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Slowing the Evolution and Outbreak of Antibiotic Resistance

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Abstract

Antibiotic resistance is a problem of significant and growing international concern, in part due to the rapid evolution of new resistances. One potentially important factor in the emergence of resistance is concentrated antibiotic use in environments such as hospitals. Such high use creates a strong selective pressure for pathogens to evolve resistance. We analyze some strategies hospitals can use to slow the evolution of resistance, and estimate the length of the delay between evolution and outbreak of resistance.

Acknowledgments

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Chapter 1

Introduction

Resistance to antibiotics is a growing international crisis. In the century since their discovery, antibiotics have become a keystone of modern medical treatments and have enabled extremely successful control and treatment for diseases such as tuberculosis. Through a combination of sluggish pharmaceutical research and fast evolution, antibiotic-resistant bacteria (ARB) now threaten this progress.

In the mid-20th century, a renaissance of antibiotic research fueled the discovery of over 20 new classes of antibiotics, each using a different chemical core to fight bacterial infections. Since then decreasing incentives have slowed this pipeline, closed academic research groups, and pulled away industry focus. New analogue drugs are still being developed, but there is a limit to the number of analogues that can be produced from a single core. Thus, although analogues are helpful, new classes of antibiotics must be discovered to achieve the rates of antibiotic development we will need to support modern medicine in the coming decades (Coates et al., 2011).

As the development of novel classes of antibiotics becomes more rare, ARB have become a larger and larger problem. Multiply drug-resistant strains such as methicillin-resistant Staphylococcus aureus, or MRSA, are dangerous and difficult to treat (Crowcroft and Catchpole, 2002), and Gram-negative bacteria may pose an even greater threat (Kumarasamy et al., 2010). To fight these strains, it is critical that we restart the antibiotic-research engine of the 1940-60s by providing greater government incentives, but it is equally critical that we develop effective policies to fight antibiotic resistance and lengthen the lifetime during which current and future drugs remain effective.

This thesis deals with the latter question: what are the best strategies for

slowing the spread and emergence of antibiotic resistance, short of developing new drugs? We approach this problem from a modeling perspective, in the hopes that theoretical insights will be able to inform the creation of more effective real-world policies. In the following sections we will first define our system, then give a brief overview of the types of anti-ARB strategies others have modeled in the past.

1.1 Our System: Hospitals

There are many important battlegrounds in the fight against antibiotic resistance, including outpatient (Goossens et al., 2005) and livestock use (Mathew et al., 2007). However, perhaps the most frequently modeled battleground is hospitals and other medical-care facilities (MCFs). These facilities have several properties that make them an important reservoir for antibiotic-resistance. These are:

- High vulnerability of patients. Patients in MCFs often have compromised immune systems, or surgical wounds that are susceptible to bacterial colonization. With many vulnerable patients in one place, bacterial infections are bound to spread rapidly unless actively suppressed.

- High volume of antibiotic use. Roughly half of all patients checked into acute care hospitals receive antibiotics. Of this use roughly 75% is to treat infections[1] while the remainder is used for prophylactic (preventative) care) (Magill et al., 2014). Such heavy use creates an environment which strongly selects for ARB.

- High turnover of patients. With the exception of specialized long-term care facilities, most MCFs treat patients only for relatively short periods of time (on the order of a week or two) (Cooper et al., 1999; Cosgrove et al., 2005). Once they are well enough, they are released back into the community, or perhaps to one of the aforementioned long-term care facilities. By allowing such patients to potentially become colonized by ARB and then leave the facility, hospitals have the potential to act as a source population and fuel ARB in the community. For example, MRSA patients often carry MRSA for months after they are released

[1] Hospital-acquired (or *nosocomial*) bacterial infections are incredibly common and account for over 90,000 deaths per year in the US alone (D'Agata et al., 2007).

from a hospital (Scanvic et al., 2001). On the other hand, if hospitals treat ARB very effectively, they also have the potential to act as a powerful sink population, almost like an ARB filter, which quickly and efficiently treats patients before releasing them back to the community free of ARB.

With these properties, fighting antibiotic-resistance in MCF settings will be especially important in the coming years.

In addition, fighting antibiotic-resistance in MCFs poses several advantages over other contexts such as outpatient and livestock use. Hospitals are organized institutions whose express purpose is to save lives and keep people healthy. In this, they provide a unique opportunity to implement large-scale, coordinated strategies. Such strategies could prove difficult to implement for outpatients, who must follow pre-defined treatment plans (and often deviate from these prescribed regimens (Kardas et al., 2005)). Similarly, it could be difficult to convince the agriculture industry to implement such strategies without clear short-term incentives. Thus unlike other contexts, hospitals have both the organizational structure and motivation to implement strategies to fight antibiotic-resistance.

In the following two sections we will describe some of the major strategies hospitals can use to fight ARB. These strategies can be grouped into two rough categories: those which focus on antibiotics themselves and the patterns with which they are used in a hospital, and those which come at the problem from a more general epidemiological perspective and focus on reducing transmission of ARB within a hospital.

1.2 Antibiotic-Use Strategies

Antibiotic-use strategies seek to minimize prevalence of antibiotic-resistance by optimally partitioning the use of several different antibiotics. Most research (Bergstrom et al., 2004; Lipsitch et al., 2000; Peña Miller and Beardmore, 2010; Chow et al., 2011) that has been done on this problem has looked at the simplifying case that a hospital has access to an infinite supply of exactly two antibiotics (antibiotic A and antibiotic B) that use different antibiotic mechanisms but are otherwise equivalent. Under this scenario a particular disease may have a susceptible strain (the S-strain), an A-resistant strain (the A-strain), a B-resistant strain (the B-strain), and a strain resistant

to both A and B (the AB-strain)[2]. Antibiotic-use strategies then seek to prescribe antibiotics A and B to patients in a hospital so as to optimize some quantity: for example, the average number of infected patients, the average number infected by a resistant strain, or the probability that the AB-strain evolves (assuming it was not previously present) from the A- and B-strains in some given time interval.

This last possibility raises an interesting assumption that is often made (Bergstrom et al., 2004; Lipsitch et al., 2000; Peña Miller and Beardmore, 2010): that the AB-strain has not yet arisen. This seems somewhat counterintuitive; multiply-resistant strains are a big concern and it is important that we learn how to deal with them. However, in the context of antibiotic-use strategies, it is often unhelpful to talk about a strain which is resistant to *all* the antibiotics allowed in your system. Such a "superbug" strain is not treatable using antibiotics. Instead, other strategies — such as isolation units — must be implemented to prevent their spread. Thus in the context of a two-antibiotic system it is not useful to talk about doubly-resistant strains; in the context of a three-antibiotic system (which we construct and analyze in Chapter 3) it is useful to talk about doubly-resistant strains but not triply-resistant strains; and so on.

In addition to the assumption that only two antibiotics exist, and the assumption that the AB-strain has not yet evolved, it is often assumed (Bergstrom et al., 2004; Lipsitch et al., 2000; Peña Miller and Beardmore, 2010; Chow et al., 2011) that resistance incurs a fitness cost. That is, in the absence of antibiotics the susceptible strain is assumed to be more fit than either the A- or B-strains, while in the presence of only one antibiotic, the singly-resistant strain is assumed to be more fit than the multiply-resistant strain. This assumption is complicated by the evolution of "compensatory" traits in ARB, or traits that reduce this fitness cost while maintaining resistance. In the absence of antibiotic use, such compensatory traits have been observed to dramatically reduce fitness costs in some ARB (Schrag and Perrot, 1996). In addition, these traits tend to evolve more rapidly than reversion to antibiotic-susceptibility, thus preventing susceptibility from replacing resistance even if antibiotic-use ceases entirely (Levin et al., 2000). Though flawed, the assumption of fitness costs is quite common. Thankfully, fitness costs are often modeled using parameters that can be set to zero to approximate the case of compensatory mutation.

[2] Bergstrom et al. and Peña Miller and Beardmore consider only the S- ,A-, and B-strains, Lipsitch et al. considers only the S- and A-strains, and Chow et al. considers all four.

Intuitively, antibiotic-use strategies can be thought of as representing attempts to vary the selective environment in the hospital (Bergstrom et al., 2004). If the environment were constant then ARB would very quickly adapt to that environment. For example, if every patient was given antibiotic A for all time then the A- and AB-strains would have a clear evolutionary advantage over the S- and B-strains. Thus these two strains would reach very high levels in the hospital very quickly, and soon most treatments would prove ineffective. In this case, ARB can be thought of as having evolved to the selective environment of the hospital. However by varying use of antibiotics A and B, the selective environment will vary, so that no one strain has a clear advantage. Hopefully, in this scenario, ARB will be unable to evolve, or at least be unable to evolve quickly, so that treatments will remain effective for as long as possible.

The most commonly modeled antibiotic-use strategies are cycling and mixing. These can be thought of respectively as attempts to vary the evolutionary environment in time and in space. Under cycling, the entire population of a hospital is assumed to take the same antibiotic simultaneously, while at some regular intervals the antibiotic-of-choice changes. For example, a hospital might choose to use antibiotic A for a week, then antibiotic B for two weeks, then repeat this cycle over and over. This represents pure temporal variation, because at any given time the hospitals is completely spatially homogeneous; everyone is taking the same drug. Under mixing, patients are randomly assigned antibiotic A with some probability p and are assigned antibiotic B with probability $1 - p$. These probabilities are assumed not to change with time. Thus mixing represents pure spatial variation, with absolutely no change in the strategy over time. Of the two, mixing more closely approximates current practices in hospitals (Bergstrom et al., 2004)

These two strategies have been modeled numerous times and have even seen some clinical studies (zur Wiesch et al., 2014) but for both practical[3] and theoretical[4] reasons it has proven quite difficult to provide a compelling case for hospitals to use one or the other.

The only other antibiotic-use strategy that is commonly modeled is combination therapy. In this strategy some or all patients receive multiple antibiotics simultaneously. This does not introduce variation into the

[3]Clinical trials tend to use historical controls, making it "difficult to distinguish the effects of cycling from the general effect of having a well-publicized, specific antimicrobial policy" (Bergstrom et al., 2004).

[4]Under some models, it is possible to show that there must always be mixing strategies that outperform cycling strategies and vice versa (Peña Miller and Beardmore, 2010).

selective environment, but is extremely advantageous for whichever patient receives this therapy, since any strain not simultaneously resistant to all antibiotics in use will be effectively treated. It may however, very strongly select for multiple resistance (for example if bacterial evolution is stress-induced (Obolski and Hadany, 2012)) and this danger may outweigh the benefits in some scenarios. Combination therapy is not considered in any of our models.

1.2.1 Volume of Antibiotic Use

A related problem is that of *volume* of antibiotic use. It is perhaps evident that all else being equal a higher volume of antibiotic use should select more strongly for resistance. Major questions surrounding volume of use include:

- Evolution: How does the volume of antibiotic use impact the rate of evolution of ARB?
- Outbreak: Once ARB have evolved, how does the volume of use impact the time scale over which ARB frequency increases?
- Optimality: What is the optimal volume of antibiotic use, taking into account rates of evolution and outbreak?

Questions like these can and have been tackled using mathematics, though surprisingly infrequently (Austin et al., 1999b).

Of particular interest when considering the volume of antibiotic use — and to a lesser extent antibiotic-use strategies — are the ethical questions they raise. Doctors must face a balancing act between treating current patients with aggressive, often prophylactic, courses of antibiotics or preserving the efficacy of antibiotics for future generations. Mathematics can be used as a tool to aid in these dilemmas, though it should not be the sole consideration. For example, modeling allows us to quantifying the problem of optimality. One can attempt to minimize the number of bacterial-infection related deaths over some period of time (say, the next 100 years). If the optimum volume of antibiotic use is found to be significantly lower than current levels, however, doctors could face the morally gray prospect of treating current patients less effectively in the hopes of treating future patients more effectively. Likewise if the optimum use is found to be very high, doctors face the psychologically easier but still morally gray decision of sacrificing antibiotic efficacy for future generations. The choice will never be easy, and given the simplifications found in any mathematical model, many theoretical results must be taken

with a grain of salt. Nevertheless modeling will be vital in our societal attempt to achieve sustainable antibiotic use.

1.3 Transmission-Reduction Strategies

Antibiotic-use strategies are quite specific to the problem of antibiotic-resistance. However there are many strategies for fighting ARB which draw on more general epidemiological ideas. In particular, a major focus of epidemiological modeling is $\mathcal{R}_0$, the basic reproductive number, which measures the average number of secondary infections resulting from a single "patient-zero." By reducing $\mathcal{R}_0$ below 1, any outbreak of a disease will inevitably dwindle and die, because it is not able to sustain itself by infecting new patients. Following this mindset, many strategies for fighting antibiotic-resistance involve trying to reduce the rate of transmission of resistant infections.

It is worth noting that most of these strategies can more accurately be described as strategies for fighting hospital-acquired infections. They do not take into account the actual *resistance* properties of ARB. Instead they try to limit the spread of bacteria through an MCF, just as they would any other infectious disease. As multiply-resistant strains become more common, these general strategies will become more important. The more resistant an infection is, the greater the likelihood initial treatment will be ineffective and the more aggressive ultimate antibiotic therapy must be. Thus it is critical to develop strategies for coping with ARB in the absence of effective treatment. Many such strategies (Beggs et al., 2006; Austin et al., 1999a) have been analyzed, particularly in the context of MRSA (Cooper et al., 2004, 1999).

The classic example of a transmission-reduction strategy is hand-washing. Most patient-to-patient contacts in a hospital setting are thought to be mediated by healthcare workers (HCWs). For example, if a nurse dresses patient 1's wound and then changes the sheets on patient 2's bed, they could transmit MRSA from patient 1 to patient 2. By washing hands thoroughly in between every patient-to-HCW contact, the rate of patient-to-patient transmission can be dramatically reduced. Models confirm that this should in theory be a remarkably effective strategy (Beggs et al., 2006; Austin et al., 1999a), however compliance with hospital hand-washing policies is notoriously bad (Larson and Kretzer, 1995) and this reduces the efficacy of this strategy. Thus, other transmission-reduction strategies are needed.

Another common transmission-reduction strategy is cohorting. Under

cohorting, the patients in a hospital are partitioned into smaller groups, and HCWs are assigned to one particular group. Interaction of HCWs with patients or workers in other groups is then discouraged or forbidden. In essence this reduces the pool of susceptible individuals any particular infected individual is capable of infecting. Analysis has found cohorting to be extremely effective in theory, particularly in combination with diligent hand-washing (Beggs et al., 2006).

Finally, it is possible to designate one particular cohort as an isolation unit. Whenever a patient is found to have been infected by ARB, or is suspected to have been infected, they are sent to the isolation unit. This effectively reduces the pool of susceptible individuals to zero as soon as a patient is moved. This strategy is vulnerable to stochastic fluctuations; it is costly to maintain a large isolation ward, but if the ward is too small it is likely to be overwhelmed by random spikes in admission of patients with resistant infections. This can result in a much larger outbreak if ARB is allowed to spread to the general hospital population. However, this can be solved by allowing inter-hospital transfers, so that nearby hospitals can lend their isolation unit space to smooth out stochastic fluctuations. Isolation units also have the fortunate property that after their introduction, they are capable of eradicating an endemic antibiotic-resistant strain, though they do so only very slowly. It is worth noting that this strategy sees wide use in Denmark and The Netherlands where it has proven extremely effective in keeping MRSA levels low, despite high levels in countries like the UK and the US (Cooper et al., 2004).

1.4 Outline

The primary antibiotic use and transmission reduction strategies can be found in Table 1.1. In addition to these strategies, volume of antibiotic use must also be considered (i.e. can it be decreased?). All of these strategies have been mathematically modeled, some of them extensively. In the following chapters we will focus primarily on antibiotic-use strategies and volume of antibiotic use.

Chapter 2 contains in-depth discussions of past modeling of antibiotic-use strategies. Common model structures and assumptions are covered in detail, along with the limitations of these models, and some important results.

Chapters 3 and 4 contain the extensions we have made to past work. In

Antibiotic Use	Transmission Reduction
Cycling	Hand-Washing
Mixing	Cohorting
Combination	Isolation Units

Table 1.1 Popular strategies used to fight ARB in hospitals.

Chapter 3 we focus on mixing and cycling. We discuss the two-antibiotic system modeled in (Chow et al., 2011) and present an ecological interpretation for their result that cycling exhibits superior control over multiply-resistant strains. We then analyze a three-antibiotic system and compare the results from this system with those from (Chow et al., 2011) and (Bergstrom et al., 2004). A primary focus of this analysis is on reducing the rate of evolution of antibiotic resistance. In Chapter 4 we shift focus and analyze the problem of community-wide ARB outbreaks. To do so we extend Bergstrom et al.'s model by coupling a hospital to its surrounding community. In order to obtain analytical results, we also simplify the system down to a single antibiotic. In our model only volume of antibiotic use can be considered, but extensions to this work could examine cycling and mixing.

Finally in Chapter 5 we suggest possible extensions to our work. Among other things, we discuss the need to confirm our ideas in Chapter 3 with systematic simulations; the need to relax certain assumptions used in Chapter 4; and the need for more in-depth explorations of the stochastic behaviors of both systems.

Code and Figures

The code used for this thesis can be found at http://math.hmc.edu/~cokasaki/thesis. Individual files are provided capable of generating every figure and of reproducing most calculations whose derivations are not included in the body of this thesis. Stochastic figures and calculations may only be reproduced qualitatively due to random number generation. We also provide image files for all of our figures. The less well-documented original code is also provided in a subfolder.

Chapter 2

Background

As discussed in Chapter 1 many models of ARB dynamics study antibiotic-use strategies. Antibiotic-use models attempt to understand the optimal way to set the volume of use of one or several antibiotics. These are the primary models we build off of in Chapters 3 and 4. In this chapter we give an introduction to the mathematical structure of these models.

2.1 Deterministic Antibiotic-Use Models

Most antibiotic-use papers use compartmental deterministic ordinary differential equation (ODE) models to account for transmission dynamics in a hospital. The most popular is the model proposed by (Bergstrom et al., 2004). This model considers a single bacterial contagion and its interactions with two antibiotics (A and B) in a hospital setting. It assumes there are three strains of this bacteria: susceptible, resistant to A, and resistant to B. As discussed in Chapter 1, it also assumes that multiple-resistance has not yet arisen, or is at such low levels in the general community that it has not yet spread to this hospital. The model then tracks the proportion of patients occupying each of four compartments: uncolonized (X), colonized by the susceptible strain (S), colonized by the A-resistant strain (R_1), and colonized by the B-resistant strain (R_2).

A diagram depicting the relationships between these compartments can be found in Figure 2.1. The allowed interactions between patients are:

- Infection. A patient in S, R_1, or R_2 may infect a patient in X. Thus patients in X move to one of the other three categories at a rate proportional to both the number of patients in X and the number

of patients in the destination compartment. The rate constant β is assumed to be the same for all three strains (that is, resistance neither inhibits nor enhances contagiousness).

- Clearance. A patient in S, R_1, or R_2 may receive successful antibiotic treatment, or their immune system may successfully defeat their infection. In either case they move into compartment X. The rate of natural immune clearance is γ for all three strains. Antibiotic A is used at rate τ_1, and antibiotic B is used at rate τ_2. These rates are assumed to be independent of infection class. In reality this is not the case: a patient with a symptomatic A-resistant infection will eventually be treated with antibiotic B or vice versa[1]. However, many infections are asymptomatic, and hospitalized patients often receive prophylactic care before their infections become symptomatic. Thus to first order antibiotic use may realistically be independent of infection class.

- Admission/Discharge. A patient may be admitted into any category from the outside community, and may be discharged from any category. Since the hospital is assumed to have a constant population, total admission rate equals total discharge rate (μ) at any given time. Thus the average length of stay is $1/\mu$. This parameter is assumed to be the same for all patients regardless of infection status. Again, this is not true in reality: patients who contract hospital-acquired infections will likely stay in the hospital for a longer period of time. Nevertheless, since many infections are asymptomatic, discharge rates are still assumed to be independent of infection class.

- Superinfection. A patient already infected by one strain may have their infection replaced by another. Thus patients may move between S, R_1, and R_2. This occurs at rates proportional to population sizes, and scaled by β (the rate of contagion), σ the fractional rate at which supercolonization is successful (as compared to normal infection), and modified by c_1 and c_2 the fitness cost of resistance.

The interactions between these compartments can then be modeled with the

[1] Antibiotic-use strategies that take this into account are called *adjustable* in (zur Wiesch et al., 2014). These are much closer to reality, and further research into adjustable cycling/mixing is needed.

following system of equations:

$$\begin{aligned} S' &= (m - S)\mu + \beta SX + \sigma\beta S(c_1R_1 + c_2R_2) - S(\gamma + \tau_1 + \tau_2) \\ R_1' &= (m_1 - R_1)\mu + \beta R_1X - \sigma\beta R_1(c_1S + (c_1 - c_2)R_2) - R_1(\gamma + \tau_2) \\ R_2' &= (m_2 - R_2)\mu + \beta R_2X - \sigma\beta R_2(c_2S + (c_2 - c_1)R_1) - R_2(\gamma + \tau_1) \\ X &= 1 - S - R_1 - R_2. \end{aligned} \tag{2.1}$$

Within this model, antibiotic-use strategies define how τ_1 and τ_2 vary with time. To explain the strategies and give them some additional formal structure we will use some assumptions and notation from (Peña Miller and Beardmore, 2010). In addition to the assumptions inherent in the underlying hospital model, we will now assume that:

- Some interval of time $[0, T]$ for $0 < T < \infty$ is of interest to us as administrators of a hospital. We only concern ourselves with optimizing over this interval.
- Patients are given precisely one antibiotic. This rules out strategies such as combination therapy, but simplifies our job as modelers.
- The rate at which patients are treated with antibiotics is constant. The size of the population is assumed to smooth out any variation in how frequently patients are prescribed antibiotics.
- Explicit spatial information is not used to inform our strategy. Antibiotics are assigned randomly with some proportion receiving antibiotic A and the remainder receiving antibiotic B. This rules out, for example, a strategy which attempts to minimize the number of neighboring patients receiving the same antibiotic.

Together, these assumptions allow us to completely specify our strategy with a single function $\zeta : [0, T] \to [0, 1]$, which represents the proportion of patients receiving treatment who receive antibiotic A at any given time. The remaining patients receive antibiotic B.

Peña Miller and Beardmore then present several sets of functions corresponding to well-known antibiotic-use strategies. A cycling strategy ζ is specified by two parameters t_1 and t_2 and is defined to be

$$\zeta(t) = \begin{cases} 1 & 0 \le t \pmod{t_1 + t_2} \le t_1 \\ 0 & t_1 \le t \pmod{t_1 + t_2} \le t_2. \end{cases} \tag{2.2}$$

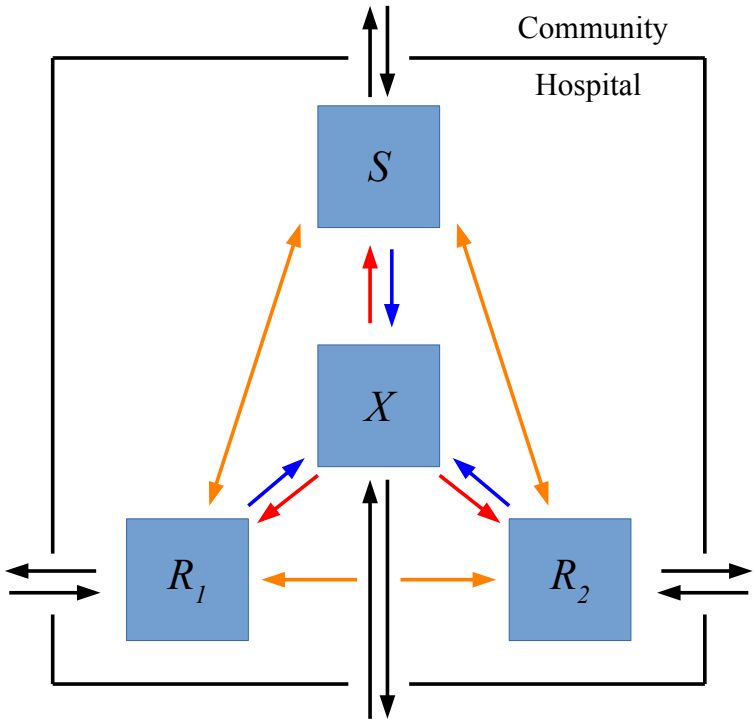

Figure 2.1 The compartments for Bergstrom et al.'s antibiotic-use model, shown in System 2.1. Patients in X are uninfected, those in S are infected by the susceptible strain, and those in R_1 or R_2 are infected by a resistant strain. There is assumed to be no multiply resistant strain. Arrows are color-coded by the process they represent. Red represents infection, yellow represents super-colonization, blue represents clearance, and black represents admission and discharge from the hospital. Figure adapted from (Bergstrom et al., 2004).

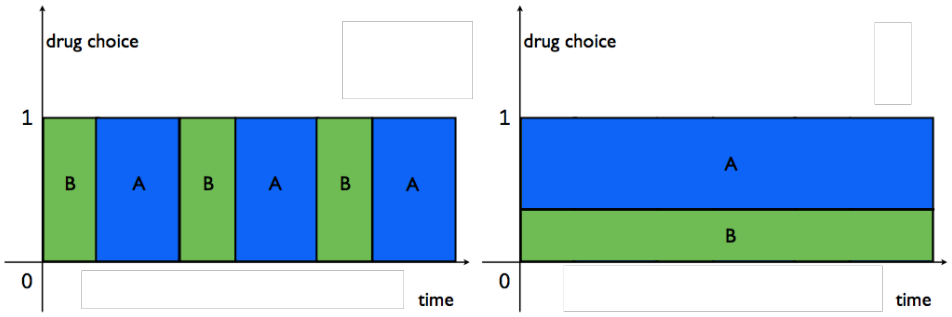

Figure 2.2 Graphical depictions of cycling (left) and mixing (right). The proportion of patients receiving antibiotic A is shown in blue, and the proportion receiving antibiotic B is shown in green. Note that the sum of the two proportions is always 1. Figure adapted from (Peña Miller and Beardmore, 2010).

A mixing strategy is specified using just one parameter $0 \leq m \leq 1$, and is defined to be the constant function $\zeta(t) = m$. Figure 2.2 graphically depicts these functions.

Now we can bring together our understanding of how antibiotic-use strategies are defined with the ODE model for ARB dynamics in hospitals. In the ODE model τ_1 and τ_2 are used to denote the rates at which drug A and B are used respectively, and each drug (if effective) is assumed to instantaneously clear any infection present. Since we also assume that the rate of antibiotic prescription is constant, we find that $\tau = \tau_1 + \tau_2$ must be constant. Thus in order to simulate a particular antibiotic-use strategy ζ we set $\tau_1(t) = \tau\zeta(t)$ and $\tau_2(t) = \tau(1 - \zeta(t))$. However this makes the assumption that physicians follow our assumed antibiotic-use protocol perfectly. This may not be the case, and (Bergstrom et al., 2004) accounts for this possibility with a parameter α that describes the probability that physicians correctly follow the assumed protocol. The remaining $\tau(1-\alpha)$ antibiotics are assigned at random, 50% to antibiotic A and 50% to antibiotic B.

An example of a simulation of this system under a cycling protocol is shown in Figure 2.3. In general, though, we do not need all the information given in such a simulation. Instead we usually wish to compute some statistics with which we can compare strategies. For example it might be informative to plot $R_1 + R_2$ over time as a measurement of the total "amount" of resistance present in the hospital. This statistic on a different simulation is shown in Figure 2.4 for two cycling protocols (both with $t_1 = t_2$), as compared

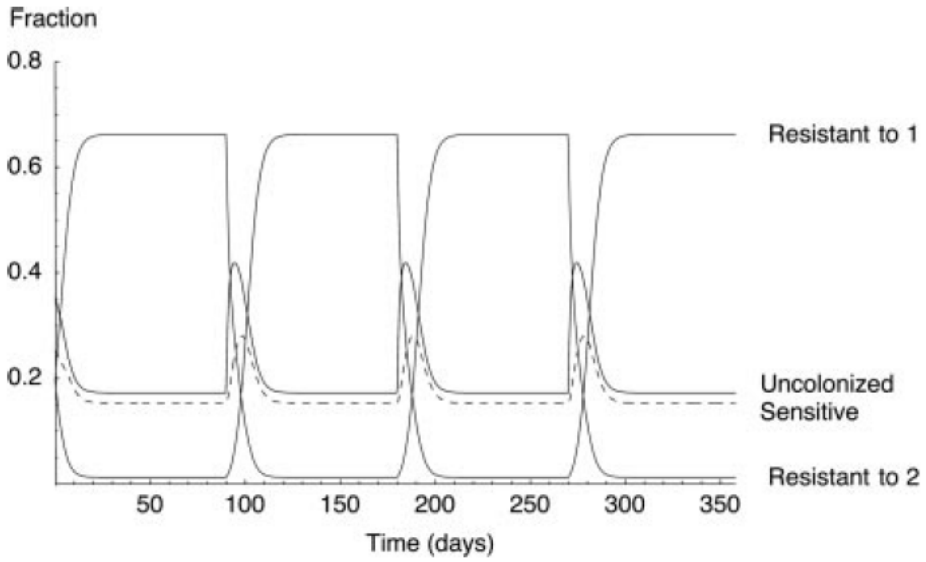

Figure 2.3 A simulation of System 2.1. Figure from (Bergstrom et al., 2004) using parameters $\beta = 1, c_1 = c_2 = 0, \gamma = 0.03, m = 0.7, m_1 = 0.05, m_2 = 0.05, \tau = 0.5, \mu = 0.1, \sigma = 0.25$, and $\alpha = 0.8$. The cycling protocol was defined as $t_1 = t_2 = 90$ days.

to a mixing protocol.

Analysis of this form (plotting statistics computed on S, X, R_1, and R_2 over time) conducted in (Bergstrom et al., 2004) was able to roughly indicate that under this model, mixing outperforms cycling, as measured both by prevalence of resistant strains and rate of evolution of new resistance. These results were questioned in (Peña Miller and Beardmore, 2010) and (zur Wiesch et al., 2014), both of which argue that only very slight expansions in what is allowed as a cycling protocol erase the advantages presented by Bergstrom et al.. Additionally, (Chow et al., 2011) argued that cycling exhibits more effective control over multiply-resistant strains. In Chapter 3 we expand on Chow et al.'s results for a three-antibiotic system.

Deterministic models have also been used to examine the volume of antibiotic use (Austin et al., 1999b). The particular model used by Austin et al. is slightly different and more complex than Bergstrom et al.'s model described above. In order to model the evolution of resistance Austin et al. takes into account the treatment history of individuals, adding additional

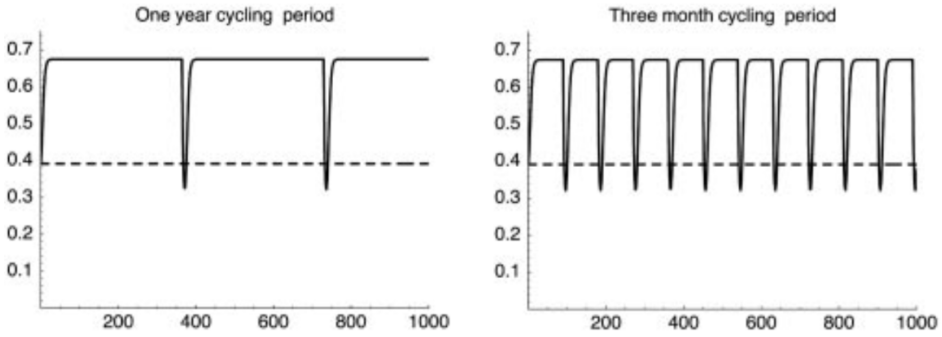

Figure 2.4 Plots of $R_1 + R_2$ over time in System 2.1 under two cycling protocols (solid line) compared to the same plots for a mixing protocol (dashed line). The cycling protocols were assumed to have $t_1 = t_2$, but the value of $t_1 + t_2$ was varied and is shown on the x-axis. Figure from (Bergstrom et al., 2004) using parameters from Figure 2.3.

classes "Treated Uncolonized" and "Treated Resistant" patients. These patients represent those who have recently been treated successfully, or unsuccessfully (e.g., resulting in selection for, or evolution of, a resistant infection). In the interests of simplicity our investigation of volume of antibiotic use in Chapter 4 will use an adapted version of Bergstrom et al.'s model rather than this more sophisticated approach.

2.2 Stochastic Antibiotic-Use Models

Stochastic antibiotic-use models are surprisingly lacking in the literature[2]. Only one antibiotic-use paper in our literature review (Bergstrom et al., 2004) confirmed that the results they obtained using deterministic models hold under analogous stochastic models. Several other papers either ignore stochasticity entirely (Peña Miller and Beardmore, 2010; Chow et al., 2011) or mention its importance only in passing (Lipsitch et al., 2000). We present some preliminary stochastic results in Chapters 3 and 4 but a more thorough analysis is beyond the scope of this thesis.

[2]Stochastic transmission-reduction models are slightly more common. See for a particularly good example (Cooper et al., 2004).

Chapter 3

Competition Between Resistant Strains

In this section we present an ecological interpretation of the results in (Chow et al., 2011) and extend the results of (Chow et al., 2011; Bergstrom et al., 2004) by considering the addition of a third antibiotic to the system. We briefly present a method for balancing the risks of evolution with the desire for effective medical treatment.

Bergstrom et al. concluded that cycling may control evolution of resistance more effectively than mixing under certain particularly symmetric parameter sets. Namely if the community prevalences m_1 and m_2 of the two resistant strains are similar, then cycling reduces the possibility of horizontal gene transfer[1] (HGT), though at the risk of increasing the rate of mutation of resistance. However, Bergstrom et al. also note that such symmetric parameter sets are rare in practice, and that even when present, monitoring is often insufficient to detect them (Bergstrom et al., 2004).

Chow et al. concluded that cycling controls the frequency of a superbug strain R_{12} more effectively than mixing, but presented no rationale for why (Chow et al., 2011).

After conducting our own analysis of Chow et al.'s system, we conclude that Chow et al.'s claims are correct and result from competition between resistant strains. In a sense resistant strains exploit the fixed resource of uninfected patients in X. Because cycling provides less effective control

[1] Horizontal gene transfer is an evolutionary process through which non-chromosomal DNA is transferred horizontally between two organisms (as opposed to vertical transfer through reproduction and mutation). Horizontal gene transfer can, for example, allow R_1 to share its resistance with R_2 without mutation.

over the frequencies of singly-resistant strains, these strains are allowed to more effectively compete with the doubly-resistant superbug. Accordingly this phenomenon should generalize to larger number of antibiotics, and the efficacy of cycling in controlling highly-resistant strains should depend greatly on the diversity and community prevalences of other resistant strains present in a given hospital.

By adding a third antibiotic we can synthesize the results of (Chow et al., 2011) and (Bergstrom et al., 2004). We conclude that by more effectively controlling highly-resistant strains, cycling provides better control over the mutation of novel combinations of resistances. Moreover since cycling still has the ability to reduce HGT under sufficiently symmetric parameter sets (Bergstrom et al., 2004) this means that cycling may in certain cases be significantly more effective at slowing evolution of ARB.

In selecting an antibiotic-use strategy in practice many factors must be considered. As noted by Bergstrom et al. symmetric parameter sets may not reflect reality in many cases, so data must be gathered on the frequencies of resistance in incoming patients. Moreover in cases of asymmetric frequencies, the relative importance of mutation vs. HGT must be evaluated in selecting an antibiotic-use strategy.

Finally, although Bergstrom et al. previously presented evidence that mixing provides superior control for the frequency of total resistance $R_1 + R_2$, more diverse sets of resistant strains call for more sophisticated approaches. What is the relative risk posed by a doubly-resistant or triply-resistant infection vs. a singly-resistant infection? We propose that a statistic centered on ultimate patient outcomes (for example: rate at which patients are incorrectly treated) should be used when evaluating the medical efficacy of an antibiotic-use strategy, in addition to statistics based on infection frequency (for example: total infection mass $1 - X$). Due to the subtleties of cycling's superior control of resistant strains, cycling still underperforms mixing under these metrics. Ultimately, then, a balance must be struck between rate of evolution by mutation, rate of evolution by HGT, and medical efficacy of treatment as measured by various metrics. We briefly present one method for balancing these concerns, but further research is needed to help advise hospitals in selecting a practical antibiotic-use strategy.

An important omission from this chapter is a detailed consideration of stochastic effects. These effects are certainly important: hospitals are usually relatively small communities and in some cases this will make the possibility of local extinction substantial. For example, by virtue of the natural periodicity of cycling strategies, cycling encourages local extinction

of rare bacterial strains — a property that could prove useful in the early stages of a resistance outbreak. However, a full analysis of stochastic effects is beyond the scope of this thesis. Potential stochastic analysis is instead discussed in Chapter 5 as an important avenue for future study.

3.1 Control of Double Resistance

In Bergstrom et al.'s model, discussed in Section 2.1, we assumed that multiple-resistance had not yet arisen. If it had, it would be a "superbug," immune to all available antibiotics. It would thus either dominate the hospital (if the basic reproductive number $\mathcal{R}_0 > 1$ in the hospital) or go through a series of local outbreaks and extinctions (if $\mathcal{R}_0 < 1$ in the hospital), each outbreak begun by admission of a new infected patient.

To our knowledge only one paper (Chow et al., 2011) has considered superbug strains in their model. That paper presents an extension to Bergstrom et al.'s model to include a doubly-resistant superbug strain. They argue that their simulations indicate cycling controls the superbug strain more effectively than mixing does. Here we present an ecological interpretation of their results.

They observed that under cycling, double-resistance remains at both lower average and lower peak levels. While this is true they do not present an explanation for why this is the case. Observing simulations of their model, like those in Figure 3.1 we can note that whenever the superbug strain $R_1 + R_2$ undergoes its characteristic downward spike, R_{12} undergoes a counterpart upward spike. Thus we argue that the control of R_{12} that Chow et al. is observing is the result of competition with singly-resistant strains. Since cycling is less effective than mixing as a control measure for singly-resistant strains, it allows R_1 and R_2 a greater competitive ability versus R_{12}.

Qualitatively we can argue that this must be true by considering what happens when R_1 and R_2 are removed from the system. If we set $R_1 = R_2 = 0$ and $m_1 = m_2 = 0$ then the only populations remaining in the hospital are S, X, and R_{12}. However, since the total rate of antibiotic use $\tau_1 + \tau_2$ is assumed to be constant, our choice of strategy no longer affects the dynamics of this system: S is susceptible to both antibiotics while R_{12} is resistant to both. Thus cycling and mixing have identical dynamics when R_1 and R_2 are absent from the system. It follows that any differences between cycling and mixing's R_{12} dynamics when R_1 and R_2 are present must be mediated by

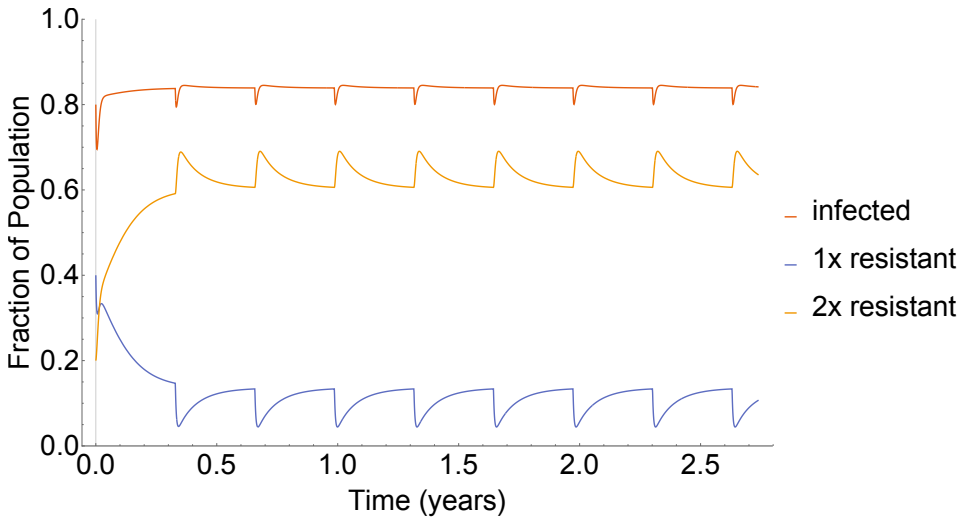

Figure 3.1 A simulation of Chow et al.'s model. Note the periodic spikes in R_{12}, in sync with the periodic dips in $R_1 + R_2$. Parameters were $\mu = 0.1, m = 0.7, m_1 = m_2 = 0.05, m_{12} = 0.0005, \gamma = 0.03, \beta = 1, c_1 = c_2 = 0.05, c_{12} = 0.15, \sigma = 0.25, \alpha = 0.8, \tau = 0.76$, as in (Chow et al., 2011). When applicable, parameters are given in units of days^{-1}. Cycling period is 240 days (120 days per antibiotic).

interactions with R_1 and R_2. These interactions may take the form of either exploitation competition[2] or interference competition[3].

Unfortunately, within the context of Chow et al.'s simple two-strain model, the nature of this competition negates any benefits otherwise accrued by reducing R_{12}. This is because pure population dynamics (while certainly useful) are not a sufficient metric for measuring the efficacy of an antibiotic-use strategy. Rather, we must also consider patient outcomes. Even though R_{12} remains at lower levels under cycling, patients on average receive less effective antibiotic treatment.

Since antibiotics are in general quite effective, resistant infections are only problematic if initial treatment is with an ineffective antibiotic. This ineffective treatment could be dangerous as the infection will continue unchecked. Thus one measure of patient outcome is the rate at which these ineffective treatment events occur.

It is important to note the weaknesses of this metric. For example, this metric reaches an absolute minimum when all antibiotic use ceases. In this scenario no patients receive any ineffective treatments, because no patients receive any treatments at all! However, by throwing out this optimum or by holding total antibiotic use τ constant, we may hope to find a more useful optimum. Because of this weakness, this metric should not be used in isolation, and any optima obtained from it should be cross-checked with other metrics such as $1-X$, the total number of infected patients (such a cross-check would, for example, rule out the no-antibiotic optimum discussed above).

Under the well-mixing assumption that allowed us to construct our ODE model in the first place, we can approximate the rate of ineffective treatment as

$$I(t) = \tau_1 R_1(t) + \tau_2 R_2(t) + (\tau_1 + \tau_2) R_{12}(t). \tag{3.1}$$

Under this I metric, mixing tends to outperforms cycling, in both superbug and non-superbug models. When hospitals cycle their antibiotics in a

[2]In ecology, exploitation occurs when two or more species that compete for a limited shared resource (prey, sunlight, etc). Since that resource is limited, the presence of competitors will tend to decrease a species' population size. In this case, with R_1 and R_2 exploiting the "resource" of susceptible patients, the population R_{12} is decreased.

[3]In ecology, interference occurs when a species actively interferes with a competitor's ability to exploit their shared resource. For example many plants release chemicals into the soil that hinder the growth of their competitors, and territorial animals may attack potential competitors. In this case, R_1 or R_2 may superinfect patients in R_{12}, thus reducing the R_{12} population. This will only occur when the fitness-cost of double-resistance is greater than that of single resistance: $c_{12} > c_1$ or c_2.

non-superbug system, the strain resistant to that antibiotic quickly rises to dominance over the other singly-resistant strain causing the product $\tau_i R_i$ to rise. Moreover, when cycling is compared to mixing under this metric in Chow et al.'s superbug model, it loses all the benefits it appeared to have when plotting pure population statistics. Although R_{12} does remain at lower levels, this proves unhelpful because it is almost entirely replaced by the singly-resistant strain that resists the current antibiotic-of-choice in the hospital. As we will see in the next section, cycling may still provide some benefits if the superbug is rare ($m_{12} \ll 1$) since cycling may encourage stochastic local extinction. However, in most other cases, evidence seems to suggest that in a superbug model, mixing is the superior strategy.

3.2 A Third Antibiotic

We now consider the case that our hospital has at its disposal not two, but three antibiotics. The primary difference between these models is the behavior of dual-resistance. In a three-antibiotic model, dually-resistant strains are no longer wholly untreatable — they are no longer superbugs — but they are nonetheless much more difficult to treat than singly-resistant strains. Further, dually-resistant strains have the potential to evolve into superbugs through HGT or mutation. Thus in the three-antibiotic case we find ourselves faced with a common dilemma in antibiotic-resistance control: how can we optimize our strategy to both maximize positive medical outcomes and minimize evolution?

Three-antibiotic systems have previously been modeled, but with several important differences from our analysis. A short response to (Bergstrom et al., 2004) extended their model to three antibiotics, but did not include doubly-resistant strains (Levin and Bonten, 2004). A recent paper constructed a very similar three-antibiotic model to ours, including doubly-resistant strains (Obolski et al., 2015), but their analysis focused on the usefulness of *restriction* of one antibiotic, rather than the optimality of cycling vs. mixing. To our knowledge no other papers beyond these two have considered three-antibiotic systems.

Ignoring the superbug for this system so that we can consider the threat of evolution, we find ourselves with eight compartments: X, S, R_1, R_2, R_3, R_{12}, R_{13}, R_{23}. The processes included in our model are almost exactly analogous to Bergstrom et al.'s model. The one difference is that for simplicity — and in order to account for rapid compensatory mutation — we set all the fitness

costs c_i and c_{ij} to 0. This gives us the system

$$\begin{aligned} S' &= (m - S)\mu \quad + \beta SX \quad - (\gamma + \tau)S \\ R_i' &= (m_i - R_i)\mu \; + \beta R_i X - (\gamma + \tau - \tau_i)R_i \\ R_{ij}' &= (m_{ij} - R_{ij})\mu + \beta R_{ij} X - (\gamma + \tau - \tau_i - \tau_j)R_{ij} \\ X &= 1 - S - \sum R_i - \sum R_{ij}. \end{aligned} \tag{3.2}$$

This system can of course naturally be extended to account for non-zero fitness costs.

The simulations of this system shown in Figure 3.2 show that under a three-antibiotic system (for a particularly symmetric parameter set) cycling appears to control double-resistance more effectively than mixing. At first, it appears to do so in a different way than in (Chow et al., 2011). In their model double-resistance spikes when single-resistance dips, and vice versa, while in our system, double-resistance and single-resistance dip and spike in unison with one another. However, deeper investigation shows that this system bears many of the same unfortunate properties as Chow et al.'s. Namely, when singly-resistant strains are removed from the system cycling ceases to show superior control for double-resistance (as can be seen in Figure 3.4). Thus, even in the three-antibiotic case the superior control of doubly-resistant strains by cycling is due not to direct control through the use of antibiotics, but instead to greater competition from singly-resistant strains. Moreover, cycling does not bestow any benefit to I (as can be seen in Figure 3.3), the rate at which patients are incorrectly treated.

However, in leaving the superbug R_{123} out of our system, we have given ourselves the ability to measure cycling's efficacy in terms of the threat of evolution. We could not do this in Section 3.1 because the superbug was already present; there was no further resistance left to evolve. Bergstrom et al. previously estimated the rate at which horizontal gene transfer will successfully evolve a superbug strain. We conduct a similar analysis, though we follow (Obolski et al., 2015) by including also an estimate of the rate at which mutation of a doubly-resistant strain will successfully evolve a superbug strain. These two statistics can be approximated as follows:

- The rate at which a triply-resistant strain evolves directly from a doubly-resistant strain through mutation is roughly proportional to r_M for

$$r_M = \tau_3 R_{12} + \tau_2 R_{13} + \tau_1 R_{23}. \tag{3.3}$$

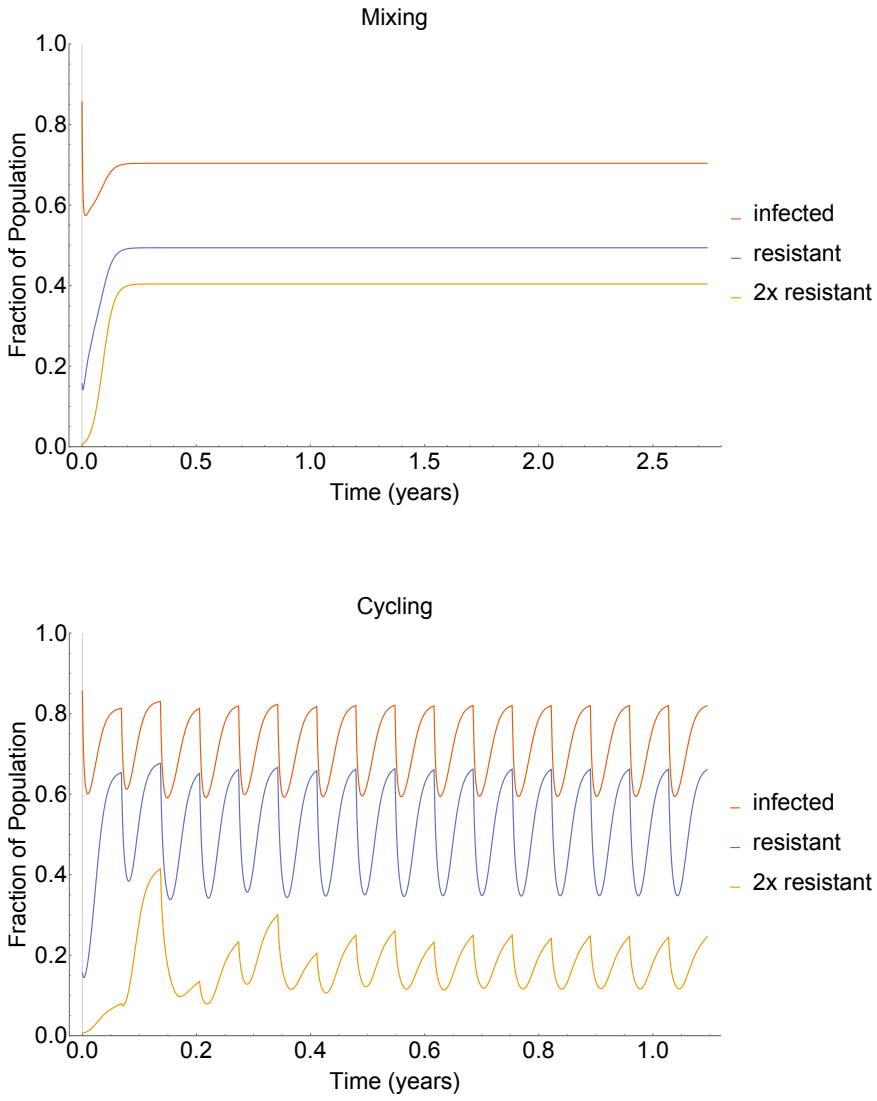

Figure 3.2 Two simulations of our three-antibiotic model, given by System 3.2. Parameters were $\mu = 0.1$, $m = 0.7$, $m_1 = m_2 = m_3 = 0.05$, $m_{12} = m_{13} = m_{23} = 0.0005$, $\gamma = 0.03$, $\beta = 1$, $c_1 = c_2 = c_3 = c_{12} = c_{13} = c_{23} = 0$, $\sigma = 0.25$, $\alpha = 0.8$, $\tau = \tau_1 + \tau_2 + \tau_3 = 0.5$. When applicable parameters are given in units of days^{-1}. Under mixing (top) $\tau_1 = \tau_2 = \tau_3$, and under cycling (bottom) $\tau_i = \tau$ for 25 days per antibiotic (total cycling period 75 days).

This makes the assumption that evolution through mutation will only occur when correct treatment of a doubly-resistant strain creates an environment which selects for the third resistance. It is conceivable that triple-resistance could arise some other way (perhaps through pleiotropic effects) but it is at least plausible that these other evolutionary pathways contribute only negligibly to r_M.

- The rate at which a triply-resistant strain evolves through horizontal gene transfer is roughly proportional to r_H for

$$r_H = (R_1+R_{12}+R_{13})R_{23}+(R_2+R_{12}+R_{23})R_{13}+(R_3+R_{13}+R_{23})R_{12}. \quad (3.4)$$

Although we assume that only a single strain can *dominate* the infection of a given patient, we may assume that the rate at which patients in a given infection class R_{ij} are *exposed* to another strain is proportional to the product of the two population sizes. We are also making the important (and tenuous) assumption that all resistance genes are equally likely to undergo horizontal gene transfer.

With these statistics in hand, we can more comprehensively measure the performance of cycling as compared to mixing. In order to do so we will usually plot these statistics versus cycling period. In the limit of very short cycling periods, cycling approaches mixing (and will thus be indistinguishable) and in the limit of very long cycling periods, cycling approaches single-antibiotic-use (which will be unacceptably ineffective in the presence of resistance). Thus we expect that if cycling is ever to outperform mixing, it should do so only for intermediate cycling periods.

To observe the benefits of these intermediate periods in our model, we can graph the averages of our performance statistics vs. cycling period. We simulate for 1000 days to allow transients to completely decay[4] and then average statistics over the last period of the cycling protocol. For comparison, we plot the corresponding values of the equivalent mixing protocol. We also plot some average population sizes for reference. The results of these simulations for the three-antibiotic system are shown in Figure 3.3. Similar results with $R_1 = R_2 = R_3 = 0$ and $m_1 = m_2 = m_3 = 0$ are shown in Figure 3.4.

In many ways this model combines the properties of Bergstrom et al.'s and Chow et al.'s models. As in (Bergstrom et al., 2004) we note that cycling

[4] As we will note in Section 3.3, transients tend to decay over a shorter time period: a few months perhaps. However, since we have not done a rigorous analysis of this rate of decay, we allow almost three years as a conservative estimate to ensure that transients are well and truly negligible.

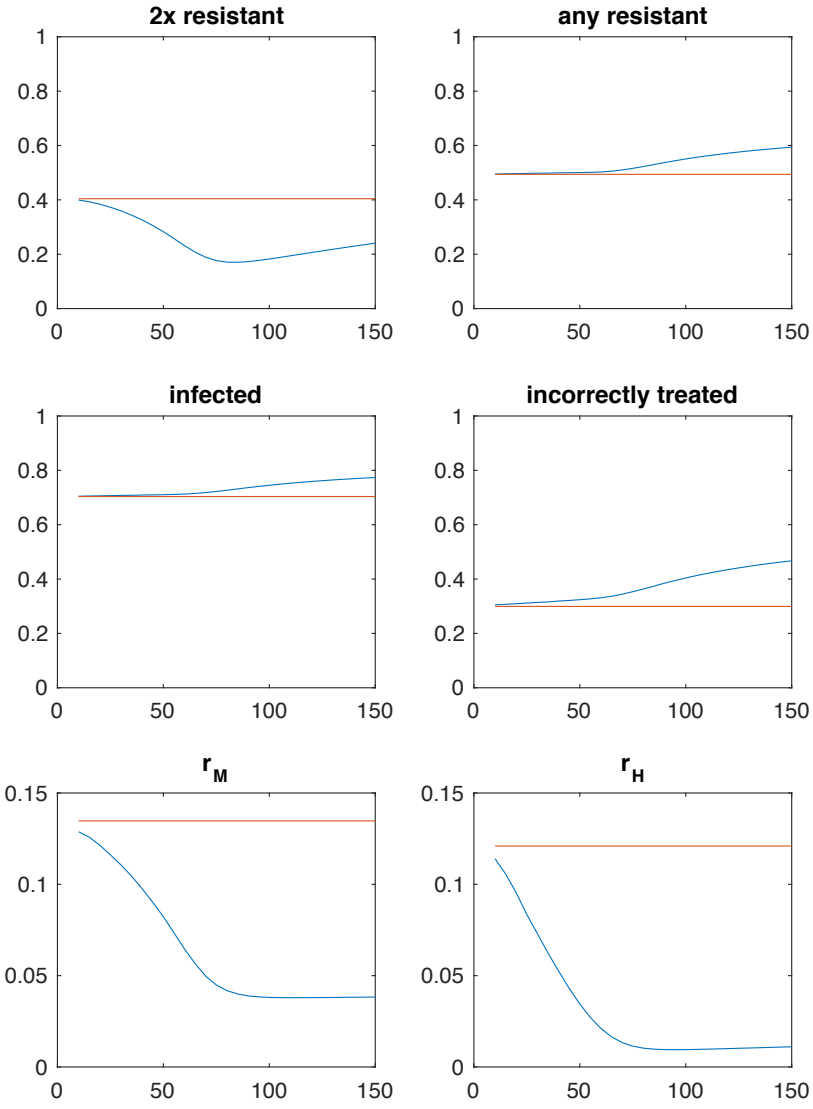

Figure 3.3 Statistics comparing cycling (blue) to mixing (red) under the three-antibiotic model given by System 3.2 as cycling period is varied. Cycling period is measured in days. For ease of calculation, cycling period is varied in steps of 5 days but the curves remain sufficiently smooth that this appears to introduce little error. Parameter values were the same as in Figure 3.2.

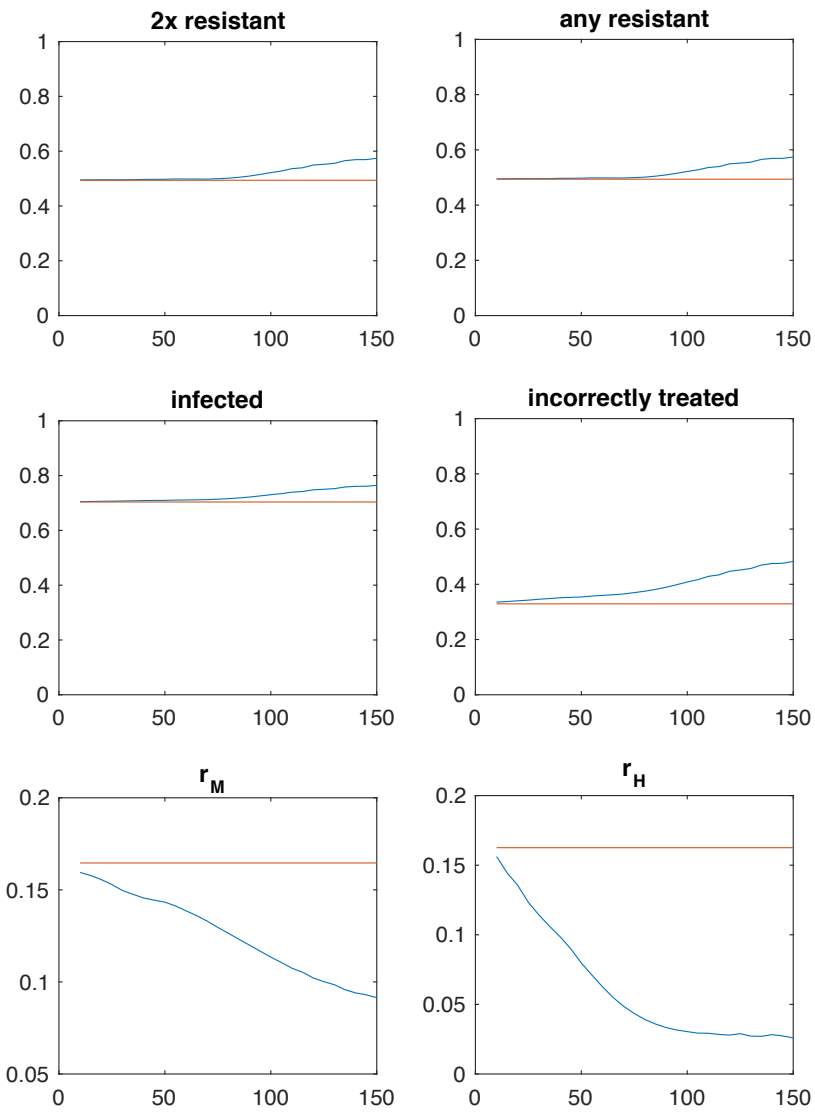

Figure 3.4 Statistics comparing cycling (blue) to mixing (red) under the three-antibiotic model given by System 3.2 as cycling period is varied. Cycling period is measured in days. For ease of calculation, cycling period is varied in steps of 5 days. Parameter values were the same as in Figure 3.2 but with $m_1 = m_2 = m_3 = 0$.

appears to confer some advantage at reducing the rate of horizontal gene transfer, at the cost of less effective treatment. Both our model and theirs also lose this property when resistant strains occur at asymmetric rates in the outside community. Under symmetric conditions, this phenomenon is explained by short-term selection for resistant strains; the strain (or strains) resistant to the current antibiotic-of-choice very quickly comes to dominate the hospital while the non-resistant strains reach very low levels. This results in the product of these populations being very small. This phenomenon breaks down under asymmetric prevalences because when the more-prevalent strain is being selected against, it is still maintained at relatively high levels by influx of patients from the community.

As we noted above, this model shares Chow et al.'s model's property that cycling more effectively controls multiple-resistance because it allows singly-resistant strains to persist at higher levels and compete with multiply-resistant strains. This model also shares Chow et al.'s model's property that the rate of ineffective treatment $I(t)$ is not improved under cycling.

The major difference that this model bears from Bergstrom et al.'s and Chow et al.'s is in the evolution metric r_M. Excluding the possibility of pleiotropy[5], only doubly-resistant strains can evolve triple-resistance. In this way, doubly-resistant strains bear a fundamental difference from singly-resistant strains that cannot be captured in a two-antibiotic model. Thus although reduced levels of double-resistance under cycling may not provide tangible benefits in terms of treatment outcomes, it *does* dramatically reduce r_M. This benefit of cycling appears to be robust to all but the largest asymmetries.

Indeed the benefit of cycling on r_M is in some cases even greater than is apparent in our deterministic model. Stochastic simulations of our model using the Gillespie stochastic simulation algorithm (SSA)[6] reveal that the dips and spikes in our deterministic solutions pave the way for long stretches of stochastic local extinction. When doubly-resistant strains are rare in the community ($m_{ij} \ll 1$) local extinction will persist for a long time before new resistant infections are imported from the community. By reducing the populations of doubly-resistant bacteria in a naturally periodic system, we

[5]The control of multiple traits by a single gene. In the presence of pleiotropy a single gene could control resistance to multiple antibiotics, thus allowing a singly-resistant strain to evolve directly into a triply-resistant strain. We assume the effect of pleiotropy is negligible.

[6]Many thanks to István Zachar on StackExchange for their implementation of the Gillespie SSA, which we use for our simulations. This implementation and a discussion of the Gillespie SSA can be found at https://mathematica.stackexchange.com/revisions/119786.

increase the probability of local extinction. In essence bringing the natural troughs of a population closer to zero makes it easier for stochastic variations to completely extinguish that population.

This phenomenon can be observed by comparing Figure 3.5 to Figure 3.2. Though the parameter values are identical, local extinction has the effect of further depressing the average prevalence of doubly-resistant bacteria, which in turn decreases r_M. Unfortunately, a quantitative estimate of the extent to which local extinction depresses doubly-resistant populations is beyond the scope of this thesis.

Notably, the benefit of reducing the rates of mutation (r_M) or HGT (r_H) is often in conflict with the cost of increasing the rate of ineffective treatment (I). In order to compare cycling to mixing we must thus devise some aggregate metric that combines both of these concerns.

3.3 Prioritization: Prevalence vs. Emergence

In (Bergstrom et al., 2004) cycling and mixing are compared by the metrics of resistance prevalence and rate of horizontal gene transfer. It was found that under very symmetric parameter sets, cycling outperforms mixing on the HGT but underperforms on resistance control. Additionally, they argued that in most cases, sufficient data is not available to show that the current parameter set favors cycling. However, let us suppose that such data was available: to our knowledge no one has presented a method for balancing the two conflicting metrics of prevalence vs. evolution. We now do so. Note that our method makes few assumptions about the specifics of the model until numerics are plugged in. It can be applied just as easily to a two-antibiotic system as a three-antibiotic system, and other effects such as transmission-reduction can also be easily included.

Let $C(t)$ denote the value of some cost function at time t. Then, given some parameters and a time interval $[0, T]$ we wish to devise an antibiotic-use protocol which minimizes

$$C = \int_0^T C(t)dt. \tag{3.5}$$

However emergence of a new resistant strain is a distinct possibility, and may occur during our interval of interest. Thus C must be a random variable. Varying our antibiotic-use protocol will vary the rate of evolution of new resistance which will vary the distribution of C. Thus, minimizing the

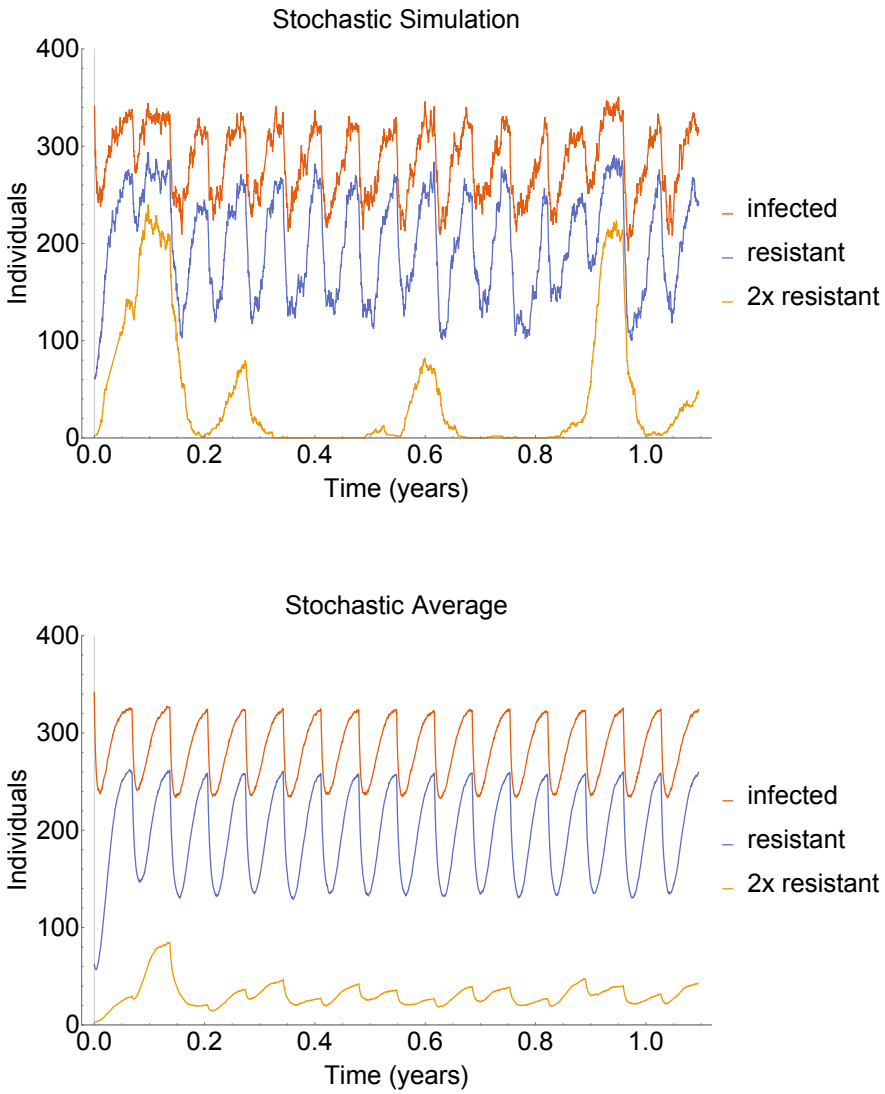

Figure 3.5 A single simulation (top) and an average of 100 simulations (bottom) of our three-antibiotic model using the Gillespie stochastic simulation algorithm. Parameter values were the same parameters as in Figure 3.2, with population size $N = 400$. Note the frequent local extinction events (top) and depressed average prevalence of doubly-resistant strains (bottom) as compared to Figure 3.2.

expected value $\mathbb{E}[C]$ gives us an aggregate metric that accounts both for incorrect treatment and rates of evolution.

We have already discussed statistics (r_M and r_H) that allow us to measure the rate of evolution through mutation or horizontal gene transfer. In general these statistics will be functions of t, and will be associated with constants of proportionality k_M and k_H. They must also be scaled by the population size N of the hospital[7], such that the true rate at which triple-resistance emerges is given by

$$r(t) = k_M N r_M(t) + k_H N r_H(t). \tag{3.6}$$

Ultimately we want to find the expectation $\mathbb{E}[C]$. This is quite complicated in general, since we have to integrate over the solution to a large system of ODEs. However, if we assume that any transients of the system decay instantaneously[8] at time $t = 0$ and at the time when emergence occurs then we can calculate $\mathbb{E}[C]$ much more easily. In other words at all times the system is assumed to be in its long-term state, which we have only ever observed to be a stable fixed point (under mixing), or a limit cycle (driven by the periodicity of a cycling strategy). To calculate $\mathbb{E}[C]$ under this assumption, let $C_1(t)$ be the value of $C(t)$ in the stable equilibrium or limit-cycle that forms before a new resistance emerges and let $C_2(t)$ be the value of $C(t)$ in the stable equilibrium or limit-cycle that forms after (shifted so that $t = 0$ is the time of emergence). Finally let $f(t)$ be the probability that triple-resistance has not yet emerged at time t. Then we find that

$$\mathbb{E}[C] = \int_0^T \left[\int_0^t C_1(t')dt' + \int_0^{T-t} C_2(t')dt' \right] f(t)r(t)dt. \tag{3.7}$$

In general finding $C_1(t)$, $C_2(t)$ and $r(t)$ is no easy task, but $f(t)$ is given by

[7] In reality $r_M(t)$ and $r_H(t)$ denote the dimensionless rate at which certain interactions occur — a doubly-resistant strain is correctly treated, or a doubly-resistant strain is exposed to a strain with its missing resistance — with each population term scaled down by N. After scaling back up by N, k_M and k_H represent the rate at which each of these interactions results in successful evolution of triple-resistance. Note that we must assume that k_M and k_H are small since otherwise evolution would occur frequently and we would have to include it as a deterministic process in our model. In essence this is a partially deterministic/partially stochastic model where all processes besides evolution are assumed to be dominated by deterministic effects but the probability of evolution is assumed to be so small that it is dominated by stochastic effects.

[8] After many simulations this appears to be a good assumption so long as the interval of interest T is on the order of years. Figure 3.2 shows a relatively standard decay of transients on the order of 1-2 months.

the solution to the initial value problem

$$\begin{aligned} f'(t) &= -f(t)r(t) \\ f(0) &= 1, \end{aligned} \tag{3.8}$$

which can be found by separating variables to be:

$$f(t) = \exp\left(-\int_0^t r(t')dt'\right). \tag{3.9}$$

However finding $r(t)$, $C_1(t)$, and $C_2(t)$ in general may require a numerical approach, a complete analysis of which is beyond the scope of this thesis. Nevertheless the following section demonstrates the utility of this method by analytically optimizing the volume of antibiotic use τ for the cost function $C(t) = I(t) = \tau R(t)$ (the rate of ineffective treatment) in a one-antibiotic system.

3.4 A Simple Example

Consider the one-antibiotic system

$$\begin{aligned} S' &= \mu m_S - S(\mu + \gamma + \tau - \beta X) \\ R' &= \mu m_R - R(\mu + \gamma - \beta X) \\ X &= 1 - S - R. \end{aligned} \tag{3.10}$$

If resistance has not yet evolved then $R(0) = m_R(0) = 0$. Since the community is much larger than the hospital we will assume that its dynamics are much slower and that $m_R(T) = 0$ even at the end of our interval-of-interest. Then we can analytically solve for the steady-state values of our cost function $I(t)$ before and after resistance evolves in the hospital, which we call I_1 and I_2. I_1 is trivial. If we assume $R = 0$ then

$$I_1 = \tau R = 0. \tag{3.11}$$

To calculate I_2 we must find the fixed point with $m_R = 0$ and $R > 0$, namely

$$\begin{aligned} \mathbf{x}_2 &= (S, R, X) \\ &= \left(\frac{\mu m_S}{\tau}, 1 - \frac{\mu + \gamma}{\beta} - \frac{\mu m_S}{\tau}, \frac{\mu + \gamma}{\beta}\right). \end{aligned} \tag{3.12}$$

In the next chapter we will derive approximations for how m_R changes with time (as it will surely increase when $R > 0$ for any extended period of time). However since empirical evidence suggests that m_R tends to stay low for long periods of time (Austin et al., 1999b), $m_R = 0$ is a good approximation so long as our period-of-interest is not on the scale of decades or centuries.

Now we can calculate

$$\begin{aligned} I_2 &= \tau R \\ &= \tau\left(1 - \frac{\mu+\gamma}{\beta}\right) - \mu m_S. \end{aligned} \tag{3.13}$$

Since HGT is impossible in a one-antibiotic system we can set

$$\begin{aligned} r &= k_M N r_M \\ &= k_M N \tau R \\ &= k_M N\left[\tau\left(1 - \frac{\mu+\gamma}{\beta}\right) - \mu m_S\right]. \end{aligned} \tag{3.14}$$

Finally, putting it all together, we find that

$$\begin{aligned} \mathbb{E}[I] &= \int_0^T \left[\int_0^t I_1(\tau)d\tau + \int_0^{T-t} I_2(t')dt'\right] f(t)r(t)dt \\ &= \int_0^T re^{-rt}(T-t)I_2 dt \\ &= I_2\left(T - \frac{1-e^{-rT}}{r}\right) \\ &= \frac{I_2}{r}\left(rT - (1-e^{-rT})\right) \\ &= \frac{\left(rT + e^{-rT} - 1\right)}{k_M N}. \end{aligned} \tag{3.15}$$

Thus to minimize $\mathbb{E}[I]$ we need to minimize $rT + e^{-rT}$. This, in turn, reduces to minimizing

$$A\tau + Be^{-A\tau}, \tag{3.16}$$

where

$$A = k_M N\left(1 - \frac{\mu+\gamma}{\beta}\right)T \qquad \text{and} \qquad B = e^{k_M N^2 \mu m_S T}.$$

This minimum occurs at

$$\tau_{\text{opt}} = \frac{\ln B}{A} = \frac{\mu m_S}{\left(1 - \frac{\mu+\gamma}{\beta}\right)}. \tag{3.17}$$

Note that this optimum is, remarkably, independent of T, N, and k_M. As a quick representative calculation, suppose that both the average length of stay in an emergency room is $\frac{1}{\mu} = 1.5$ days; the average time-to-clearance due to natural immune system processes is independently $\frac{1}{\gamma} = 7$ days; a single patient contacts on average of 10 other patients per day, with a probability 0.1 of contagion per contact, so that $\beta = 1$ infection per patient per day per fraction of population uninfected; and roughly 1% of the outside population is infected, so that $m_S = 0.01$. Then we find that

$$\tau_{\text{opt}} = 0.035 \text{ per patient per day}$$

In other words, the optimal rate of antibiotic use in this (contrived) high-traffic emergency room is 3.5% of patients per day. In fact this result is robust even to reasonable changes in the cost function C. For example, we might set $C(t) = R(t)$ if we were worried about the weaknesses of the $I(t)$ metric. This gives an identical result.

The percent of patients per day that actually receive antibiotics is far higher than 3.5% (Magill et al., 2014), particularly considering that many outpatients receive prescriptions for further antibiotics. Of course this is an exceedingly simple model, and without taking into account far more complexity we certainly do not claim that dramatic reduction in antibiotic use is wise. Nevertheless this model may account for some of the very real processes that are causing the rapid evolution of resistance in bacterial populations around the world, and indicates that, like some scientists have argued (Austin et al., 1999b), decreased antibiotic use should be considered moving forward.

3.5 Discussion

Above we propose that cycling may demonstrate superior control (as compared to mixing) over multiply-resistant strains provided there is a sufficiently diverse set of less-resistant strains available to compete for infection. This phenomenon does not increase the efficacy of medical treatment, but should slow the evolution of further resistance. It is also reinforced by stochastic extinction when multiply-resistant strains are rare.

We also propose a metric $I(t)$ for measuring the efficacy of antibiotic treatment. This metric has notable weaknesses: it is globally optimized when total antibiotic use $\tau = 0$. However, in combination with other metrics, such as total infection mass $1 - X$ or total resistant infection mass $1 - X - S$, this metric will aid in measuring the efficacy of antibiotic use strategies.

Finally, we proposed a method for optimizing an antibiotic use strategy in terms of an instantaneous cost function $C(t)$. We use this method with the cost function $I(t)$ for a simple one-antibiotic system and find that $\mathbb{E}[I]$ is optimized for unrealistically small values of τ. We hope that more realistic extensions to this work can bring τ_{opt} within achievable limits, and that such work can help to lengthen the lifetime of antibiotics for future generations.

Chapter 4

Outbreak of Antibiotic Resistance

Besides evolution and efficacy of medical treatment, outbreak is the third major problem associated with ARB. After resistant strains of a given infection evolve, their frequencies increase until certain antibiotics are no longer reliable treatments for that infection (Coates et al., 2011). Slowing mutation and HGT addresses the problem of evolution, but what do we do after resistance has already evolved, and spread far enough that eradication is not feasible? If we continue to use that particular antibiotic to treat that particular infection then we continue to select for resistance, and eventually resistance will likely be fixed in the population. Though complete cessation of antibiotic use is unlikely, the dynamics of ARB outbreaks may reveal ways to slow it down.

The outbreak problem requires us to consider not just a hospital, but also the surrounding community. Within a hospital, selection for resistance is very strong and outbreak may be rapid. However in the outside community use of antibiotics will be much lower. Moreover the population of a community is likely much larger than that of the hospital that serves it. Thus even if we couple a hospital to its community, the community frequency of resistance should still increase relatively slowly. Indeed the pattern observed in epidemiological studies of resistance frequency over time tends to be sigmoidal (Austin et al., 1999b): we see long periods of very low-frequency resistance followed by a rapid rise to dominance. In the remainder of this chapter we present one possible model of this sigmoidal pattern, several measures of the time-scale of outbreak, and argue that

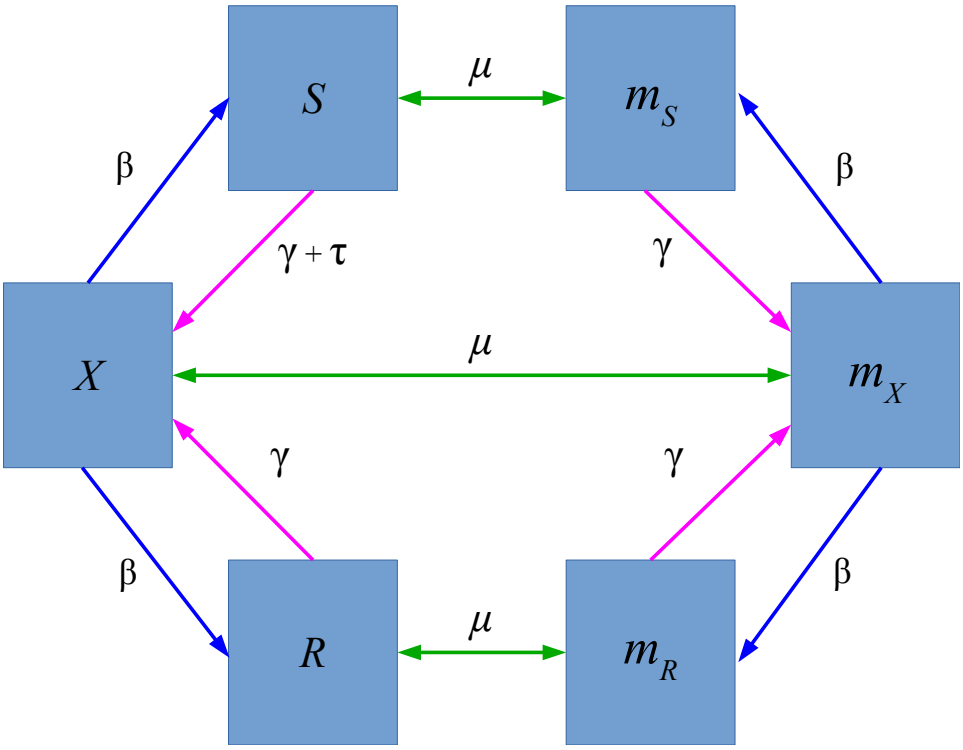

Figure 4.1 A compartmental diagram showing the processes considered in our hospital-community model. See System 4.1 for the system of equations that this diagram represents.

sufficiently concentrated antibiotic use changes the fundamental temporal pattern of emergence from a sigmoid to an exponential.

Our basic model is as follows:

$$\begin{aligned} S' &= \mu(m_S - S) + \beta SX - (\gamma + \tau)S & m_S' &= \epsilon\mu(S - m_S) + \beta m_S m_X - \gamma m_S \\ R' &= \mu(m_R - R) + \beta RX - \gamma R & m_R' &= \epsilon\mu(R - m_R) + \beta m_R m_X - \gamma m_R \\ X &= 1 - S - R & m_X &= 1 - m_S - m_R, \end{aligned} \tag{4.1}$$

where $\epsilon = N_H/N_C$ is the ratio of the population sizes of the hospital to that of the surrounding community. This model considers only the bare minimum possible processes: admission/discharge (μ), infection (β), immune clearance (γ), and antibiotic clearance (τ). A compartmental diagram of these processes is shown in Figure 4.1.

Note that for ease of analysis, we have made a number of important assumptions, including: all antibiotic use is concentrated in the hospital, μ does not vary between infection classes, superinfection is of negligible importance, and γ, β are the same inside vs. outside the hospital. Some of these assumptions are tenuous, and should be relaxed in future work.

Using this model we will derive approximate time scales for two cases: μ very large, and μ relatively small. In the former case, we see a sigmoidal outbreak pattern, while in the latter we see an exponential pattern. For intermediate μ, simulations show sigmoidal behaviors, but we have been unable to derive an approximation for this case.

In this chapter, like in Chapter 3, we omit an in-depth discussion of stochasticity, despite its importance. In this model, stochasticity has two major effects. First, with a sigmoidal outbreak curve, the population m_R may stay small for a very long time. This means the chances of stochastic extinction may be substantial, and may result in significant delay of the ultimate outbreak. We have made some progress estimating the length of this delay, and a discussion of this is included at the end of this chapter. Second, stochasticity will tend to add variability to the time-scales we derive in this chapter. Understanding the distributions of these time-scales will be of vital importance when planning for ARB outbreaks. However, a thorough analysis of both these stochastic effects is beyond the scope of this thesis and is discussed primarily as an important avenue for future work.

4.1 A Well-Mixed Community

The greatest simplification of our model we can consider is one in which the rate of admission/discharge μ is very large. If $\mu \approx \infty$ then any separation between the hospital and the community becomes negligible, and the two can be treated as a single large population. Then we can reduce our system to the following:

$$\begin{aligned} m_S' &= m_S(\beta m_X - \gamma - \epsilon\tau) \\ m_R' &= m_R(\beta m_X - \gamma) \end{aligned} \tag{4.2}$$

This system can be simplified further by assuming $\epsilon \ll 1$. Consider

$$\begin{aligned} m_X' &= -m_S' - m_R' \\ &= \epsilon\tau m_S - (m_S + m_R)(\beta m_X - \gamma) \\ &= \epsilon\tau m_S - (1 - m_X)(\beta m_X - \gamma). \end{aligned} \tag{4.3}$$

If $\epsilon = 0$ then m_X quickly approaches either 1 or γ/β. If $m_X = 1$ then $m_S = m_R = 0$. Thus to get any non-trivial behavior let us assume that m_X quickly approaches γ/β. In reality it reaches a slightly perturbed fixed point, which can be found to be a root of the binomial

$$\beta m_X^2 - (\beta + \gamma)m_X + \gamma + \epsilon\tau m_S. \tag{4.4}$$

Letting $\alpha = 1 - \frac{\gamma}{\beta}$ we find that this binomial has roots

$$\begin{aligned}
\frac{1}{2}\left(1 + \frac{\gamma}{\beta}\right) \pm \frac{1}{2\beta}\sqrt{(\beta+\gamma)^2 - 4\beta(\gamma + \epsilon\tau m_S)} &= \frac{1}{2}\left(1 + \frac{\gamma}{\beta}\right) \pm \frac{1}{2}\sqrt{\alpha^2 - 4\epsilon\frac{\tau m_S}{\beta}} \\
&= \frac{1}{2}\left(1 + \frac{\gamma}{\beta}\right) \pm \frac{1}{2}\alpha\sqrt{1 - 4\epsilon\frac{\tau m_S}{\alpha^2\beta}} \\
&\approx \frac{1}{2}\left(1 + \frac{\gamma}{\beta}\right) \pm \frac{1}{2}\alpha\left(1 - 2\epsilon\frac{\tau m_S}{\alpha^2\beta}\right) \\
&= \begin{cases} 1 - \epsilon\frac{\tau m_S}{\alpha\beta} \\ \frac{\gamma}{\beta} + \epsilon\frac{\tau m_S}{\alpha\beta}. \end{cases}
\end{aligned}$$

Note that in order to derive these results we properly need to assume not that $\epsilon \ll 1$ but rather than $\epsilon \ll \frac{\alpha^2\beta}{4\tau m_S}$. However since α, β are not small and τ, m_S are not large, this should remain a good approximation.

Since we are interested in the γ/β root we will assume for the remainder of our analysis that

$$m_X = \frac{\gamma}{\beta} + \epsilon\left(\frac{\tau m_S}{\alpha\beta}\right). \tag{4.5}$$

We can plug this into our equation for m_S to give us an alternative specification of our system in terms of m_S and m_X, with m_R now implicitly defined as $m_R = 1 - m_S - m_X$. Then

$$m_S' = m_S\left(\epsilon\left(\frac{\tau m_S}{\alpha}\right) - \epsilon\tau\right). \tag{4.6}$$

This gives us a system with characteristic time scale

$$T = \frac{\alpha}{\epsilon\tau},$$

and rescaling to $t' = Tt$ we find that

$$\dot{m}_S = m_S(m_S - \alpha). \tag{4.7}$$

Solving this equation we find that

$$m_S(t') = \frac{\alpha m_S(0) e^{-\alpha t'}}{\alpha - m_S(0)(1 - e^{-\alpha t'})} \tag{4.8}$$

The inflection point of this equation should give us a measure of the amount of time it takes for resistance to invade a system. This inflection point occurs at dimensionless time

$$t' = -\frac{1}{\alpha} \ln\left(\frac{\alpha}{m_S(0)} - 1\right) \tag{4.9}$$

This gives us a dimensional time between evolution and outbreak of

$$\frac{1}{\epsilon\tau} \ln\left(\frac{m_S(0)}{\alpha - m_S(0)}\right). \tag{4.10}$$

However when $m_R = 0$ our system has a fixed point at

$$\begin{aligned} m_S &= 1 - \frac{\gamma + \epsilon\tau}{\beta} \\ &= \alpha - \frac{\epsilon\tau}{\beta}, \end{aligned}$$

so we can plug this in as our initial condition to find that the time-to-outbreak after evolution is

$$T_{\text{approx}} = \frac{1}{\epsilon\tau} \ln\left(\frac{\alpha\beta}{\epsilon\tau} - 1\right). \tag{4.11}$$

Simulation reveals that our approximate solution for S is very close to correct, provided we use the initial conditions

$$m_S(0) = \alpha - \frac{\epsilon\tau}{\beta}, \qquad m_R(0) = \frac{\epsilon\tau}{\beta}, \qquad m_X(0) = \frac{\gamma}{\beta}. \tag{4.12}$$

However, in reality the initial condition is likely to involve the evolution of resistance in a single individual[1]. This would correspond to the initial conditions

$$m_S(0) = \alpha - \frac{\epsilon\tau}{\beta} - \frac{1}{N}, \qquad m_R(0) = \frac{1}{N}, \qquad m_X(0) = \frac{\gamma}{\beta} + \frac{\epsilon\tau}{\beta}. \tag{4.13}$$

[1]Another way to think of this is that there is a fifth process (mutation) occurring at a very, very slow rate. This process moves patients in S who are treated with antibiotics to R.

However, since both initial conditions have $m_R(0) \ll 1$ we can adjust between them by assuming that the initial outbreak of m_R is exponential[2]. Linearizing about the no-resistance initial condition, we find that the rate of exponential increase is $\beta m_X(0) - \gamma = \epsilon\tau$. Thus we can reach our empirical initial condition of $m_R(0) = \frac{\epsilon\tau}{\beta}$ over a time-scale of

$$T_{\text{shift}} = \frac{1}{\epsilon\tau} \log\left(\frac{\epsilon\tau}{\beta m_R(0)}\right). \tag{4.14}$$

Thus by shifting our time-to-outbreak by this empirical value we obtain the correct solution

$$\begin{aligned} T_{\text{mixed}} &= T_{\text{approx}} + T_{\text{shift}} \\ &= \frac{1}{\epsilon\tau} \ln\left(\frac{m_S(0)}{m_R(0)}\right) \approx \frac{1}{\epsilon\tau} \ln(\alpha N). \end{aligned} \tag{4.15}$$

This empirical solution matches our numerical simulations to a remarkable degree, as can be seen in Figure 4.2.

This estimate has two particularly attractive properties. First, it can be expressed in terms of only phase variables $m_R(0), m_S(0)$ along with total antibiotic use[3] $\epsilon\tau$. This makes it feasible to estimate from real-world data, though we do not do so here. Second, it is inversely dependent on $\epsilon\tau$. This means that we get *increasing* marginal returns when we decrease τ. Of course these returns must be balanced against the costs incurred: lower antibiotic use would likely be achieved by reducing prophylactic antibiotic use, which could result in life-threatening infections for some patients. These costs can be minimized by taking into account patient risk when prescribing prophylactic antibiotics (for example, the elderly are at greater risk and should perhaps receive more cautious prophylactic treatment). We discuss the possibilities for a risk-structured model of antibiotic use in Chapter 5, as well as some of the ethical concerns that might arise in practice.

4.2 A Weakly-Mixed Community: Early Dynamics

Of course in reality, antibiotic use is disproportionately concentrated in small populations such as hospitals. This highly concentrated antibiotic use gives

[2] This is actually a very common assumption in epidemiology, and it underlies any discussion of the basic reproductive number $\mathcal{R}_0$.

[3] Note that total antibiotic use gains a factor of ϵ because antibiotic use τ is concentrated in only an ϵ-fraction of the community.

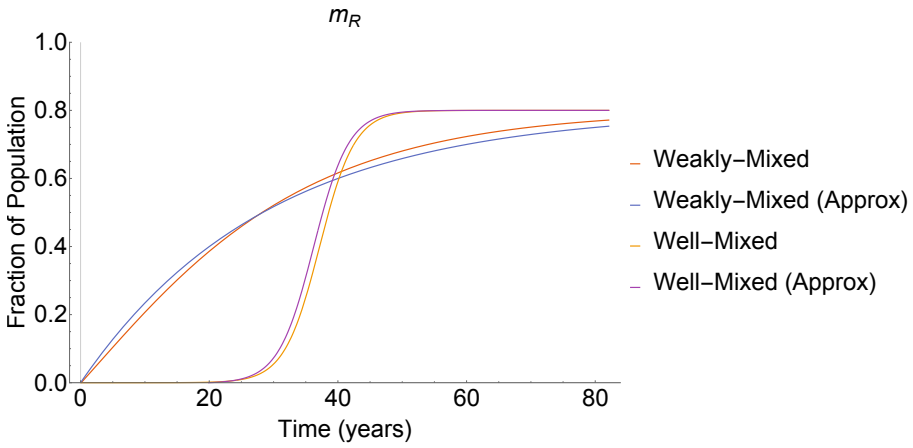

Figure 4.2 A comparison of our analytical approximations with numerical simulations for both the well-mixed (Section 4.1) and weakly-mixed cases (Sections 4.2 and 4.3). Generated with $\epsilon = 10^{-3}$, $\tau = 1$, $\beta = 0.5$, $\gamma = 1/10$, $N = 10^6$, and (for the weakly-mixed case) $\mu = 1/7$. The well-mixed approximation has been artificially offset to make the simulation beneath it more visible. We assume that the weakly-mixed case follows the T_{long} approximation for all time.

the resistant R-strain a marked advantage within the hospital. The hospital can then act as a source population: a sort of engine driving the community towards resistance. To examine this case we consider the full System 4.1:

$$\begin{aligned} S' &= \mu(m_S - S) + \beta SX - (\gamma + \tau)S & m_S' &= \epsilon\mu(S - m_S) + \beta m_S m_X - \gamma m_S \\ R' &= \mu(m_R - R) + \beta RX - \gamma R & m_R' &= \epsilon\mu(R - m_R) + \beta m_R m_X - \gamma m_R \\ X &= 1 - S - R & m_X &= 1 - m_S - m_R. \end{aligned}$$

In this system, the hospital (S, R, and X) is strongly coupled to the community (m_S, m_R, and m_X) but the community is only very weakly coupled to the hospital. This weak coupling gives us an opportunity to simplify the dynamics and obtain an analytical approximation. First however, let us make the following transformations,

$$t' = \beta t, \qquad m_Z = (1 - m_X) - \alpha, \qquad Z = (1 - X) - \alpha,$$

giving us (abusing notation to write $\mu = \mu/\beta$, $\tau = \tau/\beta$, and $\alpha = 1 - \gamma/\beta$)

$$\begin{aligned} \dot{S} &= \mu m_S - S(Z + \mu + \tau) & \dot{m}_S &= \epsilon\mu S - m_S(m_Z + \epsilon\mu) \\ \dot{R} &= \mu m_R - R(Z + \mu) & \dot{m}_R &= \epsilon\mu R - m_R(m_Z + \epsilon\mu). \end{aligned} \tag{4.16}$$

Now, since the community is only weakly coupled to the hospital, we can assume that the hospital is always instantaneously at equilibrium with the community. This allows us to treat m_S and m_R as slowly-varying parameters, giving us:

$$\begin{aligned} S &= \frac{\mu m_S}{Z + \mu + \tau} \\ R &= \frac{\mu m_R}{Z + \mu}. \end{aligned} \tag{4.17}$$

However in order to solve for these equilibria we need a value for Z. To find this note that $Z = S + R - \alpha$, which implies

$$\begin{aligned} 0 &= (Z + \alpha) - \frac{\mu m_S}{Z + \mu + \tau} - \frac{\mu m_R}{Z + \mu} \\ &= (Z + \alpha)(Z + \mu)(Z + \mu + \tau) - \mu m_S(Z + \mu) - \mu m_R(Z + \mu + \tau) \\ &= (Z + \mu)\big[(Z + \alpha)(Z + \mu + \tau) - \mu(m_R + m_S)\big] - \mu\tau m_R. \end{aligned} \tag{4.18}$$

Initially, m_R is very small. Setting $m_R = 0$ we find that $Z \approx -\mu$ is a solution to this equation. Since we know that R quickly reaches an appreciable value

in the hospital, we know that $Z + \mu$ must be on the same order as m_R so that $\frac{\mu m_R}{Z+\mu}$ can be between 0 and 1. If we assume this is the correct solution, we may set $Z = -\mu + \epsilon A$.

Plugging this into the polynomial above we find

$$m_R A[(\alpha - \mu + m_R A)(\tau + m_R A) - \mu(m_S + m_R)] - \mu\tau m_R = 0. \tag{4.19}$$

Neglecting second-order terms in m_R we can solve for

$$A = \frac{\mu\tau}{(\alpha - \mu)\tau - \mu m_S}. \tag{4.20}$$

Plugging this into our equations for S, R, and X we find that soon after resistance emerges

$$S \approx \frac{\mu m_S}{\tau}, \qquad R \approx (\alpha - \mu) - \frac{\mu m_S}{\tau}, \qquad X \approx 1 + \mu - \alpha.$$

This gives us (to first order in m_R), $S + R + X = 1$, confirming that this is a valid approximation. Note that in terms of our original parameters

$$S \approx \frac{\mu m_S}{\tau}, \qquad R \approx 1 - \frac{\gamma + \mu}{\beta} - \frac{\mu m_S}{\tau}, \qquad X \approx \frac{\gamma + \mu}{\beta}. \tag{4.21}$$

We can now plug these into our hospital equations to find how m_S and m_R vary. For simplicity, we will actually find how m_S and m_Z vary and define m_R implicitly as $m_R = \alpha + m_Z - m_S$. Consider

$$\begin{aligned} \dot{m}_Z &= \dot{m}_S + \dot{m}_R \\ &= \epsilon\mu(S + R) - (m_S + m_R)(m_Z + \epsilon\mu) \\ &\approx \epsilon\mu(\alpha - \mu) - (m_Z + \alpha)(m_Z + \epsilon\mu). \end{aligned} \tag{4.22}$$

Then m_Z will quickly reach the equilibrium point that solves

$$\begin{aligned} 0 &= (m_Z + \alpha)(m_Z + \epsilon\mu) - \epsilon\mu(\alpha - \mu) \\ &= m_Z^2 + (\alpha + \epsilon\mu)m_Z + \epsilon\mu^2, \end{aligned} \tag{4.23}$$

or

$$\begin{aligned} m_Z &= -\frac{1}{2}(\alpha+\epsilon\mu) \pm \frac{1}{2}\sqrt{(\alpha+\epsilon\mu)^2 - 4\epsilon\mu^2} \\ &= -\frac{1}{2}(\alpha+\epsilon\mu) \pm \frac{1}{2}(\alpha+\epsilon\mu)\sqrt{1 - 4\epsilon\frac{\mu^2}{(\alpha+\epsilon\mu)^2}} \\ &\approx -\frac{1}{2}(\alpha+\epsilon\mu) \pm \frac{1}{2}(\alpha+\epsilon\mu)\left(1 - 2\epsilon\frac{\mu^2}{(\alpha+\epsilon\mu)^2}\right) \\ &\approx -\frac{1}{2}(\alpha+\epsilon\mu) \pm \frac{1}{2}\left(\alpha+\epsilon\mu - 2\epsilon\frac{\mu^2}{\alpha}\right) \\ &\approx \begin{cases} -\epsilon\frac{\mu^2}{\alpha} \\ -\alpha - \epsilon\left(\mu - \frac{\mu^2}{\alpha}\right). \end{cases} \end{aligned}$$

Since the first root corresponds to a non-trivial solution for $m_S + m_R$ we select this solution. Calculating the dynamics of m_S we find that

$$\begin{aligned} \dot{m}_S &= \epsilon\mu S - m_S(m_Z + \epsilon\mu) \\ &\approx \epsilon\frac{\mu^2}{\tau}m_S - \epsilon\mu m_S\left(1 - \frac{\mu}{\alpha}\right) \\ &= -\epsilon\mu m_S\left(1 - \frac{\mu}{\alpha} - \frac{\mu}{\tau}\right). \end{aligned} \tag{4.24}$$

Rescaling by β and returning to our original dimensional parameter set, this gives us an approximate analytical solution of

$$m_S(t) = m_S(0)e^{-\epsilon\mu\left(1-\frac{\mu}{\alpha\beta}-\frac{\mu}{\tau}\right)t}. \tag{4.25}$$

and a characteristic time scale of

$$T_{\text{short}} = \frac{1}{\epsilon\mu}\left(1 - \frac{\mu}{\alpha\beta} - \frac{\mu}{\tau}\right)^{-1}. \tag{4.26}$$

This solution relies on numerous approximations: namely that the hospital dynamics are much faster than the community dynamics, and that both ϵ and m_R are very small. The approximation that m_R is very small will inevitably break down over time, but the other approximations are relatively robust. Simulations (such as those in Figure 4.2) show that when $T_{\text{short}} > 0$, our approximation is extremely accurate over the initial phase of an outbreak. For example, in one parameter set with $T_{\text{short}} \approx 38$ years,

this approximation remained valid for ≈ 3 years. In the next section we will derive an approximation for the late stages of an outbreak. In Section 4.4 we will discuss what happens when $T_{\text{short}} < 0$.

4.3 A Weakly-Mixed Community: Late Dynamics

Naturally over long time scales m_R will grow too large to use our approximations from Section 4.2. However, m_S will become small, so we will now consider this limit. Since $(\alpha - m_R)$ also becomes small, and this quantity plays a key role in our late-stage dynamics, we must also consider this small quantity. Then, using the same cubic polynomial as above (Equation 4.18)

$$(Z+\mu)[(Z+\alpha)(Z+\mu+\tau)-\mu(m_R+m_S)]-\mu\tau m_R = 0$$

we may set both of these quantities to linear functions of ϵ. Neglecting second-order terms in ϵ we obtain the solution

$$Z = \epsilon\mu\frac{\mu m_S - (\mu+\tau)(\alpha-m_R)}{(\mu+\alpha)(\mu+\tau)}. \tag{4.27}$$

This gives us

$$\begin{aligned} S &= \frac{\mu m_S}{Z+\mu+\tau} \approx \frac{\mu}{\mu+\tau}m_S \\ R &= \frac{\mu m_R}{Z+\mu} \qquad \approx m_R\left[1-\frac{\mu m_S-(\mu+\tau)(\alpha-m_R)}{(\mu+\alpha)(\mu+\tau)}\right]. \end{aligned} \tag{4.28}$$

This solution correctly gives $S+R-Z = \alpha + O(\epsilon^2)$ and is thus a valid approximation. Plugging these values back into our differential equations for m_S and m_R we find that

$$\begin{aligned} \dot{m}_Z &= \dot{m}_S + \dot{m}_R \\ &= \epsilon\mu(S+R) - (m_Z+\alpha)(m_Z+\epsilon\mu) \\ &= \epsilon\mu\left(\alpha + \frac{\mu m_S-(\mu+\tau)(\alpha-m_R)}{(\mu+\alpha)(\mu+\tau)}\right) - (m_Z+\alpha)(m_Z+\epsilon\mu) \\ &= -\left(m_Z^2 + (\alpha+\epsilon\mu)m_Z - \epsilon\mu^2\left(\frac{\mu m_S-(\mu+\tau)(\alpha-m_R)}{(\mu+\alpha)(\mu+\tau)}\right)\right). \end{aligned} \tag{4.29}$$

Analogous to our solution for m_Z above, this gives us a fast solution of

$$m_Z \approx -\frac{\epsilon\mu^2\alpha}{\mu+\alpha}. \tag{4.30}$$

Finally we may plug in our approximations for m_S and m_Z to our equation for $\dot{m}_S$ to find that

$$\begin{aligned}\dot{m}_S &= \epsilon\mu S - m_S(m_Z + \epsilon\mu) \\ &\approx \epsilon\mu\left(\frac{\mu}{\mu+\tau}m_S\right) - m_S\left(-\frac{\epsilon\mu^2\alpha}{\mu+\alpha} + \epsilon\mu\right) \\ &= -\epsilon\mu m_S\left(1 - \frac{\mu\alpha}{\mu+\alpha} - \frac{\mu}{\mu+\tau}\right). \end{aligned} \tag{4.31}$$

Thus, rescaling by β we find that over longer periods of time our system follows an approximate analytical solution of

$$m_S(t) = m_S(0)e^{-\epsilon\mu\left(1-\frac{\mu\alpha}{\mu+\alpha\beta}-\frac{\mu}{\mu+\tau}\right)}. \tag{4.32}$$

and a characteristic time scale of

$$T_{\text{long}} = \frac{1}{\epsilon\mu}\left(1 - \frac{\mu\alpha}{\mu+\alpha\beta} - \frac{\mu}{\mu+\tau}\right)^{-1}. \tag{4.33}$$

This time scale T_{long} is always strictly larger than T_{short}.

This gives us a far better approximation for long time scales. For a general comparison of our T_{long} approximation with numerical simulations see Figure 4.2. This result does not match our long-term numerical results as well as our T_{short} approximation matches short-term results. Nevertheless it is close enough to be useful. Moreover, in the next section we will derive a threshold value for μ past which our exponential results are invalid and we observe sigmoidal behavior. This is far preferable to the immediate-outbreak behavior we see in our weakly-mixed model. Reducing τ reduces this threshold value, and it is our hope that at the very least τ can be kept low enough to avoid the exponential outbreaks we have derived in these past two sections.

4.4 A Critical Value

Our T_{short} approximation is very accurate over short time-scales. However, if

$$\frac{\mu}{\alpha\beta} + \frac{\mu}{\tau} > 1,$$

or more simply if

$$\mu > \mu_{\text{crit}} = \frac{\tau}{1+\frac{\tau}{\alpha\beta}}, \tag{4.34}$$

then $T_{\text{short}} < 0$. Past this critical value, our exponential results are invalid and our system instead acts as though it were well-mixed. That is, when $\mu > \mu_{\text{crit}}$ our numerical solution for m_S qualitatively resembles the sigmoidal solutions derived in Section 4.1, although with a very different time-to-outbreak. This critical value thus gives us a way of measuring the mixedness of our system. Of course, as we increase μ to very large values our numerical solution for m_S approaches our well-mixed solution, as expected.

An equivalent way of obtaining this result is through direct application of the approximations from Section 4.2. Initially we found that

$$R \approx 1 - \frac{\mu + \gamma}{\beta} - \frac{\mu m_S}{\tau}.$$

This solution may be negative, leaving only the trivial solution for R. Intuitively, μ artificially deflates the hospital reproductive number $\mathcal{R}_0$, and past a certain point $\mathcal{R}_0 < 1$. In reality, of course, the cases being filtered away by μ are being added to the surrounding community rather than truly disappearing. To zero-th order in ϵ, $\mathcal{R}_0 < 1$ precisely when $\mu > \mu_{\text{crit}}$.

If $\mu_{\text{crit}} < \mu \ll \infty$ we obtain a sort of partially-mixed case. This case exhibits sigmoidal behavior, but we have been unable to approximate its time-to-outbreak T_{partial}. Moreover the relationship between T_{mixed} and the T_{partial} is not consistent: for values of μ close to μ_{crit} we find $T_{\text{partial}} < T_{\text{mixed}}$ but for some larger values $T_{\text{mixed}} < T_{\text{partial}}$. Since sigmoidal outbreaks are observed in practice, reality is likely to be partially-mixed, making an approximation for T_{partial} an important avenue for future work.

4.5 Adding Stochasticity

Although we omit a thorough analysis of all the effects of stochasticity on our model, we will offer a brief analysis of one simple stochastic problem: by how much does stochastic extinction delay the average outbreak?

It is easiest to do this with a well-mixed system, since the large population size of the community allows us to make useful approximations. First, we can modify our differential equations to a stochastic system. We will assume our time step Δt is small enough that the probability of more than one event happening in a single time step is negligible. We will also expand our non-dimensionalized population variables m_S and m_R to dimensional variables so that we can resolve the correct discrete steps. Then, letting N be the total population and $M_R = Nm_S, M_R = Nm_R, M_X = Nm_X = N - M_S - M_R$ our

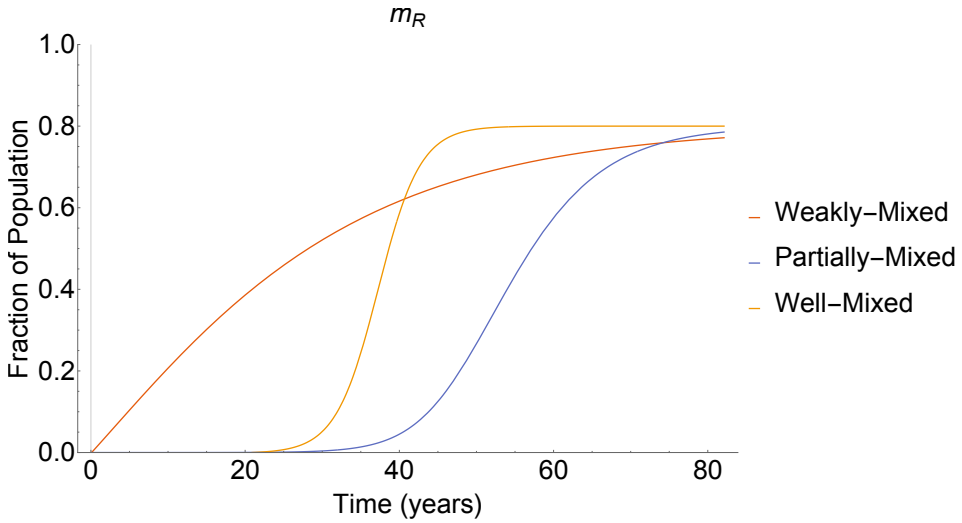

Figure 4.3 A comparison of our numerical simulations around the value of μ_{crit}. Generated with $\epsilon = 10^{-3}, \tau = 1, \beta = 0.5, \gamma = 1/10, N = 10^6$. The weakly-mixed curve has $\mu = \frac{1}{2}\mu_{\text{crit}}$. The partially-mixed curve has $\mu = 2\mu_{\text{crit}}$. The well-mixed curve is our analytical approximation for $\mu = \infty$.

transition probabilities become:

$$\mathbb{P}[\Delta M_S, \Delta M_R, \Delta t] = \begin{cases} \frac{\beta}{N} M_S M_X \Delta t & \Delta M_S = 1 \\ \frac{\beta}{N} M_R M_X \Delta t & \Delta M_R = 1 \\ (\gamma + \epsilon\tau) M_S \Delta t & \Delta M_S = -1 \\ \gamma M_R \Delta t & \Delta M_R = -1 \end{cases} \tag{4.35}$$

with the probability of no-change defined implicitly (as 1 minus the sum of the probabilities above). Using this system we will investigate the effect of stochastic emergence of resistance and die-off of resistance outbreaks on the time-to-endemicity.

Unfortunately, this is a non-linear system, which we lack the tools to directly deal with analytically. Instead, however, we can approximate the initial outbreak of resistance as linear by assuming $N \gg 1$ and thus that M_X remains approximately constant even as M_R grows. In fact this approximation should be very robust, since even in deterministic simulations with N relatively small (such as that in Figure 4.4) this approximation holds.

This gives us the system

$$\mathbb{P}[\Delta M_R, \Delta t] = \begin{cases} \frac{\beta}{N} M_R M_X(0) \Delta t & \Delta M_R = 1 \\ \gamma M_R \Delta t & \Delta M_R = -1. \end{cases} \tag{4.36}$$

From here we can calculate the probability of the outbreak event O, given an "initial" outbreak of $M_R = k$. This we can calculate to be

$$\begin{aligned} \mathbb{P}[O|M_R = k] &= \sum_{i \in \{-1,0,1\}} \mathbb{P}[\Delta M_R = i, \Delta t] \mathbb{P}[O|M_R = k + i] k \Delta t \\ \mathbb{P}[O|M_R = 0] &= 0 \\ \mathbb{P}[O|M_R = m] &= 1, \end{aligned} \tag{4.37}$$

where $m \leq N$ is the number of cases at which we declare an outbreak has occurred. Solving this recurrence gives

$$\mathbb{P}[O|M_R = k] = \frac{1 - \xi^k}{1 - \xi^m} \tag{4.38}$$

where

$$\xi = \frac{N\gamma}{\beta M_X(0)}.$$

Assuming that $\xi < 1$, $m \gg 1$, and $k \approx 1$ we can approximate this probability as

$$\mathbb{P}[O|M_R = k] \approx 1 - \xi^k. \tag{4.39}$$

Thus the probability that resistance outbreaks in the general community given that it emerged in one sick individual is roughly $1 - \xi$. This approximation is very accurate[4]. However we can often evaluate ξ more effectively, since the pre-outbreak fixed point is known to be

$$m_X(0) = \frac{M_X(0)}{N} = \frac{\gamma}{\beta} + \frac{\epsilon\tau}{\beta},$$

which gives us

$$1 - \xi = 1 - \frac{1}{1 + \frac{\epsilon\tau}{\gamma}} \approx \frac{\epsilon\tau}{\gamma}. \tag{4.40}$$

[4]We ran 1000 simulations with $1 - \xi = 1/1.1 \approx 0.909$. Each began with a single resistant individual and did not allow susceptible individuals to evolve resistance. After 4 years, 9.2% had outbroken, and after 8 years no further outbreaks had taken place.

Armed with this result we can evaluate the expected time to outbreak. Let r be the rate at which resistance evolves. Any particular evolution of resistance will lead to outbreak only with probability $\epsilon\tau/\gamma$. Thus the rate at which outbreak begins is $\epsilon\tau r/\gamma$. Note that this rate assumes that outbreaks are independent events. If N is sufficiently large and r is sufficiently small this is likely to be a good approximation.

This gives us an average time-to-outbreak of

$$\mathbb{E}[T_{\text{outbreak}}] \approx T_{\text{mixed}} + \frac{\gamma}{\epsilon\tau r}. \tag{4.41}$$

Evaluating r as we did in Chapter 3 to be

$$\begin{aligned} r &= k_M N r_M \\ &= k_M N(\epsilon\tau m_S) \\ &= k_M N(\epsilon\tau)\left(\alpha - \frac{\epsilon\tau}{\beta}\right) \\ &\approx k_M N(\epsilon\tau\alpha), \end{aligned} \tag{4.42}$$

we can then calculate the average-time-to-outbreak to be

$$\mathbb{E}[T_{\text{outbreak}}] \approx \frac{1}{\epsilon\tau}\ln(\alpha N) + \frac{\gamma}{(\epsilon\tau)^2 k_M N\alpha}. \tag{4.43}$$

It might at first seem that the new stochastic delay term is much larger than the T_{mixed} term, since $\epsilon^2 k_M$ may be very small, but we have good reason to believe that the T_{mixed} term may dominate. First, with N_H on the order of $10^2 - 10^3$ and N_C on the order of $10^5 - 10^6$, the term $\epsilon^2 N$ cancels to roughly order 1. This means that the stochastic term $\frac{1}{(1-\xi)r}$ scales primarily with $1/k_M$ which to our knowledge is not a well-studied parameter. However, resistance is often observed very soon[5] after an antibiotic is introduced. Since outbreak appears to occur over a time-scale of decades, we conclude that T_{mixed} is the dominant term.

In an attempt to verify our results numerically, we simulated the well-mixed system using the Gillespie stochastic simulation algorithm (SSA)[6]. An individual run of our stochastic simulation is shown in Figure 4.4 for comparison with the deterministic simulation. Note that the stochastic

[5] Usually within two years (Coates et al., 2011).

[6] In reality we simulated a slightly different system, in which the mutation process is included, so as to more correctly match our approximation.

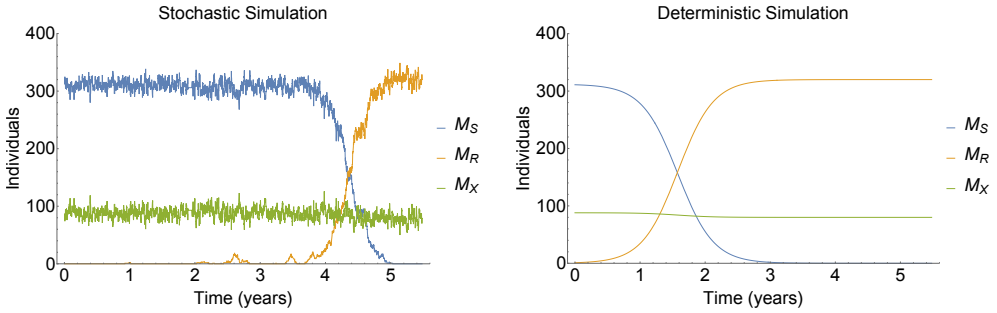

Figure 4.4 A comparison of our deterministic and stochastic simulations. Generated with $\epsilon = 10^{-2}$, $\tau = 1$, $\beta = 0.5$, $\gamma = 1/10$, $N = 400$. Stochastic simulation begins with $M_R = 0$ and assumes that with probability $k_M = 4 \times 10^{-3}$ that a patient in M_S who is treated with antibiotics will develop a resistant infection. The small value of N was necessary for timely evaluation of the Gillespie SSA.

simulation undergoes stochastic extinction several times[7] before undergoing true outbreak several years later. Further investigation is also needed into the width of the distribution of T_{outbreak}, which appears to be quite large in our simulations, though this may be an artifact of our small value of N.

In Figure 4.5 we show the percentage out of 100 simulations that have outbroken as a function of time[8]. The mean time-to-outbreak was roughly 1000 days. Since our deterministic model predicts a time-to-outbreak of 575 days, this evaluates to a stochastic delay of about 425 days. Our approximation predicts a stochastic delay of about 860 days. It is perhaps not surprising that our approximation is an overestimate; for time purposes we had to simulate on a system with unrealistically small N and unrealistically large k_M. This will tend to break the major assumption that individual outbreak events are independent. Thus while our result does correctly predict the order of magnitude of the stochastic delay, further investigation is needed into the accuracy of our estimated delay for realistic parameter sets.

[7] A detailed look at the simulation reveals that it undergoes stochastic extinction 6 times!

[8] Specifically, we plotted the percentage at which R has reached half of its endemic-state value.

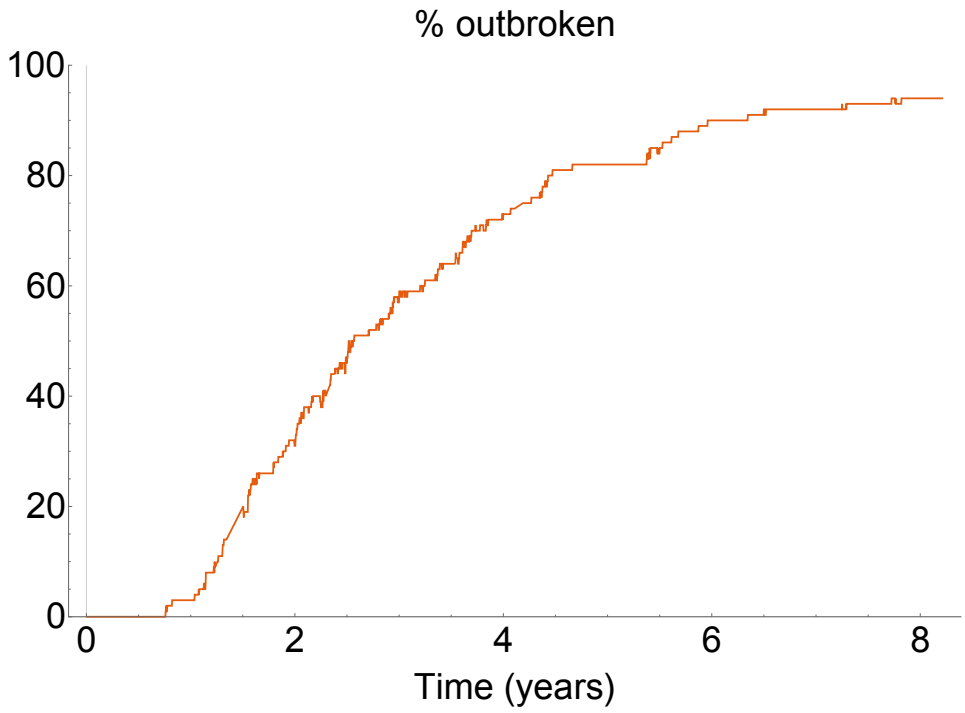

Figure 4.5 The percentage of simulations in which an outbreak has occurred as a function of time. Generated with $\epsilon = 10^{-2}$, $\tau = 1$, $\beta = 0.5$, $\gamma = 1/10$, $N = 400$ over 100 runs of the Gillespie SSA. Begins with $M_R = 0$ and assumes that with probability $k_M = 0.004$ a patient in M_S who is treated with antibiotics will develop a resistant infection. For these parameters our deterministic $T_{\text{mixed}} \approx 1.57$ years and a stochastic $T_{\text{outbreak}} \approx 3.71$ years.

4.6 Discussion

Above we derive approximate measures of time-to-outbreak for two simple deterministic models of antibiotic resistance. First, we assumed well-mixing between the hospital and the community and found that with an initially small population of resistant infections the emergence of resistance followed a sigmoidal pattern with outbreak time

$$T_{\text{approx}} = \frac{1}{\epsilon\tau} \ln\left(\frac{m_S(0)}{m_R(0)}\right).$$

Then, we relaxed this assumption and separated the hospital from the community. This allowed resistance to achieve rapid dominance in the hospital, turning the hospital into a source population and driving resistance back into the community. In this separated model, we found that the initial outbreak of resistance followed an exponential decay towards an endemic state, with characteristic time-scale

$$T_{\text{short}} = \frac{1}{\epsilon\mu}\left(1 - \frac{\mu}{\alpha\beta} - \frac{\mu}{\tau}\right)^{-1}.$$

The long-term outbreak followed the same qualitative behavior, but with a larger characteristic time-scale

$$T_{\text{long}} = \frac{1}{\epsilon\mu}\left(1 - \frac{\mu\alpha}{\mu+\alpha\beta} - \frac{\mu}{\mu+\tau}\right)^{-1}.$$

However, if

$$\mu > \frac{\tau}{1+\frac{\tau}{\alpha\beta}}$$

then we found that outbreaks no longer follow an exponential pattern. Instead, past this threshold even a coupled hospital-community system exhibits sigmoidal emergence. Since epidemiological studies have observed resistance following a sigmoidal emergence pattern we hypothesize that in most cases μ exceeds this threshold.

We can think of our weakly-mixed approximations as a sort of worst-case scenario. In these models, outbreak occurs immediately and there is little we can do to slow it down. Consider, for example our (contrived) example from

Chapter 3 of a high-traffic emergency room with the following parameters:

$$
\begin{aligned}
N_H &= 400 \\
N_C &= 400,000 \\
\mu &= \frac{1}{1.5}\ \text{day}^{-1} \\
\gamma &= \frac{1}{7}\ \text{day}^{-1} \\
\beta &= 1 \text{ infection per patient per day per fraction uninfected} \\
\tau &= 1 \text{ per day.}
\end{aligned}
$$

In this scenario on average every patient receives antibiotics every day (or half of all patients receive antibiotics twice a day, etc). This is of course far more than the calculated 3.5% optimum use. With these parameters

$$T_{\text{long}} = \frac{2}{3} \times 10^4 \text{ days} \approx 20 \text{ years.}$$

On the other hand a "best case scenario"[9] is embodied by T_{mixed}, which under these parameters comes out to almost 35 years. Note that T_{mixed} and T_{long} represent fundamentally different quantities. In the well-mixed case, the community will enjoy roughly 35 years of nearly resistance-free life, while in the weakly-mixed case resistance increases slowly but steadily over that time. Of course, neither scenario is sufficient for the needs of our medical system. We hope to rely on effective antibiotics for generations to come, but with characteristic time-scales of 20-35 years, resistance will be ubiquitous in less than a century.

In their current form these results are theoretical and not of great practical use in informing hospital policy. In particular, further analysis must be conducted on the stochastic properties of these systems, which we have only begun to address. Since there appears to already exist observational support for the rough validity of our results (the observed sigmoidal outbreak pattern mentioned above), it seems likely that with a few natural extensions this work could prove quite useful. More discussion on such extensions will be provided in Chapter 5.

[9] The partially-mixed case actually generates a larger time-to-outbreak for some intermediate values of μ. Estimating the optimal value for μ and the resulting time-to-outbreak is a potential avenue for further study.

Chapter 5

Conclusions and Future Work

In this thesis we extend previous work on antibiotic-use strategies and propose a new avenue of inquiry: slowing the outbreak of antibiotic resistance in the community. Previous work has analyzed the relative merits of cycling vs. mixing using a variety of models and methods. Such work has, however, generally neglected many important features of realistic hospital systems in order to simplify their analysis. Four of these notable features are the existence of more than two antibiotics, the stochastic dynamics of cycling protocols, the stochastic evolution of new resistance, and the dynamics of the surrounding community.

We have extended previous results to account for these four features, though much work still needs to be done on all of these topics. In particular, we found that:

- The existence of more than two antibiotics allows less-resistant strains to compete with more-resistant strains, lending some advantages to cycling.
- Stochastic local extinction lends significant advantages to cycling when attempting to control rare resistant strains.
- The stochastic evolution of new resistance can be accounted for relatively easily by calculating the expected value of the integral of a cost function over a time interval $[0, T]$.
- The outbreak of antibiotic resistance in the community can be delayed by decreasing τ, and particularly by ensuring that τ is low enough that $\mu_{\text{crit}} > \mu$.

Much further work still remains to be done to solidify our results and shape them into practical tools for hospital management. In the remainder of this chapter we will discuss the many different ways to extend the ideas presented in this thesis.

5.1 Extending Chapter 3

In Chapter 3 we concluded that cycling may hold significant advantages over mixing when attempting to control diverse populations of multiply-resistant strains. However, we presented little evidence of the generality of this claim, choosing instead to analyze the three-antibiotic case and generalize our results conceptually from there. A natural extension to our work would be to systematically test our claims in simulation. Such an extension might consider cases with higher numbers of antibiotics, or with varying levels of multiple-resistance present (i.e., a simulation in which perhaps R_{123} and R_{14} have evolved but R_{24} has not yet). It also remains to be shown the extent to which stochastic local extinction reduces the average prevalences of rare resistant strains under cycling vs. mixing.

We also hope to see $\mathbb{E}[C]$ optimized for more realistic systems. This would inevitably increase the complexity of our models, so that $\mathbb{E}[C]$ would have to be optimized numerically. For example, with varying levels of multiple-resistance one would have to account for multiple possible evolution contingencies. However, provided sufficient computational power, this method should be flexible enough to deal with relatively realistic scenarios.

5.2 Extending Chapter 4

In order to obtain analytic results in Chapter 4 we constructed a simple model that captured the behavior we wished to study. Much like previous models of antibiotic-use strategies, this model relied on a number of assumptions. While we hope these assumptions are accurate enough for our results to have some theoretical legitimacy, many of them could be relaxed to obtain more realistic results. For example:

- The rate of antibiotic use will likely vary between patients. Symptomatic patients will receive more aggressive antibiotic treatment, while asymptomatic patients may merely be given prophylactic antibiotics.

- The rate of admission/discharge μ may also be dependent on symptoms. Symptomatic patients in the m_S or m_R class will be more likely to enter the hospital, since they could be hospitalized as a result of their infection. Likewise, symptomatic patients in the S or R class will be less likely to exit the hospital[1].

- The infection rate β may be different in a hospital. Patients are vulnerable to infection, which will tend to increase β, but hygiene standards are better which will tend to decrease β.

- The immune clearance rate γ may be lower in a hospital, since patients are immune-compromised.

Relaxing the first two assumptions would be relatively difficult, since we would have to add several additional compartments to account for symptomatic/asymptomatic infections. This does not lessen these importance of accounting for the effects, but it is worth noting that relaxing the last two assumptions would be fairly easy, and would only require us to reset a few parameter values within our existing model.

Additionally, as we noted in Chapter 4 the largest time-to-outbreak in our model actually occurs somewhere in the partially-mixed regime. Though we have been unable to find a tractable analytic approximation for this regime, this is a potential avenue for future study.

Finally we could extend our work in Chapter 4 by looking at multiple antibiotics. As we saw in Chapter 3, behavior can change dramatically when we add additional antibiotics to our system, even in the absence of substantive changes to the rest of our model. Adding a second antibiotic would also allow us to study the effect of cycling vs. mixing on the time-to-outbreak for new resistance.

In fact, once multiple antibiotics have been added to our model, we could combine the work of Chapters 3 and 4. In Section 3.4 we optimized $\mathbb{E}[C]$ by assuming that $m_R = 0$ throughout our period-of-interest. However in Chapter 4 we relaxed that assumption and examined how m_R might change with time. This could naturally be incorporated into our $\mathbb{E}[C]$ framework to obtain a more realistic result. In fact, by extending our community-hospital model to large numbers of antibiotics, integrating it with our $\mathbb{E}[C]$ framework, and parameterizing it with real-world data we could potentially construct a model of real practical use to hospital administrators. It is our hope that

[1] For example, patients infected with MRSA have stays on average almost 1.3 times as long as those infected with the antibiotic-susceptible strains, MSSA (Cosgrove et al., 2005)

eventually this sort of model is built and is able to help inform practical hospital policy.

5.3 Integrating Stochasticity

Both Chapters 3 and 4 are based primarily on deterministic simulations. However, stochasticity plays an important role in both systems. As we saw in Chapter 3, small hospital sizes can lead to large stochastic variations. Moreover, in the context of a cycling strategy, where deterministic variation is already occurring, these stochastic variations have the potential to encourage stochastic extinction of rare strains. Estimating the importance of this effect for controlling multiple-resistance in hospitals will be a crucial area for future research.

More work is also needed on the effect of stochasticity on time-to-outbreak, particularly given the wide range of outbreak times shown in our stochastic simulations. Is this wide range due to the small population sizes we were forced to simulate for computational feasibility, or is it fundamental to the system? In either case, future work should follow (Cooper et al., 2004) and search for ways to utilize stochasticity to slow or prevent outbreaks. For example, if macro-scale outbreaks are triggered by a relatively small stochastic upticks in frequences, monitoring efforts could detect these stochastic upticks in the hopes of suppressing the outbreak before it happens — perhaps through the use of temporary isolation wards.

5.4 Risk-Structured Models

One final possibility not yet represented in the literature is the possibility of grouping the population based on risk. For example, combination therapy[2] is highly advantageous to the individual patient. Since some patients have more vulnerable immune systems than others, it might make sense to treat these patients using combination therapy. By stratifying the population based on individual risk level we could potentially shift use of prophylactic antibiotics more heavily onto those most in need, while simultaneously reducing prophylactic antibiotic treatment on those with healthier immune systems. The former change would have the effect of saving more lives, while the latter would reduce selection for resistance. Hopefully these two

[2]Discussed in Chapter 1. Under combination therapy a single patient receives multiple antibiotics simultaneously.

would combine in order to, on net, save more lives *and* slow emergence of new resistance.

This approach will be much closer to reality (Weinstein, 1998) than models which assume a homogeneous population. Further, the problem formulation is conducive to translation into a stochastic, individual-based model. This type of model would be particularly useful, because it could help provide insight into what thresholds doctors should use when determining which patients to assign combination therapies to, and which patients to avoid assigning unnecessary antibiotics to.

In the latter case — where some patients do not receive prophylactic care — it is important that physicians are trained to be aware of their own implicit biases. Implicit bias in healthcare has been repeatedly shown to be a serious concern (Green et al., 2007; Teachman and Brownell, 2001). If we implement a system where some patients receive prophylactic care while others do not, the possibility of racial and other biases is not just present, it is overwhelming. A quantitative system, carefully constructed with an awareness of the implicit biases already encoded in existing medical data, might be recommended to partially circumvent the many problems that arise when decisions are left to the discretion of human beings who are unfortunately but inherently biased.

Bibliography

Austin, Daren J, Marc JM Bonten, Robert A Weinstein, Sarah Slaughter, and Roy M Anderson. 1999a. Vancomycin-resistant enterococci in intensive-care hospital settings: Transmission dynamics, persistence, and the impact of infection control programs. *Proceedings of the National Academy of Sciences* 96(12):6908–6913.

Austin, Daren J, Karl G Kristinsson, and Roy M Anderson. 1999b. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proceedings of the National Academy of Sciences* 96(3):1152–1156.

Beggs, Clive B, Catherine J Noakes, Simon J Shepherd, Kevin G Kerr, P Andrew Sleigh, and Katherine Banfield. 2006. The influence of nurse cohorting on hand hygiene effectiveness. *American Journal of Infection Control* 34(10):621–626.

Bergstrom, Carl T, Monique Lo, and Marc Lipsitch. 2004. Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. *Proceedings of the National Academy of Sciences of the United States of America* 101(36):13,285–13,290.

Chow, Karen, Xiaohong Wang, Roy Curtiss III, and Carlos Castillo-Chavez. 2011. Evaluating the efficacy of antimicrobial cycling programmes and patient isolation on dual resistance in hospitals. *Journal of Biological Dynamics* 5(1):27–43.

Coates, Anthony RM, Gerry Halls, and Yanmin Hu. 2011. Novel classes of antibiotics or more of the same? *British Journal of Pharmacology* 163(1):184–194.

Cooper, Ben S, Graham F Medley, and Geoffrey M Scott. 1999. Preliminary analysis of the transmission dynamics of nosocomial infections: Stochastic and management effects. *Journal of Hospital Infection* 43(2):131–147.

Cooper, Ben S, Graham F Medley, Sheldon P Stone, Christopher C Kibbler, Barry D Cookson, Jennifer A Roberts, Georgia Duckworth, Rosalind Lai, and Shah Ebrahim. 2004. Methicillin-resistant Staphylococcus aureus in hospitals and the community: Stealth dynamics and control catastrophes. *Proceedings of the National Academy of Sciences of the United States of America* 101(27):10,223–10,228.

Cosgrove, Sara E, Youlin Qi, Keith S Kaye, Stephan Harbarth, Adolf W Karchmer, and Yehuda Carmeli. 2005. The impact of methicillin resistance in Staphylococcus aureus bacteremia on patient outcomes: Mortality, length of stay, and hospital charges. *Infection Control & Hospital Epidemiology* 26(02):166–174.

Crowcroft, Natasha S, and Mike Catchpole. 2002. Mortality from methicillin resistant Staphylococcus aureus in England and Wales: Analysis of death certificates. *BMJ* 325(7377):1390–1391.

D'Agata, Erika MC, Pierre Magal, Damien Olivier, Shigui Ruan, and Glenn F. Webb. 2007. Modeling antibiotic resistance in hospitals: The impact of minimizing treatment duration. *Journal of Theoretical Biology* 249(3):487 – 499. doi:http://dx.doi.org/10.1016/j.jtbi.2007.08.011. URL http://www.sciencedirect.com/science/article/pii/S0022519307003943.

Goossens, Herman, Matus Ferech, Robert Vander Stichele, Monique Elseviers, ESAC Project Group, et al. 2005. Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. *The Lancet* 365(9459):579–587.

Green, Alexander R, Dana R Carney, Daniel J Pallin, Long H Ngo, Kristal L Raymond, Lisa I Iezzoni, and Mahzarin R Banaji. 2007. Implicit bias among physicians and its prediction of thrombolysis decisions for black and white patients. *Journal of General Internal Medicine* 22(9):1231–1238.

Kardas, Przemyslaw, Scott Devine, Amanda Golembesky, and Craig Roberts. 2005. A systematic review and meta-analysis of misuse of antibiotic therapies in the community. *International Journal of Antimicrobial Agents* 26(2):106–113.

Kumarasamy, Karthikeyan K, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fafhana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, et al. 2010. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. *The Lancet Infectious Diseases* 10(9):597–602.

Larson, Elaine L, and Edna K Kretzer. 1995. Compliance with handwashing and barrier precautions. *Journal of Hospital Infection* 30:88–106.

Levin, Bruce R, and Marc JM Bonten. 2004. Cycling antibiotics may not be good for your health. *Proceedings of the National Academy of Sciences of the United States of America* 101(36):13,101–13,102.

Levin, Bruce R, Véronique Perrot, and Nina Walker. 2000. Compensatory mutations, antibiotic resistance and the population genetics of adaptive evolution in bacteria. *Genetics* 154(3):985–997.

Lipsitch, Marc, Carl T Bergstrom, and Bruce R Levin. 2000. The epidemiology of antibiotic resistance in hospitals: Paradoxes and prescriptions. *Proceedings of the National Academy of Sciences* 97(4):1938–1943.

Magill, Shelley S, Jonathan R Edwards, Zintars G Beldavs, Ghinwa Dumyati, Sarah J Janelle, Marion A Kainer, Ruth Lynfield, Joelle Nadle, Melinda M Neuhauser, Susan M Ray, et al. 2014. Prevalence of antimicrobial use in US acute care hospitals, May-September 2011. *JAMA* 312(14):1438–1446.

Mathew, Alan G, Robin Cissell, and S Liamthong. 2007. Antibiotic resistance in bacteria associated with food animals: A United States perspective of livestock production. *Foodborne Pathogens and Disease* 4(2):115–133.

Obolski, Uri, and Lilach Hadany. 2012. Implications of stress-induced genetic variation for minimizing multidrug resistance in bacteria. *BMC Medicine* 10(1):89.

Obolski, Uri, Gideon Y Stein, and Lilach Hadany. 2015. Antibiotic restriction might facilitate the emergence of multi-drug resistance. *PLoS Comput Biol* 11(6):e1004,340.

Peña Miller, Rafael, and Robert Beardmore. 2010. Antibiotic cycling versus mixing: The difficulty of using mathematical models to definitively quantify their relative merits. *Mathematical Biosciences & Engineering* 7(4):923–933.

Scanvic, Agnes, Ljiljiana Denic, Stéphanie Gaillon, Pascal Giry, Antoine Andremont, and Jean-Christophe Lucet. 2001. Duration of colonization by methicillin-resistant Staphylococcus aureus after hospital discharge and risk factors for prolonged carriage. *Clinical Infectious Diseases* 32(10):1393–1398.

Schrag, Stephanie J, and Véronique Perrot. 1996. Reducing antibiotic resistance. *Nature* 381(6578):120.

Teachman, Bethany A, and Kelly D Brownell. 2001. Implicit anti-fat bias among health professionals: Is anyone immune? *International Journal of Obesity & Related Metabolic Disorders* 25(10).

Weinstein, Robert A. 1998. Nosocomial infection update. *Emerging Infectious Diseases* 4(3):416.

Zachar, István. 2017. Gillespie stochastic simulation algorithm. Mathematica. URL https://mathematica.stackexchange.com/q/119786/.

zur Wiesch, Pia Abel, Roger Kouyos, Sören Abel, Wolfgang Viechtbauer, and Sebastian Bonhoeffer. 2014. Cycling empirical antibiotic therapy in hospitals: Meta-analysis and models. *PLoS Pathog* 10(6):e1004,225.