of the hospital population will be colonized with bacteria resistant to both drugs. Therefore, the Deterministic Random Drug Model underestimates the impact of the new drug on the reduction of the overall resistant population for smaller populations. Introduction of the new drug appears to be quite effective for reducing the average proportion of the hospital who will be colonized with dual resistant bacteria across one year. Furthermore, in comparing Tables 3.5 and 3.7, on average the introduction of a new drug may reduce the total level of resistance by approximately 40-63% for small hospital units of less than 50.

3.3 Stochastic Targeted Drug Model

As with the Stochastic Random Drug Model, the transitions modified by the addition of the new antibiotic are λ_{17}, λ_{18}, λ_{19}, and λ_{20}, where τ_3. Table 3.9 shows the transitions for the Stochastic Targeted Drug Model.

As previously done in the Stochastic Base Model and the Random Drug Model, we calculate the appropriate values of g_i for the use in the explicit tau-leaping method. Focusing on transitions λ_{17}, λ_{18}, λ_{19}, and λ_{20}, if we choose

$$|\Delta x_1| < \frac{\epsilon}{5}x_1, \qquad |\Delta x_2| < \frac{\epsilon}{5}x_2, \qquad |\Delta x_3| < \frac{\epsilon}{5}x_3, \qquad |\Delta x_4| < \frac{\epsilon}{5}x_4, \qquad |\Delta x_5| < \frac{\epsilon}{3}x_5,$$

we can bound the relative change in each transition by ϵ:

$$\text{Reaction 17:} \qquad \frac{|\Delta\lambda_{17}|}{\lambda_{17}} \leq \frac{|\Delta x_1|}{x_1} + \frac{|\Delta x_1|}{x_1} + \frac{|\Delta x_1|}{x_1} + \frac{|\Delta x_4|}{x_4} < \epsilon$$

$$\text{Reaction 18:} \qquad \frac{|\Delta\lambda_{18}|}{\lambda_{18}} \leq \frac{|\Delta x_2|}{x_2} + \frac{|\Delta x_2|}{x_2} + \frac{|\Delta x_2|}{x_2} + \frac{|\Delta x_2|}{x_2} + \frac{|\Delta x_4|}{x_4} < \epsilon$$

$$\text{Reaction 19:} \qquad \frac{|\Delta\lambda_{19}|}{\lambda_{19}} \leq \frac{|\Delta x_3|}{x_3} + \frac{|\Delta x_3|}{x_3} + \frac{|\Delta x_3|}{x_3} + \frac{|\Delta x_3|}{x_3} + \frac{|\Delta x_4|}{x_4} < \epsilon$$

$$\text{Reaction 20:} \qquad \frac{|\Delta\lambda_{20}|}{\lambda_{20}} \leq \frac{|\Delta x_4|}{x_4} + \frac{|\Delta x_4|}{x_4} + \frac{|\Delta x_4|}{x_4} < \epsilon.$$

Table 3.8: Transition rates $\lambda_j(\mathbf{x}^N)$ as well as the corresponding state changes $\mathbf{v}_j$ for the Stochastic Targeted Drug Model, $j = 1, 2, \ldots, 5$.

Event	Transition Rate	$\mathbf{v}_j$
$\downarrow X_2^N \uparrow X_1^N$	$\lambda_1 = \mu x_2^N m_S^N$	$e_1 - e_2$
$\downarrow X_3^N \uparrow X_1^N$	$\lambda_2 = \mu x_3^N m_S^N$	$e_1 - e_3$
$\downarrow X_4^N \uparrow X_1^N$	$\lambda_3 = \mu x_4^N m_S^N$	$e_1 - e_4$
$\downarrow X_5^N \uparrow X_1^N$	$\lambda_4 = \mu x_5^N m_S^N + \beta^N x_1^N x_5^N$	$e_1 - e_5$
$\downarrow X_1^N \uparrow X_2^N$	$\lambda_5 = \mu x_1^N m_1^N$	$-e_1 + e_2$
$\downarrow X_3^N \uparrow X_2^N$	$\lambda_6 = \mu x_3^N m_1^N$	$e_2 - e_3$
$\downarrow X_4^N \uparrow X_2^N$	$\lambda_7 = \mu x_4^N m_1^N$	$e_2 - e_4$
$\downarrow X_5^N \uparrow X_2^N$	$\lambda_8 = \mu x_5^N m_1^N + \beta^N (1 - c_1) x_2^N x_5^N$	$e_2 - e_5$
$\downarrow X_1^N \uparrow X_3^N$	$\lambda_9 = \mu x_1^N m_2^N$	$-e_1 + e_3$
$\downarrow X_2^N \uparrow X_3^N$	$\lambda_{10} = \mu x_2^N m_2^N$	$-e_2 + e_3$
$\downarrow X_4^N \uparrow X_3^N$	$\lambda_{11} = \mu x_4^N m_2^N$	$e_3 - e_4$
$\downarrow X_5^N \uparrow X_3^N$	$\lambda_{12} = \mu x_5^N m_2^N + \beta^N (1 - c_2) x_3^N x_5^N$	$e_3 - e_5$
$\downarrow X_1^N \uparrow X_4^N$	$\lambda_{13} = \mu x_1^N m_{12}^N$	$-e_1 + e_4$
$\downarrow X_2^N \uparrow X_4^N$	$\lambda_{14} = \mu x_2^N m_{12}^N$	$-e_1 + e_4$
$\downarrow X_3^N \uparrow X_4^N$	$\lambda_{15} = \mu x_3^N m_{12}^N$	$-e_3 + e_4$
$\downarrow X_5^N \uparrow X_4^N$	$\lambda_{16} = \mu x_5^N m_{12}^N + \beta^N (1 - c_{12}) x_4^N x_5^N$	$e_4 - e_5$
$\downarrow X_1^N \uparrow X_5^N$	$\lambda_{17} = \mu x_1^N m_X^N + (T - \frac{p x_4^N}{N} + \gamma) x_1^N$	$-e_1 + e_5$
$\downarrow X_2^N \uparrow X_5^N$	$\lambda_{18} = \mu x_2^N m_X^N + (\frac{1}{2}(T - \frac{p x_4^N}{N}) + \gamma) x_2^N$	$-e_2 + e_5$
$\downarrow X_3^N \uparrow X_5^N$	$\lambda_{19} = \mu x_3^N m_X^N + (\frac{1}{2}(T - \frac{p x_4^N}{N}) + \gamma) x_3^N$	$-e_3 + e_5$
$\downarrow X_4^N \uparrow X_5^N$	$\lambda_{20} = \mu x_4^N m_X^N + (p + \gamma) x_4^N$	$-e_4 + e_5$

Therefore, we set $g_i = 5, i = 1, \ldots, 4$ and $g_5 = 3$. Figures 3.3, 3.4, and 3.5 illustrate one realization for $p = .15$, $p = .30$, and $p = .45$ respectively. Recall p is the total proportion of patients which can be identified as colonized with bacteria resistant to both drugs.

Table 3.9 summarizes the average results for $p = .30$. If we compare the deterministic model to the stochastic model with different population values, we can see that the deterministic model again under estimates the effect of the addition of the new antibiotic within a small unit of a hospital. Furthermore, comparison of Tables 3.5 and 3.9 indicate the new drug may effectively reduce the total proportion of patients resistant to some antibiotic on average by 44-62% over no treatment

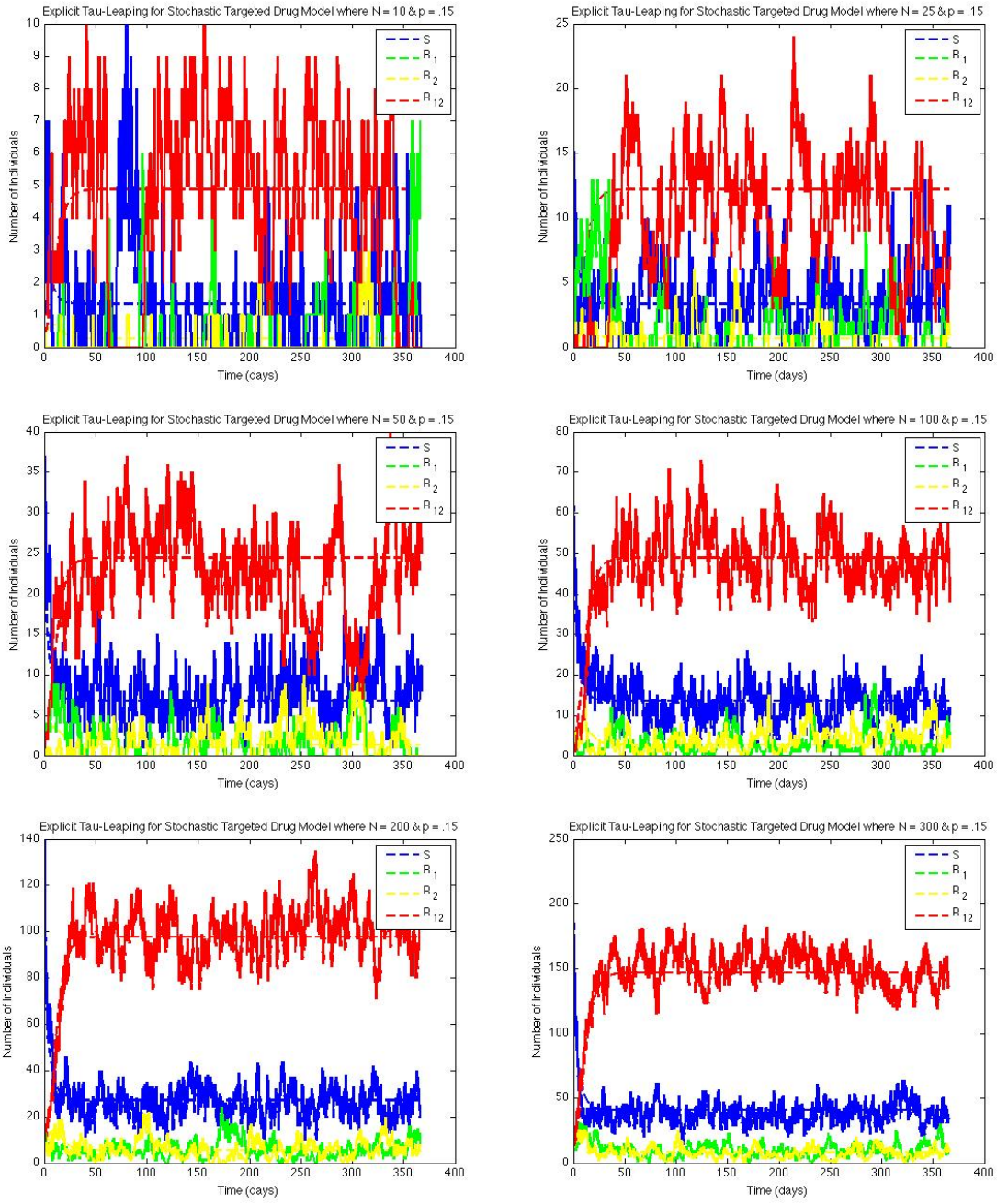

Figure 3.3: Results for Stochastic Targeted Drug Model where N = 10, 25, 50, 100, 200, 300 with p = .15 compared to the corresponding deterministic results (the straight lines)

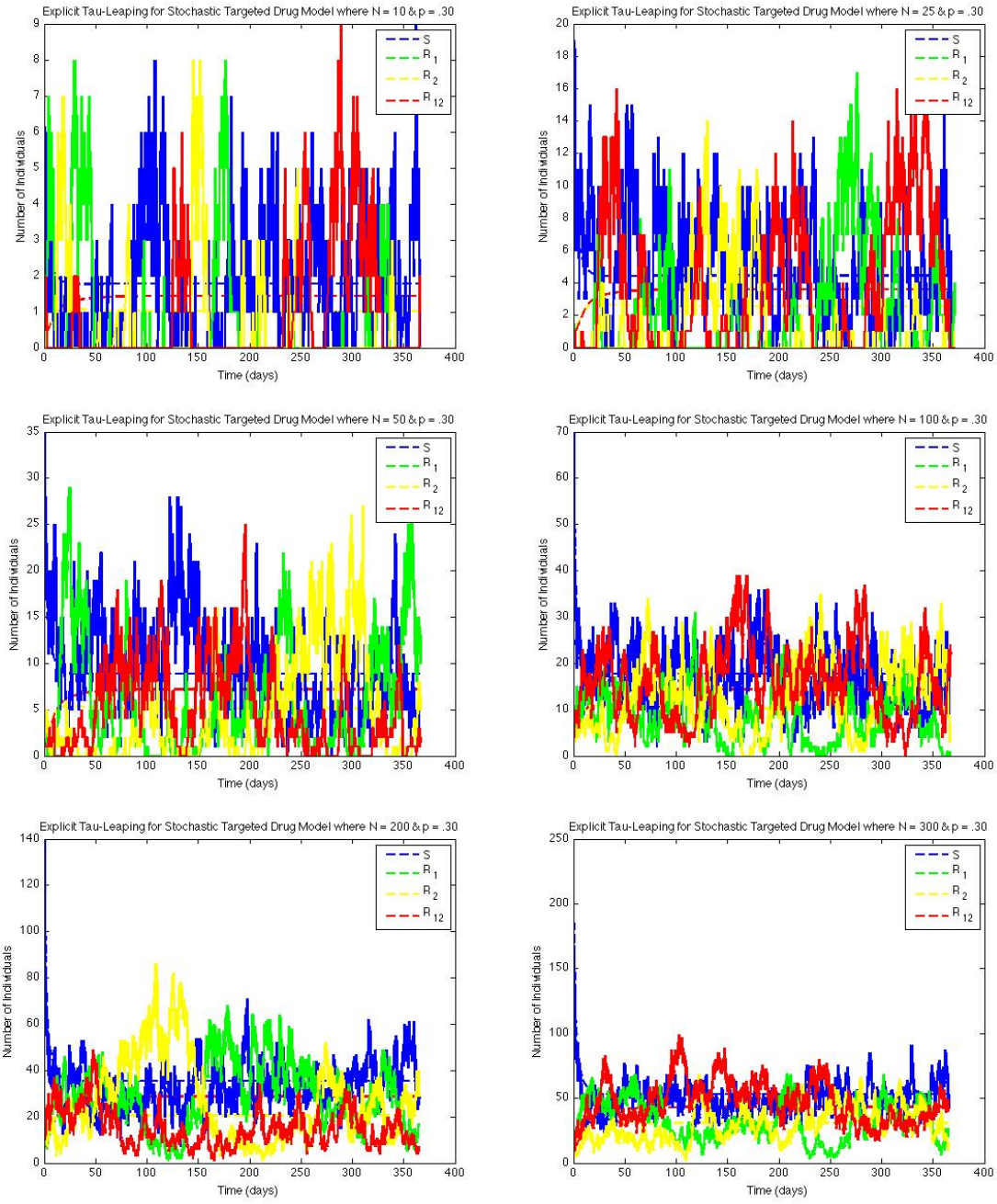

Figure 3.4: Results for Stochastic Targeted Drug Model where N = 10, 25, 50, 100, 200, 300 with p = .30 compared to the corresponding deterministic results (the straight lines)

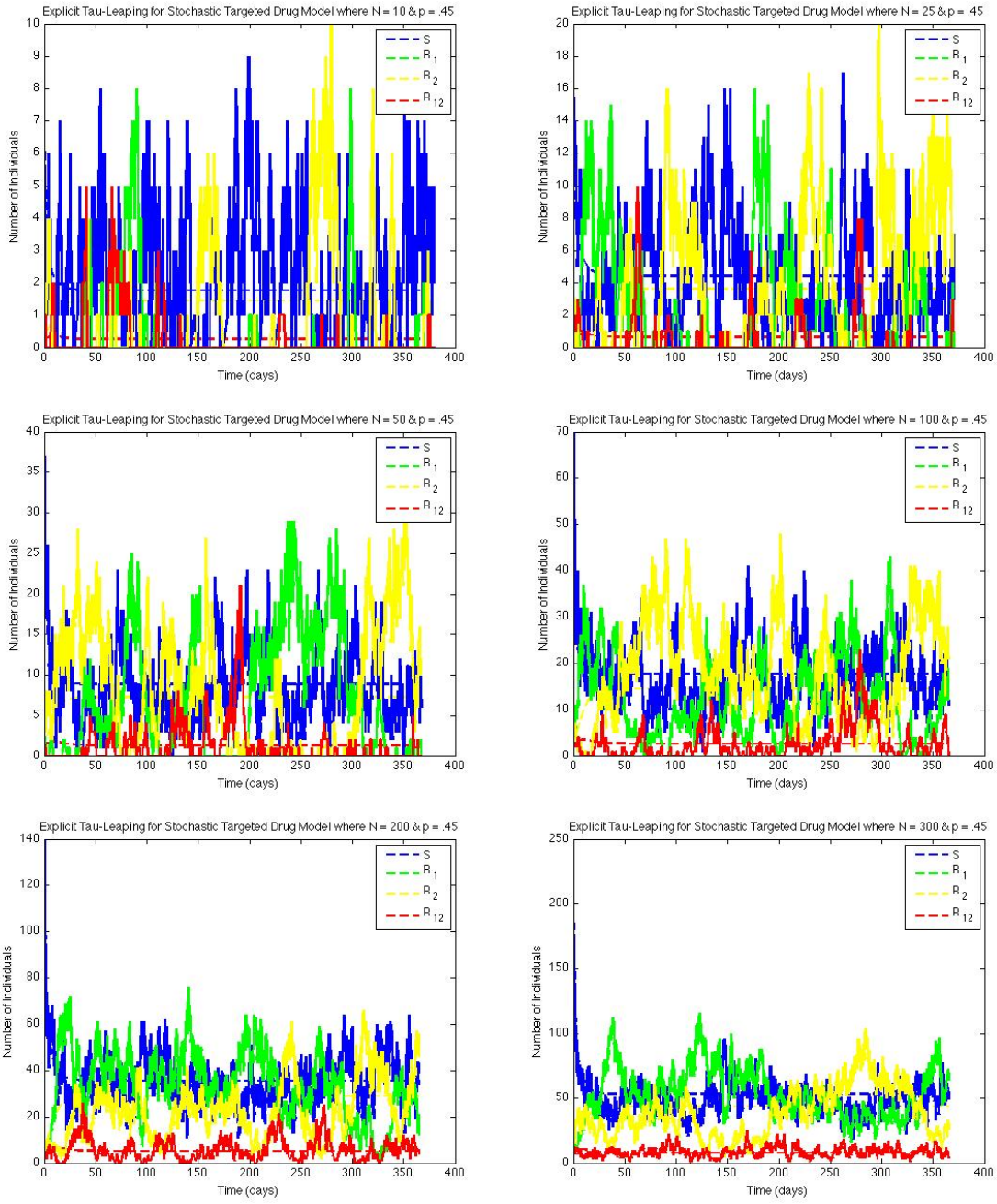

Figure 3.5: Results for Stochastic Targeted Drug Model where N = 10, 25, 50, 100, 200, 300 with p = .45 compared to the corresponding deterministic results (the straight lines)

when 30% of those dual resistant patients can be identified.

Table 3.9: Average Proportion of Population Colonized with Resistant Bacteria over 1 Year with varying Population sizes for the Stochastic Targeted Drug Model vs. Deterministic Targeted Drug Model

Targeted Drug Model Population	10	25	50	100	200	300	Deterministic
Proportion - Dual Resistance	.10	.12	.12	.13	.14	.14	.14
Proportion - Total Resistance	.31	.34	.33	.34	.35	.35	.34

3.4 Comparison Between Stochastic Random Drug Model and Stochastic Targeted Drug Model

If we want to compare the Stochastic Random Drug Model (SRDM) and the Stochastic Targeted Drug Model (STDM), we see that for a small value of N, there is a very small difference on the effect of the resistant population under different administration protocols. Table 3.10 summarizes the average proportion of the population colonized with a resistant strain in small population units when varying the prescription administration protocol. When the population size is small, for example, in an ICU where $N = 10$, giving the three drugs at the same rate but randomly to patients, might even do a slightly better job of lowering the total resistance than when we target only the dual resistant population. This does not hold for larger populations in our model where using a targeted approach seems to help more in the overall reduction of resistance.

Table 3.10: Total Resistance of Stochastic Models for Small Populations

Model	$N = 10$	$N = 25$
SRDM Proportion	.30	.35
STDM Proportion	.31	.34

CHAPTER 4

INVERSE PROBLEM

In Chapters 2 and 3, we developed both deterministic and stochastic models to describe the spread of bacteria within a hospital. Given specified parameter values for the deterministic and stochastic models, we illustrated the potential trajectory for the state variables across time. The process of solving for state variables given parameter values is known as the "forward problem". However, these parameter values were estimates based on literature or a "rule-of-thumb" approach. In order to more accurately describe the spread of bacteria within a given hospital and to assure accuracy of the model, it is necessary to assign parameter values dependent on data measured within a hospital. Determining the parameter values given data for the state variables is know as the "inverse problem". Banks, et. al. [4] say "[that] [f]inding the solutions to an inverse problem is, in general, nontrivial because of non-uniqueness difficulties that arise. This undesirable feature is often due to noisy data and insufficient number of observations."

In this section, we only set up the inverse problem for solving for a select number of parameters, which we call $\vec{q}$, for the Base Model. The inverse problem can be described by the following.

Given data, ${y_i}^d$, we seek to estimate

$$\vec{q} = [q_1, q_2, \ldots, q_n]$$

such that

$$J(\vec{q}) = \sum_{i=1}^{N_t} |y_m(t_i; \vec{q}) - {y_i}^d|^2$$

is minimized where $y_m(t_i; \vec{q})$ is the solution to the Base Model at time t_i for $i = 1, 2, \ldots, N_t$, given the parameter $\vec{q}$ and ${y_i}^d$ is data collected at time t_i. Actual data is

not readily available; therefore, we determine the likelihood of obtaining accurate parameter estimates by using simulated data. We simulate data by first running simulations to the Base Model discussed in Section 2.1 using a given set of parameters. We then add noise to the solution using the equation:

$$\hat{y_i^d} = y_m(t_i, \vec{q}) + nl \cdot rand_i$$

where nl represents a given noise level and $rand_i$ is normally distributed random numbers with zero mean and variance 1.0 [4]. Figure 4.1 shows the simulated noisy data at a noise level of 1%.

Using the exact parameters and initial guesses given in Table 4.1, we try to estimate only the parameters

$$\vec{q} = [\beta, m_S, m_1, m_2]$$

at a 1% noise level initially to obtain a baseline for variability in the parameters estimates given relatively "good" data. These parameters were chosen based on the sensitivity analysis found in Joyner et. al. [13]. In an actual hospital setting, we assume we may only have a limited amount of data on the type of bacteria present at a given time. For example, if a hospital had collected data on the whole population and fairly accurately knew the proportion colonized with each type of bacteria, i.e., S, R_1, R_2, and R_{12} then we might obtain a different estimate for parameter values that if we only had data on the proportion of the population colonized with just dual resistance for instance. Therefore, we analyzed the possible outcomes for $\vec{q}$ given only specified data and calculated the relative error for each estimate. The results are given in Table 4.2. Notice that in many instances the relative error is extremely large. These results indicate that it is necessary to search for other techniques and/or algorithms to obtain better estimates for parameter values. Further analysis is beyond the scope of this thesis.

Table 4.1: Exact Parameter Values for the Base Model Inverse Problem

Parameters	Exact Values	Initial Guesses
β	1	1.05
m_S	0.7	0.735
m_1	0.06	0.063
m_2	0.05	0.0525

Table 4.2: Inverse Problem - Approximate q-values & Percent Relative Error

Type	$\vec{q} = [\beta, m_S, m_1, m_2]$	% Relative Error
S, R_1, R_2, R_{12}	q=[1.0006, 0.7004, 0.0603, 0.0492]	r=[0.06, 0.06, 0.47, 1.69]
R_1, R_2, R_{12}	q=[0.9583, 0.6510, 0.0602, 0.0491]	r=[4.17, 6.10, 0.27, 1.83]
R_1, R_2	q=[1.8151, 1.5172, 0.0621, 0.0506]	r=[81.51, 116.74, 3.46, 1.28]
R_{12}	q=[0.8005, 0.4805, -.1380, 0.2172]	r=[19.95, 31.35, 330.08, 334.48]
R_1	q=[2.4463, 1.4980, 0.0618, 0.1110]	r=[144.63, 114.00, 3.02, 121.96]
R_2	q=[3.8465, 1.2619, 0.3355, 0.0512]	r=[284.65, 80.27, 459.17, 2.41]
$R_1 + R_2$	q=[1.7711, 1.5040, 0.1372, -0.0244]	r=[77.11, 114.86, 128.61, 148.76]
$R_1 + R_2 + R_{12}$	q=[0.8315, 0.4627, 0.0628, 0.0229]	r=[16.85, 33.90, 4.70, 54.27]

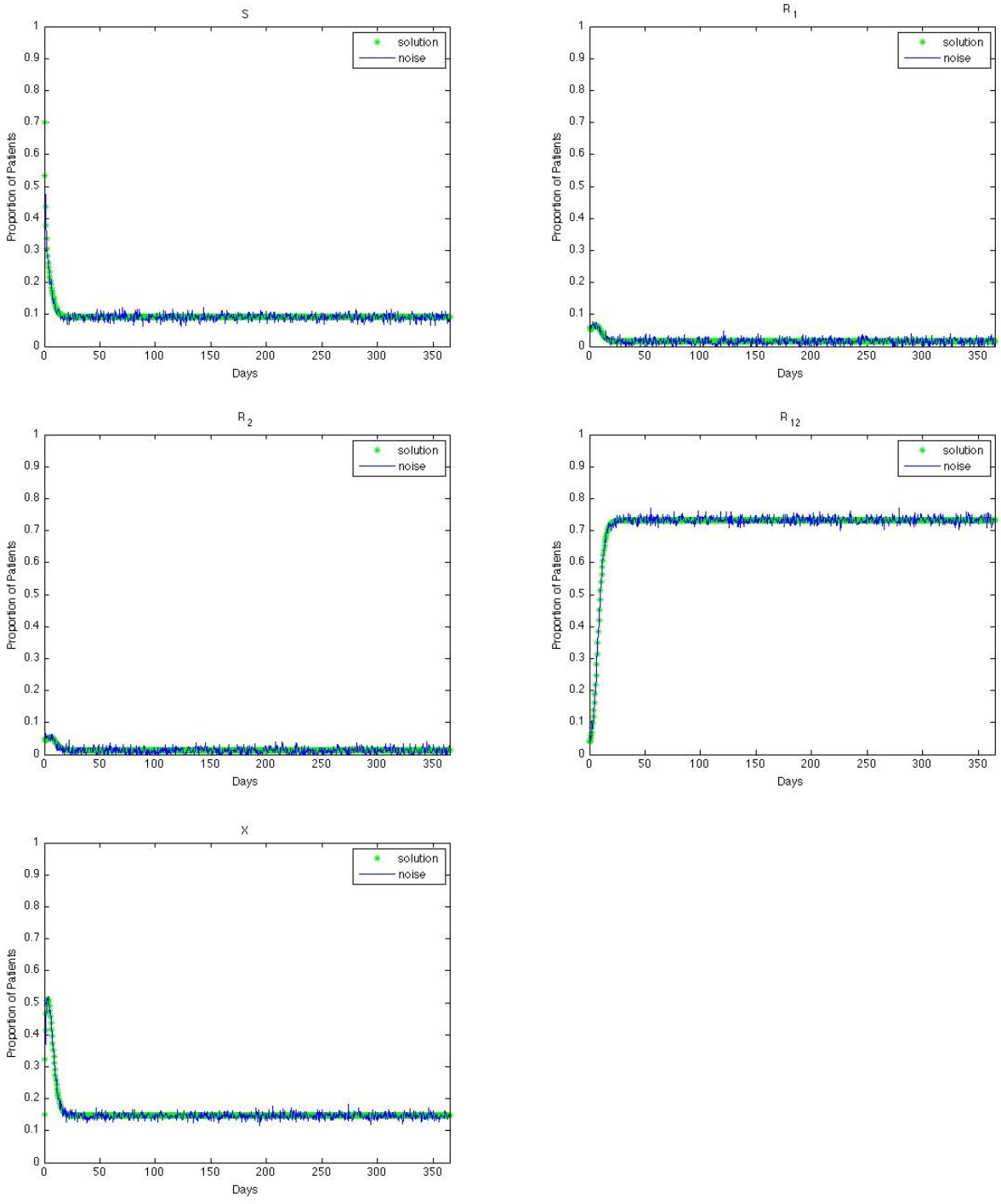

Figure 4.1: Simulated Data for Each State Variable for the Base Model at a 1% Noise Level

CHAPTER 5

CONCLUSION

In this thesis we sought to understand how adding a new antibiotic to the regimen affected antibiotic resistance. We began by adapting a deterministic model from Chow, [9], to create a model of a hospital containing two groups of patients colonized with bacteria resistant to a single antibiotic and one group colonized with bacteria resistant to both antibiotics. This model, the Base Model, was used for comparison purposes. With no treatment protocols, approximately 70% of the patients within the hospital were colonized with bacteria resistant to some drug.

To incorporate the third drug, we constructed the Random Drug and Targeted Drug Models. In the Random Drug Model, the probability of using any of the three drugs was equal. Using this treatment protocol, the total resistance in the hospital was reduced to 35% of the patients within the hospital colonized with some type of resistance. The last deterministic model, the Targeted Drug Model, only allowed treatment with the new drug on a proportion of the dual resistant patients. We ran the model with three different proportions and results indicated that if one could accurately identify and treat 30% of the dual resistant patients, the total resistance drops to 32% of the patients within the hospital having some type of resistance.

Next, we developed corresponding stochastic models to more accurately model the effects of treatment on small population sizes, such as units within a hospital. We used continuous-time Markov Chains and the explicit tau-leaping method to determine the average effect of the new drug for 500 realizations across one year. We concluded that the deterministic models greatly underestimated the positive effects of the new drug in reducing the overall proportion of patients colonized with

resistant bacteria in small units. Furthermore, for small units there does not appear to be a significant benefit of using one administration protocol over another.

Lastly, we gave some background and set up the inverse problem for the Base Model. The results indicated additional techniques were needed to accurately determine the parameters given a data set. This is considered future work.

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