Simple Models of Antibiotic Cycling

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December 30, 2004
Running title: Antibiotic cycling
Key words: heterogeneous environments, resistance management

Abstract

The use of environmental heterogeneity is an old but potentially powerful method for managing biological systems. Determining the optimal form of environmental heterogeneity is a difficult problem. One family of heterogeneous management strategies that has received attention in the medical community is the periodic cycling of antibiotic usage to control antibiotic resistance. This paper presents a theory for the optimization of antibiotic cycling based on a density independent model of transmission and immigration of evolutionarily static strains. In the case of two pathogen strains, I show that the population's asymptotic growth rate is a monotonically increasing function of the oscillation period under certain common assumptions. Monte Carlo simulations show that this result fails in more general settings, but suggest that antibiotic cycling seldom provides a significant improvement over alternative mixing practices. The results support the findings of other researchers that antibiotic cycling does not offer significant advantages over idealized conventional practice. However, cycling strategies may be preferable in some special cases.

1 Introduction

The spatial and temporal fluctuations of a population's environment are collectively referred to as environmental heterogeneity. Environmental heterogeneity complicates our understanding of biological systems. Ecologists have worked hard to untangle the interactions between environmental heterogeneity and ecological processes (Shorrocks & Swingland, 1990; Kolasa & Pickett, 1991; Hutchings *et al.*, 2000). Heterogeneity can effect population demography (Henson & Cushing, 1997; Coale, 1972), population viability (Beissinger, 1995), life history strategy (Brommer *et al.*, 2000), and evolution (McPeek & Holt, 1992; Hutson *et al.*, 2001; Frank & Slatkin, 1990). Environmental heterogeneity also attracts the interest of population geneticists as a possible factor in polymorphism maintenance (Kirzhner *et al.*, 1998; Hedrick, 1986; Felsenstein, 1976).

Environmental heterogeneity may play an important role in managing the evolution of antibiotic resistance. While the emergence of drug resistance is a general problem in medicine, antibiotic resistance in hospital-acquired infections deserves special attention. The incidence of resistance in hospital-acquired infections is much higher than observed in community-acquired infections (Monnet *et al.*, 1998). Antibiotic-resistant infections have been shown to increase mortality rates (Raymond *et al.*, 2003) and reduce treatment efficacy in hospitals (Niederman, 2001). The heavy use of antimicrobial agents in hospitals imposes strong selective pressures on resident bacterial flora and has lead to the emergence of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and other difficult-to-treat bacterial infections (Gaynes, 1997). Faced with the growing prevalence of antibiotic resistance, the medical community is reevaluating approaches to antibiotic usage.

The conventional approach to antibiotic usage in hospitals is a decentralized policy. Patients are prescribed antibiotics at the physician's discretion, and no efforts are made to coordinate treatment among patients. It is not uncommon for two patients with the same diagnosis to receive different treatments, and no temporal or spatial restrictions are placed on the availability of treatments. This decentralized approach to antibiotic usage is popularly referred to as a mixing strategy because of the variety of treatments in use at any one time. Mixing should not be confused with combination treatments, where individual patients may receive two or more treatments simultaneously. Throughout this paper, it is assumed that a given patient is never treated with more than one antibiotic. Ideally, treatment patterns in mixing strategies are free of spatial and other correlations. These correlations are certainly present in practice. There are several measures under consideration for decreasing treatment correlation effects (Fridkin, 2003), but the analysis of these effects falls outside the scope of this paper.

Cycling strategies have been proposed as alternatives to mixing strategies (Kollef *et al.*, 1997; Kollef, 2003; Hodges & White, 2001). Antibiotic cycling strategies periodically rotate treatments in and out of usage, and place minor restrictions upon which treatments are available for use at a given time. While mixing strategies are characterized by spatial heterogeneity in patient treatments, cycling strategies are characterized by temporal heterogeneity.

Do mixing strategies and cycling strategies affect management problems differently? Both the cycling and mixing strategies introduce heterogeneity into the environment of pest organisms. If environmental heterogeneity limits the efficiency of reproduction, both strategies seem likely to limit the abundance of pest species. Beyond this point, my intuition fails. It is unclear if cycling strategies or mixing strategies offer more effective management. The problem of determining the optimal environmental heterogeneity will be referred to as the "cycling problem" in this paper.

Existing theoretical work on the cycling problem argues that mixing strategies outperform all other strategies, but only provides empirical evidence to this effect. Bonhoeffer *et al.* (1997) and Bergstrom *et al.* (2004) use numerical simulation with random samplings of the feasible parameter space as grounds for preferring mixing strategies. While some medical studies suggest that cycling strategies are not harmful (Dominguez *et al.*, 2000) and may improve on mixing strategies (Gruson *et al.*, 2003), consensus opinion appears to favor mixing strategies.

We seldom need reasons to be wary of consensus, but in this case there are two. First, the work Salo & Tahvonen (2002) provides a preliminary example where cyclic solutions describe the optimal usage of a renewable resource. Second, the dynamics of a periodically forced system can, in general, depend in a complex way on the pattern of forcing. An important classical example is the second-order linear

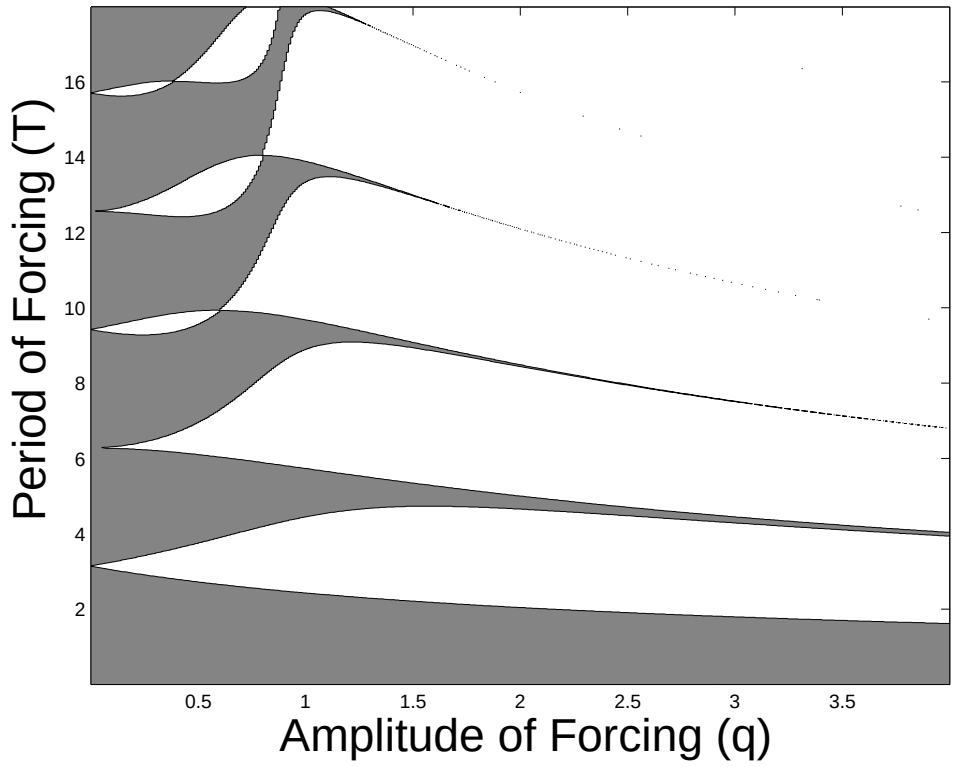

Figure 1: Lagrange stable regions of the Meissner equation, Eq. (1.1), as a function of the forcing amplitude q and the forcing period $T = t_1 + t_2$ with equal phase periods ($t_1 = t_2$). Asymptotically unbounded solutions can only exist in the unshaded region.

non-autonomous differential equation known as the Meissner equation (Richards, 1983; Arscott, 1964),

$$\frac{d^2x}{dt^2} + \{1 + qu(t) - q\,[1 - u(t)]\}\,x = 0, \tag{1.1}$$

$$\text{where} \quad u(t) = \begin{cases} 0 & \text{if } 0 \le t \bmod (t_1 + t_2) < t_1, \\ 1 & \text{if } t_1 \le t \bmod (t_1 + t_2) < t_1 + t_2, \end{cases}. \tag{1.2}$$

The system is forced with amplitude q for a positive phase with period t_1 and a negative phase with period t_2, for a total period $T = t_1 + t_2$. The notation "a mod b" stands for the remainder of a divided by b. Mechanically, the Meissner equation describes a frictionless mass-spring system where the fixed end of the spring oscillates according to a square wave. Eq. (1.1) resembles the biologically motivated models I will discuss in this paper. The interaction strengths are set by the underlying biology, but the phase periods t_1 and t_2 may vary with the management strategy.

When $t_1 = t_2$, the $q \times T$ parameter space is divided into Lagrange stable regions, where the solution is asymptotically bounded, and resonate regions, where solutions can grow exponentially (see Fig. 1). For small amplitudes q, solutions are only unstable for resonance horns with periods near the integer multiples of π. If we fix the forcing amplitude at $q = 1/2$, we observe that the stability of solutions is an oscillatory function of the phase periods t_1 and t_2 (see Fig. 2). The Meissner equation shows that a periodically forced system can be sensitive to the pattern of forcing it experiences.

In this paper, I will approach the cycling problem using an immigration–selection model of evolutionarily static strains of infection, with density-independent growth and the objective of minimizing the population's asymptotic growth rate. Minimization of population growth is similar to the

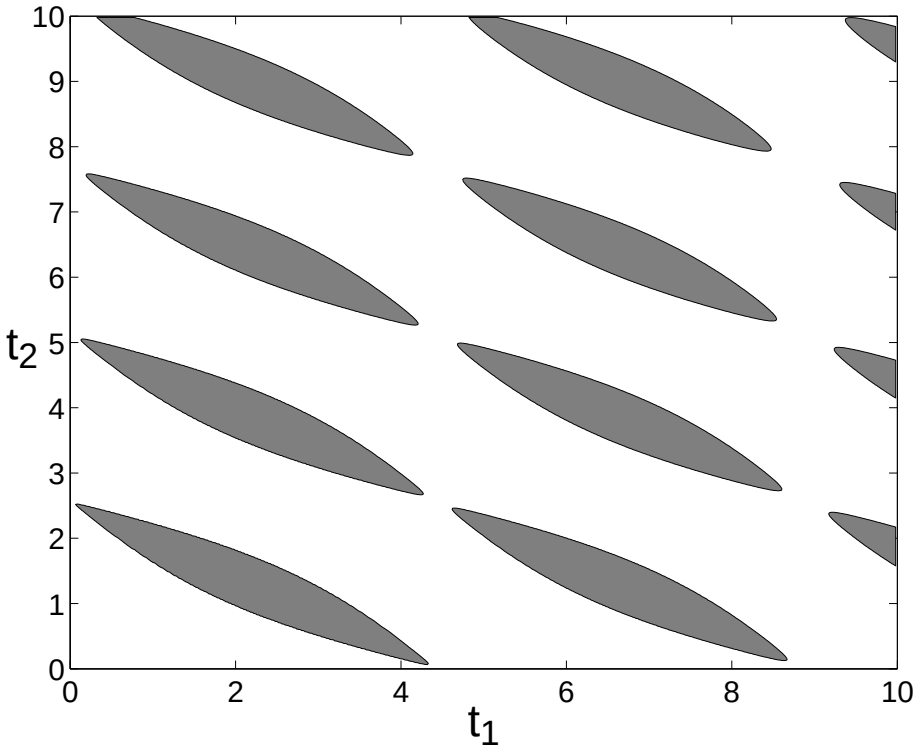

Figure 2: Lagrange stable regions of the Meissner equation, Eq. (1.1), as a function of the phase periods t_1 and t_2, when the amplitude $q = 1/2$. Asymptotically unbounded solutions can only exist in the shaded region.

minimization of mean fitness in a nonlinear quasi-species equation (Eigen, 1971; Nowak, 1992), but computationally more convenient. The study of density-independent models provides insight into the potential complexity of solutions to the general cycling problem. For general density-independent immigration–selection models, solutions to the cycling problem must be obtained on a case-by-case basis. There are, however, special cases where we can construct exact or approximate general principles for solution of the cycling problem. In the special case of two types with autonomous, symmetric immigration rates, faster cycling results in slower growth rates. I will also show that for immigration–selection models, spatial heterogeneity in the form of mixing strategies is similar to infinitely rapid environmental cycling. Thus, there is at least one class of models where cycling strategies are always outperformed by mixing strategies. Numerical simulations show that, for more general problems, the specific form of this result fails. These results suggest that, in general, it is rare to find a globally optimal cycling strategy that significantly outperforms an optimal mixing strategy.

The models in this paper rely on the theory of first order systems of linear differential equations, and I make use of Floquet theory, matrix algebra, and standard numerical methods in my analysis. The models are presented in the context of antibiotic resistance management, but are also applicable in general pest management settings.

In Section 2, I present a numerical investigation of cycling in a simplification of the Lipsitch–Bergstrom model. In Section 3, I construct two general immigration–selection matrix models. In Section 4, I analyze the case of antibiotic cycling between two drugs with two strains of infection, and constructively demonstrate that the asymptotic growth rate is an increasing function of the cycling period. In this special case, mixing strategies will always perform better than the equivalent cycling strategies, and I further demonstrate the existence of an optimal mixing strategy. In Sections 5 and 6, I discuss the extension of the immigration–selection model to an arbitrary number of strains. Section 5 shows that, in the absence of immigration, the asymptotic growth rate is independent of the cycling period. Section 6 presents another mixing optimality result for multiple strains with a 2-phase strategy when immigration is symmetric. Numerical counterexamples to mixing optimality under general conditions are presented in Section 7 for the cases of autonomous, asymmetric immigration and non-autonomous, symmetric immigration. I conclude with a summary of the results and a discussion of the effects of management strategy on the evolution of drug resistance.

2 A Reduced Lipsitch–Bergstrom Model

Lipsitch & Bergstrom (2002) have developed a useful model for the study of antibiotic resistance in an intensive care unit. The Lipsitch–Bergstrom model is a system of coupled differential equations that describes admittance and discharge of hospital patients while there is ongoing competition among a wild-type bacteria and two strains of antibiotic-resistant bacteria treatable with alternate antibiotics. Specifically, the general Lipsitch–Bergstrom model is a mass–action chemostat equation

$$\dot{S} = \mu\left(m_S - S\right) + \gamma_1 I_1 + \gamma_2 I_2 + \gamma_{12} I_{12} - \left(\beta_1 I_1 + \beta_2 I_2 + \beta_{12} I_{12}\right) S, \tag{2.1}$$

$$\dot{I}_{12} = \mu\left(m_{12} - I_{12}\right) - \gamma_{12} I_{12} + \left[\beta_{12} S + \sigma\left(\beta_{12} - \beta_1\right) I_1 + \sigma\left(\beta_{12} - \beta_2\right) I_2\right] I_{12}, \tag{2.2}$$

$$\dot{I}_1 = \mu\left(m_1 - I_1\right) - \gamma_1 I_1 + \left[\beta_1 S + \sigma\left(\beta_1 - \beta_2\right) I_2 + \sigma\left(\beta_1 - \beta_{12}\right) I_{12}\right] I_1, \tag{2.3}$$

$$\dot{I}_2 = \mu\left(m_2 - I_2\right) - \gamma_2 I_2 + \left[\beta_2 S + \sigma\left(\beta_2 - \beta_1\right) I_1 + \sigma\left(\beta_2 - \beta_{12}\right) I_{12}\right] I_2. \tag{2.4}$$

The state variables I_j represent the abundance of colonized patients treatable with antibiotics 1 (I_1), 2 (I_2), or both antibiotics 1 and 2 (I_{12}), and the state variable S represents the abundance of uncolonized patients. Parameters $m_j \geq 0$ are the relative abundance of uncolonized individuals ($j = S$) or colonized individuals treatable with antibiotics $j \in \{12, 1, 2\}$ in community being serviced by the hospital such that $m_S + m_{12} + m_1 + m_2 = 1$. The parameter $\mu \geq 0$ is the "dilution rate", representing the rate at which individuals are admitted and discharged from the hospital. Parameters $\beta_j \geq 0$ are colonization rates of strains treatable with antibiotics $j \in \{12, 1, 2\}$. Parameters γ_j are the rates at which individuals are cleared from infected state I_j to the susceptible state S either spontaneously or by treatment. In the Lipsitch–Bergstrom model, it is assumed that $\gamma_{12} \geq \gamma_1 \geq 0$ and $\gamma_{12} \geq \gamma_2 \geq 0$. The parameter $\sigma \in [0, 1]$ is the probability that one strain can displace another.

To facilitate the analytical analysis of the cycling problem, we assume the following: (1) all colonized patients receive one of two antibiotics, 1 or 2, both of which are effective against the wild-type bacteria so that the level of universally treatable patients I_{12} is constant, (2) neither antibiotic is generally preferable to the other, and (3) the two strains of resistant bacteria are the same except for their resistance to opposite antibiotics. Under these assumptions, the dynamic equations for the expected abundance of patients colonized with bacteria resistant to antibiotic 1 (I_1) and bacteria resistant to antibiotic 2 (I_2) from the Lipsitch–Bergstrom model reduce to a Lotka–Volterra model with immigration,

$$\frac{dI_1}{dt} = m + I_1\left(1 - I_1 - I_2\right) - \gamma u(t) I_1, \tag{2.5}$$

$$\frac{dI_2}{dt} = m + I_2\left(1 - I_1 - I_2\right) - \gamma\left[1 - u(t)\right] I_2, \tag{2.6}$$

where m is the admittance rate of colonized patients, $u(t)$ is the fraction of patients treated with antibiotic 2, $1 - u(t)$ is the fraction of patients treated with antibiotic 1, and γ is the clearance rate when patients receive effective treatment. One potential goal of management may be to minimize the asymptotic average infection level

$$J = \lim_{T\to\infty} \frac{1}{T} \int_0^T I_1(t) + I_2(t) dt. \tag{2.7}$$

Equations closely related to Eqs. (2.5)-(2.7) were first studied by Rowthorn & Brown (2003) as an optimal control problem. Rowthorn & Brown were only able to provide a partial solution because the equations fail to satisfy certain sufficient convexity conditions (Arrow & Kurz, 1970). The same difficulty would arises here if we employed an optimal-control approach, but some enlightenment can be found by numerically investigating the performance of periodic 2-phase bang-bang control strategies. Bang-bang controls are controls that only take on extreme values. In our case, the controls may only take values 0 or 1. Let $u(t)$ be defined by Eq. (1.2). Numerical experiments indicate that optimal management occurs in the limit as $T = t_1 + t_2 \to 0$, with $t_1 = t_2$ (see Figures 3 and 4). This strategy of infinitely rapid cycling appears to be equivalent to a mixed control strategy with $u(t) = 1/2$. Biologically, the mixing strategy should be interpreted as treating half the new cases with one of the drug and half with the other drug, not as each patient being treated with a combination of the two drugs. All mixing strategies should be interpreted similarly.

The above results are consistent with the findings of Rowthorn & Brown and with studies of Lipsitch & Bergstrom (2002). However, the asymptotic average infection level J generally depends upon the system's initial condition, and I have been unable to prove the existence of a unique, globally attracting periodic solution for arbitrary control strategies in Eqs. (2.5)-(2.6). Thus, although no difficulties with non-uniqueness were observed in my numerical experiments, the results have not been rigorously confirmed.

3 Matrix Models

The complexity associated with even the reduced Lipsitch–Bergstrom model make it difficult to intuitively understand when and why mixing strategies appear preferable to cycling strategies. To illuminate this question, we turn to the simplest non-trivial scenario, that of a linear immigration–selection models. This section derives two forms of an immigration–selection model I will use in this paper.

When populations are small enough to grow independent of resource and interaction constraints, their growth may be approximately described by a Bellman–Harris branching process (Athreya & Ney, 1972). If an appropriate time scale is used and event rates are age-independent, the branching process will be a Poisson process. Standard techniques (Athreya & Ney, 1972) show that under these assumptions, the rates of change in the expected abundances I_i of individuals of type i satisfy the linear equation

$$\dot{I}_i = \sum_j q_{ij} I_j, \tag{3.1}$$

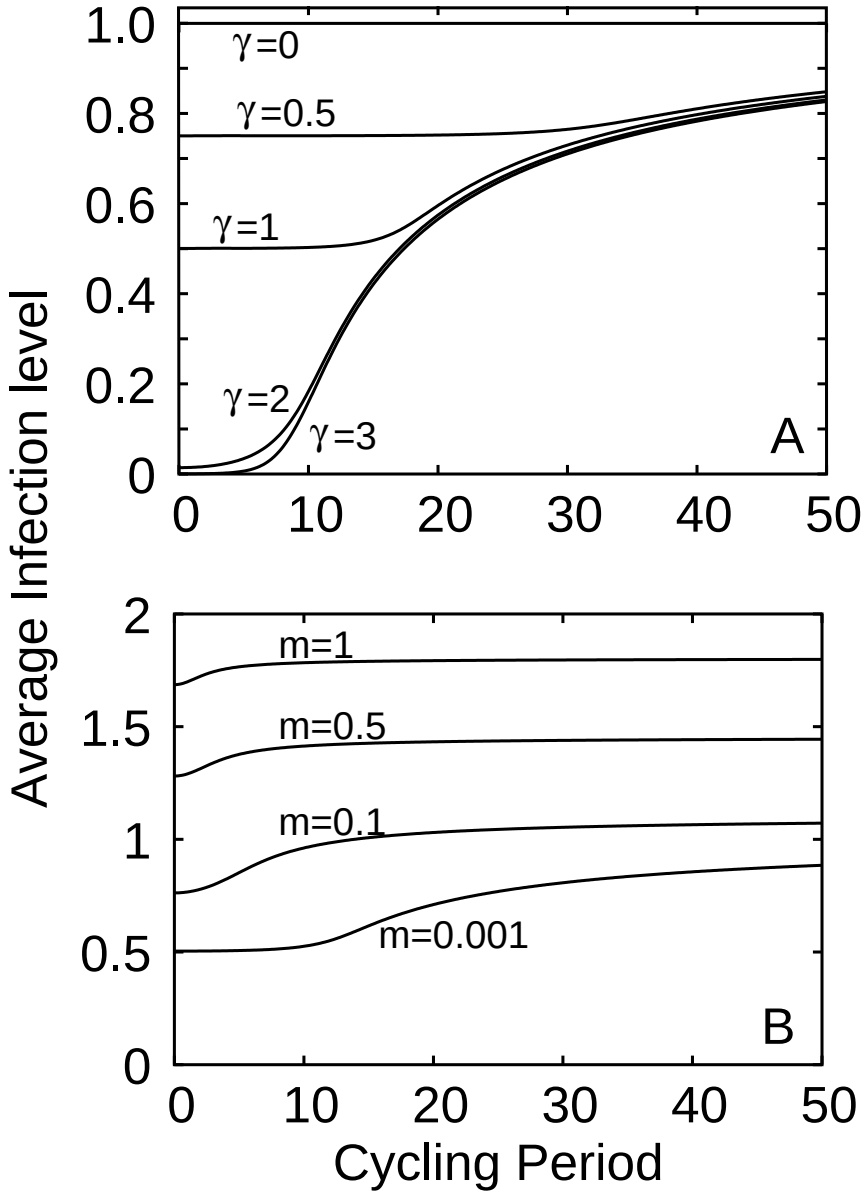

Figure 3: The asymptotic average infection level, described by Eq. (2.7), as a function of the total cycling period $T = t_1 + t_2$,$t_1 = t_2$, for the Rowthorn–Brown model with a 2-phase management strategy: (A) an immigration rate $m = 1/10,000$ for several clearance rates γ, and (B) a clearance rate $\gamma = 1$, for several immigration rates m. As the cycling period increases, the asymptotic average infection level increases.

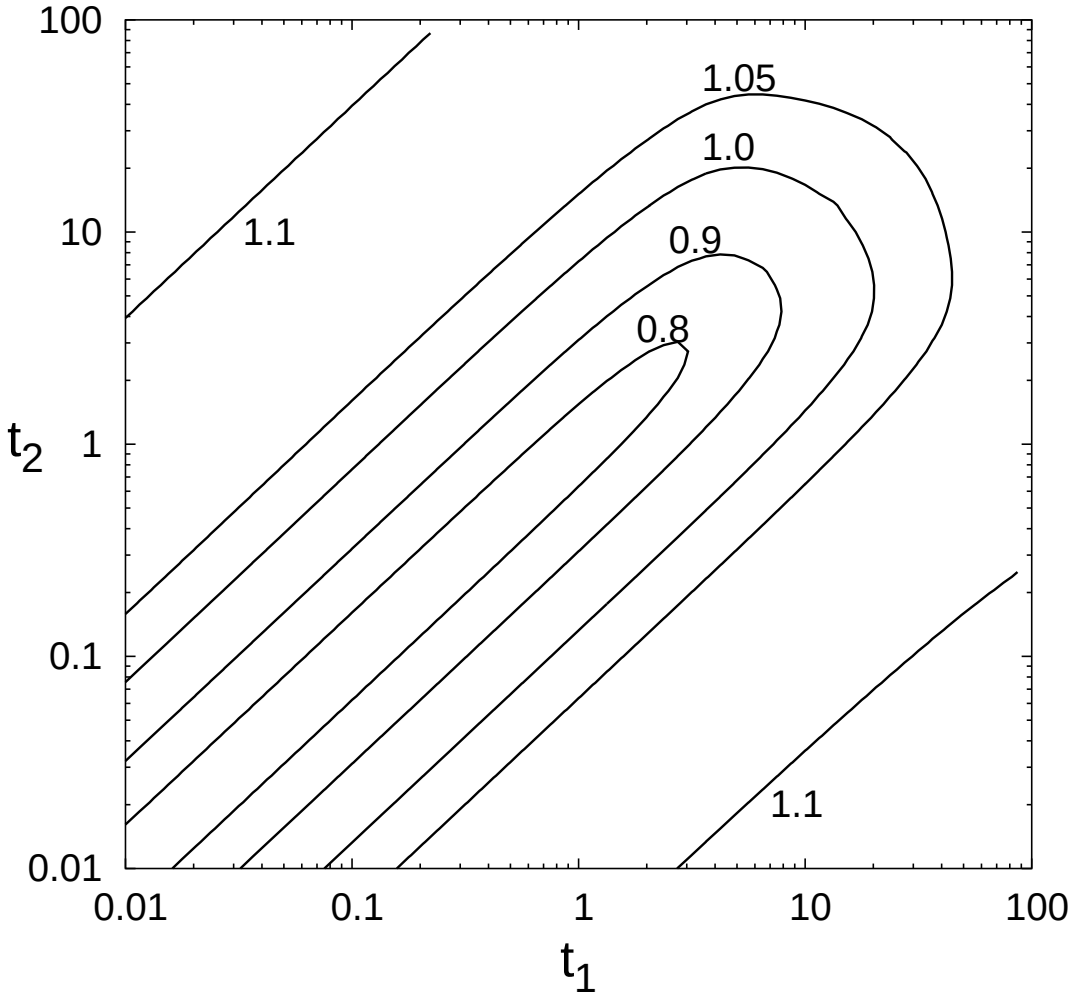

Figure 4: A contour plot of the asymptotic average infection level in the Rowthorn–Brown model as a function of the treatment phase periods t_1 and t_2, for clearance rate $\gamma = 1$ and immigration rate $m = 0.1$. Optimal 2-phase management obtains an asymptotic average infection level of $J = 0.76$.

where the sum is carried out over all types, and the transition rates q_{ij} are the expected changes in the number of individuals of type i per individual of type j, per unit of time. In matrix notation,

$$\frac{dI}{dt} = QI, \tag{3.2}$$

where the transition rate matrix $Q = [q_{ij}]$.

In the case of bacterial colonization and infection of hospital patients, the matrix Q incorporates the effects of transmission, clearance, and immigration. The structure of Q depends on the relationships among these events. If transmission, clearance, and immigration are independent, let

$$Q = M + F - D, \tag{3.3}$$

where F is a non-negative diagonal matrix of transmission rates, D is a non-negative diagonal matrix of clearance rates, and M is a Markov process generator matrix of immigration rates with non-positive diagonal entries and non-negative off-diagonal entries so that all the columns of M sum to zero. Models of the form (3.3) will be referred to as transmission-independent immigration models.

Alternatively, immigration events may be strongly correlated with transmission events, while clearance remains an independent process. In this case, let

$$Q = MF - D, \tag{3.4}$$

where F and D are as defined for Eq. (3.3) but M is a diagonally-dominate stochastic matrix of immigration probabilities. Models of the form (3.4) will be referred to as transmission-dependent immigration [1] models. In both cases, Q is quasi-nonnegative, admitting negative entries only along the main diagonal.

The rates q_{ij} also depend upon the details of the interactions between organisms and the antibiotics. Each drug k may have a different rate matrix Q_k resulting from different transmission rates, clearance rates, and immigration patterns in the drug's presence. When different fractions u_k of the infected population are treated with each drug k, the changes in the expected abundances satisfy

$$\frac{dI}{dt} = \left[\sum_k u_k(t) Q_k\right] I \tag{3.5}$$

where $\sum u_k = 1$, $u_k \geq 0$. Different management strategies correspond to different choices of $u_k(t)$. In this paper, I will be concerned with cycling strategies, where $u_k \in \{1, 0\}$. Our objective in choosing a management strategy will be to minimize the spread of infection by minimizing the average asymptotic growth rate of the infection abundances.

4 Two Strains with Transmission-Dependent Immigration

We begin with a simple case. Consider the case of two strains of infection with strongly correlated immigration and transmission and two drug treatments. If we stipulate immigration to be symmetric, and independent of antibiotic in use, the abundances satisfy

$$\frac{dI}{dt} = \left[u(t) Q_2 + (1 - u(t))\, Q_1\right] I \tag{4.1}$$

where

$$Q_1 = MF_1 - D_1, \quad Q_2 = MF_2 - D_2, \tag{4.2}$$

$$F_1 = \begin{bmatrix} \bar{r}_1 + r_1 & 0 \\ 0 & \bar{r}_1 - r_1 \end{bmatrix}, \quad F_2 = \begin{bmatrix} \bar{r}_2 + r_2 & 0 \\ 0 & \bar{r}_2 - r_2 \end{bmatrix}, \tag{4.3}$$

$$D_1 = \begin{bmatrix} \bar{d}_1 + d_1 & 0 \\ 0 & \bar{d}_1 - d_1 \end{bmatrix}, \quad D_2 = \begin{bmatrix} \bar{d}_2 + d_2 & 0 \\ 0 & \bar{d}_2 - d_2 \end{bmatrix}, \tag{4.4}$$

$$M = \begin{bmatrix} 1 - m & m \\ m & 1 - m \end{bmatrix}, \tag{4.5}$$

[1] The special form of immigration I adopt here may alternatively be interpreted as mutation in both Eqs. 3.3 and 3.4.

$u(t)$ represents the proportion of infections being treated with drug 2 at time t, and $1-u(t)$ represents the proportion of infections being treated with drug 1 at time t. $\bar{r}_i$ may be interpreted as the mean transmission rate of the strains while subject to drug i, and r_i describes the difference in transmission between strains. Similarly, $\bar{d}_i$ describes the mean clearance rate by drug i and d_i describes the difference in clearance rates between strains. Let us also assume that both strains have positive transmission rates and clearance rates ($\bar{r}_i > |r_i| > 0$ and $\bar{d}_i > |d_i| > 0$). m represents the probability that an immigration event of the alternative strain occurs, rather than a transmission event.

Each choice of $u(t)$ describes a management strategy. An equally weighted mixing strategy, for instance, corresponds to $u(t) = 1/2$. There are uncountably many choices for $u(t)$. One simple family of cycling strategies is the family of 2-phase strategies, where $u(t)$ takes the form described by Eq. (1.2). During the first phase of the cycle, which has duration t_1, all infections are treated with drug 1. During the second phase of the cycle, which has duration t_2, all infections are treated with drug 2. The parameter $T = t_1 + t_2$ represents the total period of one cycle, and will be focus of much of our analysis. It will also be convenient to define $\hat{t}_1 = t_1/T$ and $\hat{t}_2 = t_2/T$ as the phase fractions of treatments 1 and 2 respectively.

The abundances after completion of one cycle of a 2-phase cycling strategy, given initial abundances $I(0)$, may be represented in terms of the matrix exponential (Moler & Loan, 2003) as

$$e^{t_2 Q_2} e^{t_1 Q_1} I(0). \tag{4.6}$$

The matrix

$$\Psi = e^{t_2 Q_2} e^{t_1 Q_1} \tag{4.7}$$

is referred to as the monodromy matrix in Floquet theory (Yakubovich & Starzhinskii, 1975). The monodromy matrix Ψ completely describes the aperiodic component of the underlying linear equation. Using the monodromy matrix, for instance, the population abundances after n cycles will be

$$\Psi^n I(0). \tag{4.8}$$

The average asymptotic growth rate in the number of infections may be defined in terms of the monodromy matrix Ψ as

$$\bar{f} = \frac{1}{T} \ln\left[\rho\left(\Psi\right)\right], \tag{4.9}$$

where the spectral radius $\rho(\Psi)$ represents the magnitude of the largest eigenvalue of the monodromy matrix(Horn & Johnson, 1985). Intuitively, the average asymptotic growth rate is the rate at which a simple population must grow to "keep up with" the structured population's growth.

To construct $\bar{f}$, we need a closed-form representation for the spectral radius $\rho(\Psi)$. The Lagrange interpolation formula for the matrix exponential (Moler & Loan, 2003) is especially convenient. Given an $N \times N$ matrix Q with N distinct eigenvalues $\lambda_1, \lambda_2, \ldots \lambda_N$,

$$e^{Qt} = \sum_{n=1}^{N} e^{\lambda_n t} L_n(Q), \quad \text{where} \quad L_n(Q) = \prod_{i \neq n} \left(\frac{Q - \lambda_i E}{\lambda_n - \lambda_i} \right), \tag{4.10}$$

where E represents the identity matrix. When Q is a 2×2 matrix,

$$e^{Qt} = \frac{1}{\phi} e^{\sigma t} \sinh(\phi t) \left(Q - \sigma E\right) + e^{\sigma t} \cosh(\phi t) E, \tag{4.11}$$

where $\sigma = (\lambda_1 + \lambda_2)/2$, and $\phi^2 = \sigma^2 - \lambda_1 \lambda_2$, $\lambda_1 \neq \lambda_2$. The eigenvalues λ_1 and λ_2 are calculated using the quadratic formula. Eq. (4.11) gives a closed form representation for the matrix exponential in terms of Q. By applying Eq. (4.11) to Eq. (4.7), we can obtain an explicit, though cumbersome, representation for Ψ. The characteristic equation of Ψ,

$$\det\left[\Psi - \rho E\right] = 0, \tag{4.12}$$

is then a quadratic polynomial in ρ, and can be solved explicitly.

As our primary example, consider the case of $d_1 = d_2 = 0$. With some manipulation, we can show that the spectral radius

$$\rho = z \exp\left\{ t_1 \left[(1-m)\,\bar{r}_1 - \bar{d}_1 \right] + t_2 \left[(1-m)\,\bar{r}_2 - \bar{d}_2 \right] \right\}, \tag{4.13}$$

where z is the largest real root of

$$z^2 - 2Bz + 1 = 0, \tag{4.14}$$

$$B = \frac{m^2\bar{r}_2\bar{r}_1 + r_2 r_1\,(1-2m)}{\phi_2\phi_1}\sinh(\phi_1 t_1)\sinh(\phi_2 t_2) + \cosh(\phi_1 t_1)\cosh(\phi_2 t_2)\,, \tag{4.15}$$

$$\phi_1^2 = m^2\bar{r}_1^2 + (1-2m)r_1^2, \tag{4.16}$$

$$\phi_2^2 = m^2\bar{r}_2^2 + (1-2m)r_2^2. \tag{4.17}$$

Using the quadratic formula to solve for z and applying Eq. (4.13) to Eq. (4.9),

$$\bar{f} = \left\{\hat{t}_1\left[(1-m)\,\bar{r}_1 - \bar{d}_1\right] + \hat{t}_2\left[(1-m)\,\bar{r}_2 - \bar{d}_2\right]\right\} + \frac{1}{T}\operatorname{arccosh}[B]\,. \tag{4.18}$$

The closed form representation for $\bar{f}$ given by Eqs. (4.15)-(4.18) is a complete description of the asymptotic growth, and implies the following:

Theorem 1. *If $d_1 = d_2 = 0$ and $0 \le m \le 1/2$, then $\bar{f}$, as give by Eq.* (4.18)*, is a monotonic increasing function of the cycling period T.*

A proof of Theorem 1 is given in Appendix A. From Theorem 1, we see that $\bar{f}$ obtains its minimum in the limit as $T \to 0$. Faster cycling will always lead to slower asymptotic growth.

One of the central difficulties in dealing with the matrix exponential when compared with the scalar exponential function is that for general matrices Q_a and Q_b,

$$e^{Q_b}e^{Q_a} \neq e^{Q_b+Q_a}. \tag{4.19}$$

But, according to the Lie product formula (Horn & Johnson, 1985),

$$\lim_{T\to 0}\left(e^{TQ_b}e^{TQ_a}\right)^{n/T} = e^{n(Q_b+Q_a)}\,. \tag{4.20}$$

In our case, the limit in Eq. (4.20) should be interpreted as progressively decreasing the cycle time T, while keeping the total observation time nT fixed. Applied to the system described by Eq. (4.2),

$$\lim_{T\to 0, nT\text{ fixed}} \Psi^n(T) = e^{nT(\hat{t}_2 MF_2 + \hat{t}_1 MF_1 - \hat{t}_2 D_2 - \hat{t}_1 D_1)}\,. \tag{4.21}$$

The reader can observe that Eq. (4.21) is equivalent to growing the population for a time nT under a new treatment with transmission and clearance rates

$$F_{\text{new}} = \hat{t}_2 F_2 + \hat{t}_1 F_1 \quad \text{and} \quad D_{\text{new}} = \hat{t}_2 D_2 + \hat{t}_1 D_1. \tag{4.22}$$

In essence, this new treatment is a mixture of the 2 original treatments with a fraction $\hat{t}_1$ of the population subject to drug 1 and the remaining fraction $\hat{t}_2$ of the population subject to drug 2. Thus, the cycling strategy converges to a mixing strategy in the limit of infinitely fast cycling. In general, rapid cycling is closely approximated by a mixing strategy with the same phase-fractions. For cases where Theorem 1 applies, we conclude that a cycling strategy never limits population growth as well as a mixing strategy with the same phase fractions.

Having demonstrated the optimality of mixing over cycling in the case of $d_1 = d_2 = 0$, we determine a globally optimal mixing strategy. The asymptotic growth rate under mixing is

$$\bar{f}_{\text{mix}} = \lim_{T\to 0}\bar{f}(T) \tag{4.23}$$

$$= (1-m)(\bar{r}_1\hat{t}_1 + \bar{r}_2\hat{t}_2) + \sqrt{m^2\left(\bar{r}_1\hat{t}_1 + \bar{r}_2\hat{t}_2\right)^2 + (1-2m)\left(r_1\hat{t}_1 + r_2\hat{t}_2\right)^2}. \tag{4.24}$$

Using the relation $\hat{t}_2 = 1 - \hat{t}_1$, we can show

$$\frac{d^2\bar{f}_{\text{mix}}}{d\hat{t}_1^2} = \frac{m^2(1-2m)(\bar{r}_1 r_2 - \bar{r}_2 r_1)^2}{\left[\sqrt{m^2\left(\bar{r}_1\hat{t}_1 + \bar{r}_2\hat{t}_2\right)^2 + (1-2m)\left(r_1\hat{t}_1 + r_2\hat{t}_2\right)^2}\right]^3}. \tag{4.25}$$

Eq. (4.25) is non-negative as long as $m < 1/2$, implying $\bar{f}_{\text{mix}}$ is convex in $\hat{t}_1$ (equivalently, $\hat{t}_2$). It follows that there is a unique locally optimal mixing strategy which is also globally optimal. In the special case $\bar{r}_1 = \bar{r}_2, r_1 = -r_2$, the optimal phase fractions are $\hat{t}_1 = \hat{t}_2 = 1/2$. For $\bar{r}_1 \neq \bar{r}_2$, the optimal phase fractions can be calculated using convex minimization techniques.

An alternative scenario may be that clearance rates differ among infection strains under each cycle phase, but reproductive rates are constant across both cycle phases ($d_1 \neq d_2, \bar{r}_1 = \bar{r}_2, r_1 = r_2$). In this case, minimization of the asymptotic average growth rate over all 2-phase cycling strategies again leads to a unique optimal mixing strategy.

However, there are cases where a 2-phase cycling strategy can offer an improvement on a mixing strategy: cases where $d_1 = (1-m)r_1$ and $d_2 = (1-m)r_2$ are concave in T rather than convex for any positive phase fractions $\hat{t}_1$ and $\hat{t}_2$.

5 Multiple Strains without Immigration

In the absence of immigration, the cycling problem is relatively easy to solve. When we expose N different strains to a K-phase cycling strategy, with phase periods t_k, the monodromy matrix

$$\Psi = \prod_{k=1}^{K} e^{t_k(F_k - D_k)} = e^{T\sum_{k=1}^{K} \hat{t}_k (F_k - D_k)}, \tag{5.1}$$

where $\hat{t}_k = t_k/T$ and $T = \sum_{k=1}^{K} t_k$. The simplification in Eq. (5.1) is possible because diagonal matrices commute. Here, Ψ will be a diagonal matrix, and the diagonal entries of Ψ will be the eigenvalues. It follows directly from Eq. (4.9) that

$$\bar{f} = \max\left\{ \text{diag } Q : Q = \sum_{k=1}^{K} \hat{t}_k \left(F_k - D_k\right) \right\}. \tag{5.2}$$

Thus, the asymptotic growth rate is independent of the cycle period T. Minimizing $\bar{f}$ is a convex programming problem in the phase fractions $\hat{t}_k$, with linear constraints, and can be constructively solved using numerical methods. This solution should also be a good general approximation when immigration is slow.

6 Multiple Strains with Transmission-Independent Immigration

As mentioned in Section 3, there are two potential approaches for incorporating immigration. We now consider the case, described by Eq. (3.3), where transmission, clearance, and immigration are independent events. In a 2-treatment model, abundances satisfy Eq. (4.1) but with $Q_1 = M_1 + F_1 - D_1$ and $Q_2 = M_2 + F_2 - D_2$. When a 2-phase cycling strategy is applied,

$$\Psi = e^{\hat{t}_2 T Q_2} e^{\hat{t}_1 T Q_1}, \tag{6.1}$$

where T, $\hat{t}_1$, and $\hat{t}_2$ retain their previous definitions. If M_1 and M_2 are symmetric, we can prove that the average asymptotic growth rate $\bar{f}$ is an increasing function of the cycling period T using a general result of Cohen *et al.* (1982) (see Appendix B).

Theorem 2. *If the monodromy matrix Ψ is given by Eq.* (6.1)*, M_i is symmetric, and F_i and D_i are diagonal non-negative for $i = 1, 2$, then the average asymptotic growth rate $\bar{f} = \frac{1}{T}\log\{\rho[\Psi(T)]\}$ of a 2-phase on-off cycling strategy described by phase periods t_1 and t_2 is a monotone increasing function of $T = t_1 + t_2$.*

This result does not extend to cases of asymmetric immigration or multi-phase cycling strategies, however, and suggests that there may be an important difference between 2-phase and multiple-phase management strategies.

7 Multiple Strains with Transmission-Dependent Immigration

When we consider models with multiple infectious strains and multiple drug treatments, classical mathematical analysis is less profitable. Instead, I will analysis some specific examples of multiple strain models with transmission-dependent immigration numerically.

The examples shown in Figs. 5, 6, and 7 and described in Appendix C illustrate some cases where the asymptotic growth rates are not monotone increasing functions of the cycle period. For a given set of phase fractions, increasing the cycling period may either improve or degrade the effectiveness of a management strategy. This is not especially surprising, in light of the Meissner equation, but we are left with an unanswered question for these general cases: Will the best cycling strategy improve on the best mixing strategy for resistance management?

In a strict sense, the answer is elementary. Mixing strategies are a strict subset of cycling strategies, so optimal cycling can never be worse than optimal mixing. But from a practical standpoint, the question appears more difficult. For Examples 1-3, described in Appendix C, numerical calculations indicate that the globally optimal management strategies are mixing strategies. But, a sample size of 3 is small. To provide some intuition, the space of transmission-dependent immigration models was randomly sampled, and a numerical optimization algorithm was used to compare cycling and mixing strategies. $N \times N$ immigration matrices, M, were selected from the ensemble

$$\left\{ (1-m)E + m \sum_{j=1}^{N^2} u_j P_j \right\} \tag{7.1}$$

where m is uniformly distributed on the interval $(0, 1/2)$, E is the identity matrix, u is uniformly distributed over the N^2-dimensional simplex, and P_j is a random $N \times N$ permutation matrix. Matrix dimensions ranged from 2×2 to 10×10 with up to 4 different environments. The Birkhoff–von Neumann theorem, that every doubly-stochastic matrix may be represented as convex combination of $N(N-2)+2$ or fewer permutation matrices (Horn & Johnson, 1985; Marcus & Minc, 1964), ensures that the full set all doubly-stochastic matrices are reachable. Independent log-normal and uniform simplex distributions were used to generate random transmission and clearance rates. Matrix exponentiation was performed using Matlab's implementation of the matrix exponential.

The simulations I have performed suggest the following patterns. First, both cycling and mixing strategies can significantly improve management results over the use of a single drug. Non-optimal mixing or cycling strategies can also significantly degrade performance. Second, near-optimal cycling strategies often do not improve on near-optimal mixing strategies. In cases where near-optimal cycling strategies do improve on near-optimal mixing strategies, this improvement appears to be small. Figure 8 shows one such example, where 3 antibiotics are cycled to treat three strains of infection. Optimal mixing obtained $\bar{f} = 3.9$, while optimal cycling obtained $\bar{f} = 3.8$. These numerical experiments should be viewed cautiously, but suggest that optimized cycling strategies generally provide only a small improvement relative to optimized mixing strategies.

8 Discussion

The biology of management strategies for antibiotic usage includes complications that I have not addressed. In particular, new strains of drug resistance can evolve under the selective pressures of treatment. The implications of a management strategy for the evolution of new strains of resistance is an important consideration.

One path by which new drug-resistant strains can evolve is through horizontal gene transfer, sometimes resulting in the appearance of multi-drug resistance. It would be desirable to minimize the probability of horizontal gene transfer at the same time we maximize antibiotic efficacy, such that the antibiotic will be of use to future patients as well as current patients. Both current and future patients will benefit from cycling strategies that reduce horizontal gene transfer while increasing treatment efficacy. We should work to identify these situations. Complications arise when the benefits to current and future patients do not coincide. Consider a situation where a certain mixing strategy is optimal in the sense of

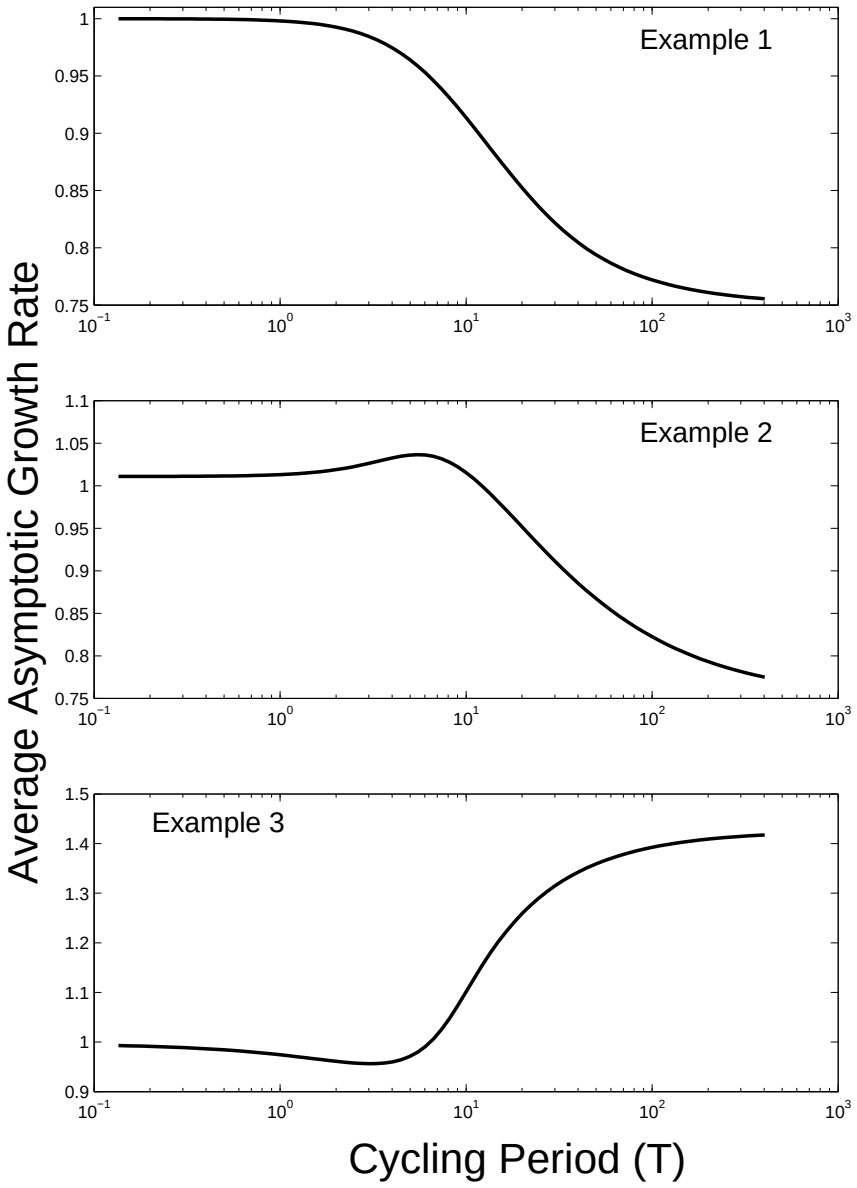

Figure 5: Three examples of the behavior of the average asymptotic growth rate $\bar{f}$ as a function of the cycling period T. Example 1 corresponds to the matrices in Eq. (C.1), example 2 corresponds to the matrices from Eq. (C.2), and example 3 corresponds to the matrices from Eqs. (C.3)-(C.5). $\bar{f}$ was calculated for each with the corresponding fractional exposure times described in the appendix. Examples 2 and 3 show that $\bar{f}$ need not be a monotone function of the cycling period.

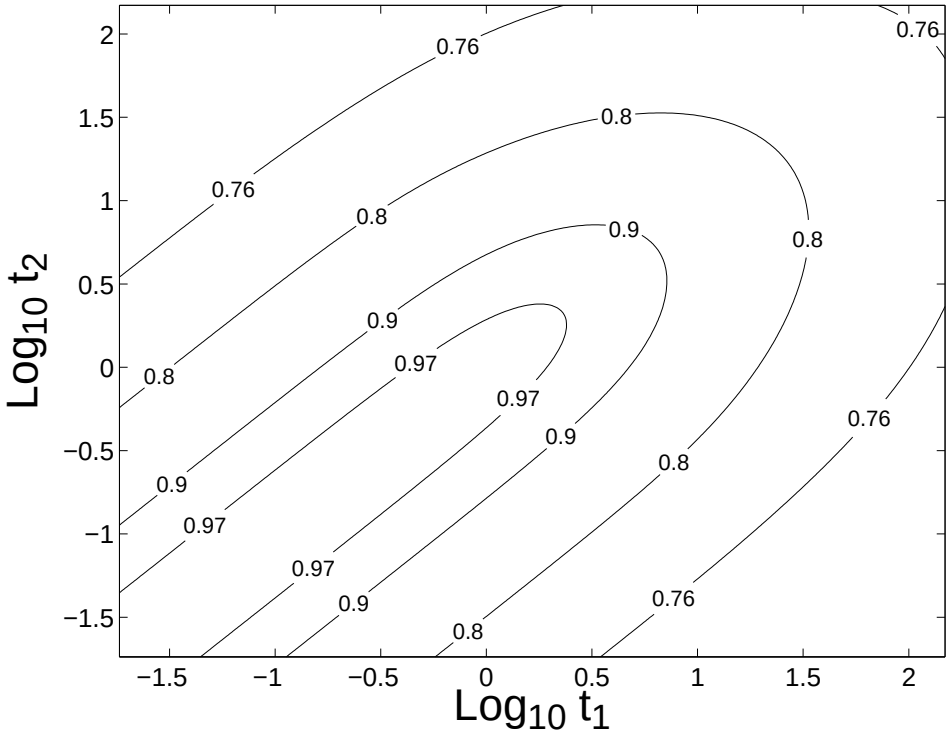

Figure 6: A contour plot of the asymptotic growth rate as a function the phase periods for Example 1, with phases given in Eq. (C.1).

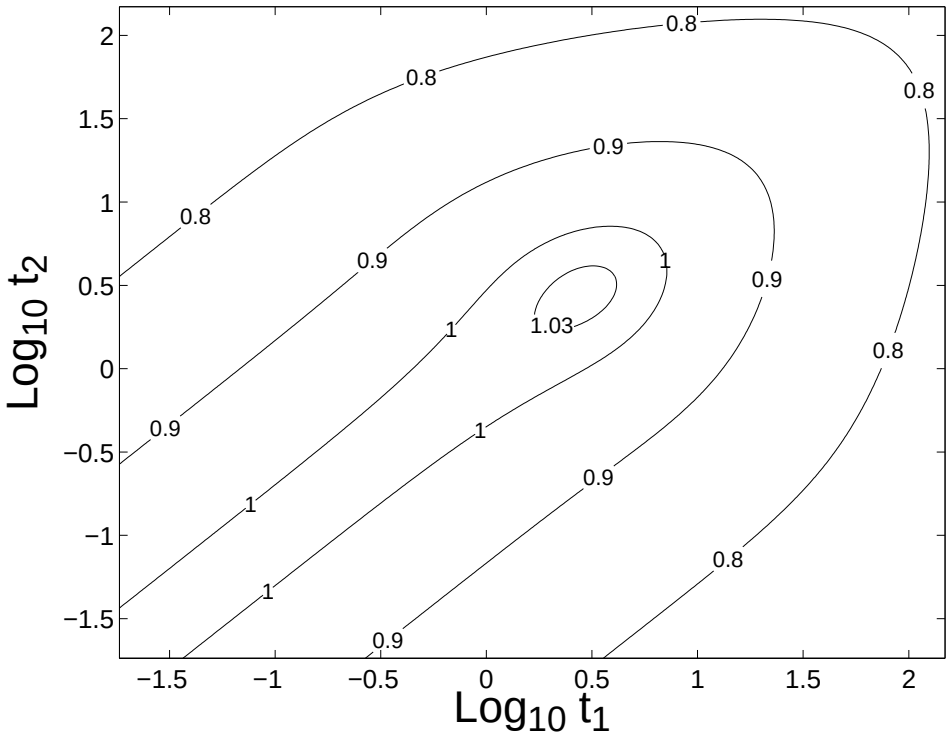

Figure 7: A contour plot of the asymptotic growth rate as a function of the phase periods for Example 2, with phases given in Eq. (C.2).

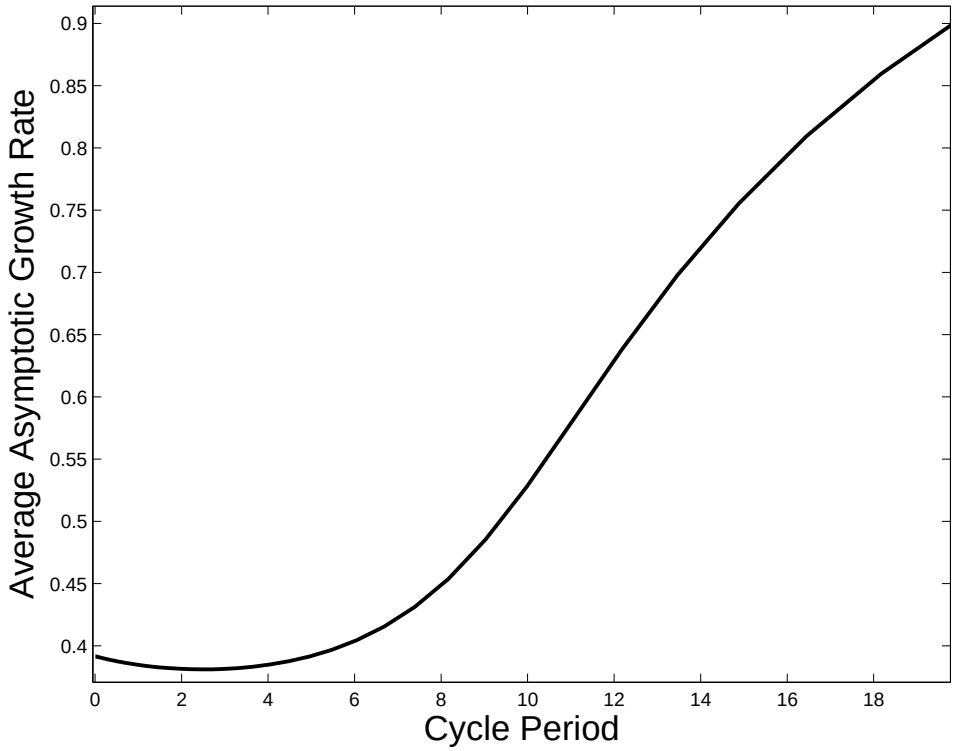

Figure 8: The average asymptotic growth rate as a function of cycling period for Example 4 along $\hat{t}_1 = 0.27$, $\hat{t}_2 = 0.46$, $\hat{t}_3 = 0.27$. Simulations suggest that a cycling period of $T \approx 2.5$ is globally optimal.

minimizing growth and transmission. If we introduce a cycling strategy that uses the same phase fractions, the correlation in abundances of different strains may decrease, leading to a decrease in the probability of horizontal gene transfer. However the overall efficacy of treatment will also decrease, compared to the optimal mixing strategy. Determining an optimal cycling strategy requires evaluating a trade-off between current treatment efficacy and future treatment efficacy. Determination of this trade-off is perhaps more of an ethical conundrum than of a scientific question: What health costs are we willing to impose on currently ill patients for the benefit of future patients?

Drug resistance can also evolve gradually, as a response to selective pressure from an antibiotic. In this respect, antibiotics are sometimes considered a non-renewable resource (Laxminarayan & Brown, 2001). There are many factors that control the rate of evolution of drug resistance. These include the size of the population experiencing selection, mutation rates, the strength of selection, and the shape of the adaptive landscape on which selection is occurring. These factors are influenced by spatial and temporal environmental heterogeneity. The work presented here indirectly suggests that longer cycle periods will correspond to smoother adaptive landscapes and faster evolution of resistance. But the problem of minimizing the evolution rate is more appropriately addressed with different methods.

The methods I have used are not necessarily well suited for addressing questions of the evolution of novel strains of infection. Instead, I have focused on determining drug management strategies, and optimal environmental heterogeneity in general, based on the fitness of pre-existing strains of infection. If the fitness of a strain of infection is independent of the drug treatment adopted, no benefits can be achieved by modifying policies for managing drug usage in a hospital. When fitness does depend on the antibiotic treatment, rational management policies may improve treatment efficacy. Treatment efficacy may depend on management strategy through the cost and availability of drugs, the prevalence of drug resistance outside hospitals, spatial and temporal environmental heterogeneity, and other factors. Optimizing management strategy with respect to temporal heterogeneity is what I've referred to as the "cycling problem".

In this paper, I have presented a linear theory for the cycling problem, along with numerical examples and solution in several special cases. The results support the preference of conventional mixing strategies over cycling strategies as a method for the introduction of environmental heterogeneity into management policies. Cycling and mixing strategies are equivalent management strategies unless there is immigration, mutation, or some other form of interaction among strains of infection. In most cases, interactions bias the dynamics in favor of mixing strategies, but cycling may improve on mixing when interactions are strongly asymmetric. Under global optimization constraints, cycling was only rarely observed to improve on mixing. Many open questions remain. It seems possible, for instance, that cycling strategies may be preferred in cases where there are significant seasonal dynamics. In addition, externalities such as limited drug availability in developing nations may make cycling an attractive resistance management strategy.

More work on matrix models and alternative approaches is necessary to fully understand the effects of environmental heterogeneity in biological systems management. The problem of eigenvalue optimization has received recent attention in applied mathematics (Burke *et al.*, 2001) and may be of use here. One potentially fruitful approach may be the application of bilinear optimal control theory (Mohler, 1970, 1973). Another direction of future work may include alternative forms of immigration that describe the population dynamics in a hospital more accurately. Preliminary work on this front suggests results similar to those presented here. Other future work may include periodically forced competition models and further work on existing optimal-control models. In closing, careful use of environmental heterogeneity remains a promising option in biological systems management, but one which will only be realized by a close interaction between theory, experiment, and practice.

Acknowledgments

The author would like to thank G. Brown for helpful discussion, M. Kot and three anonymous reviewers for helpful comments on the manuscript, and C. Bergstrom for encouraging this research and contributing a preliminary version of the results of Section 5. This work was supported in part by NSF VIGRE grant DMS-9810726.

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A Proof of Theorem 1

Lemma 1. *If $G(x)$ is convex for $x \geq 0$ and $G(0) \leq 0$, then $G(x)/x$ is increasing for all $x > 0$.*

This Lemma is closely related to the fact that the average rate of change of a convex function over an interval is an increasing function of the righthand end point.

Proof. Let $0 < x_1 < x_2$. By the definition of convexity of $G(x)$,

$$G(x_1) \leq \left(1 - \frac{x_1}{x_2}\right) G(0) + \frac{x_1}{x_2} G(x_2). \tag{A.1}$$

Dividing by x_1,

$$\frac{G(x_1)}{x_1}. \leq \frac{x_2 - x_1}{x_1 x_2} G(0) + \frac{G(x_2)}{x_2} \tag{A.2}$$

Since $\frac{x_2 - x_1}{x_1 x_2} > 0$ and $G(0) \leq 0$,

$$\frac{x_2 - x_1}{x_1 x_2} G(0) \leq 0, \tag{A.3}$$

so Eq. (A.2) also implies

$$\frac{G(x_1)}{x_1} \leq \frac{G(x_2)}{x_2} \tag{A.4}$$

for all $0 < x_1 < x_2$. Thus, $G(x)/x$ must be an increasing function for all $x > 0$. □

Lemma 2. *If $\phi_1 > 0$, $\phi_2 > 0$, and $-1 \leq a \leq 1$, then* $\operatorname{arccosh} B(T; a)$, *with* $B(T; a) = a \sinh(\phi_1 T) \sinh(\phi_2 T) + \cosh(\phi_1 T) \cosh(\phi_2 T)$, *is convex in T, with minimum value 0 at $T = 0$.*

Proof. First, $B(T; -1) = \cosh(\phi_1 T - \phi_2 T)$ and $a_1 > a_2$ implies $B(T; a_1) > B(T; a_2)$ for all T. So $B(T, a) \geq 1$ for all $a \geq -1$. Now,

$$\left(B^2 - 1\right)^{3/2} \frac{d^2}{dT^2} \operatorname{arccosh} B = \\ (1 - a^2) \left[B(\phi_2 \sinh \phi_1 T - \phi_1 \sinh \phi_2 T)^2 + 2(B - 1)\phi_1 \phi_2 \sinh \phi_1 T \sinh \phi_2 T\right]. \tag{A.5}$$

The second derivative is non-negative as long as $a^2 \leq 1$, $T \geq 0$. This implies convexity. Since $B(T; a) = B(-T; a)$, the minimum value is at $T = 0$ and is 0. □

Lemma 3. *If $0 \leq m \leq 1/2$, then*

$$-1 \leq \frac{m^2 \bar{r}_1 \bar{r}_2 + r_1 r_2 (1 - 2m)}{\phi_1 \phi_2} \leq 1, \tag{A.6}$$

where ϕ_1 and ϕ_2 are given by Eqs. (4.16) *and* (4.17).

Proof. If $m = 0$, or $m = 1/2$, Eq. (A.6) is true by inspection. If $0 < m < 1/2$,

$$0 \leq \frac{m^2}{1-2m}\left(\frac{r_1}{\bar{r}_1} - \frac{r_2}{\bar{r}_2}\right)^2, \tag{A.7}$$

$$0 \leq \frac{m^2}{1-2m}\left(\frac{r_1^2}{\bar{r}_1^2} - 2\frac{r_1 r_2}{\bar{r}_1 \bar{r}_2} + \frac{r_2^2}{\bar{r}_2^2}\right), \tag{A.8}$$

$$2\frac{r_1 r_2}{\bar{r}_1 \bar{r}_2}\frac{m^2}{1-2m} \leq \frac{m^2}{1-2m}\left(\frac{r_1^2}{\bar{r}_1^2} + \frac{r_2^2}{\bar{r}_2^2}\right), \tag{A.9}$$

$$\left(\frac{m^2}{1-2m}\right)^2 + 2\frac{r_1 r_2}{\bar{r}_1 \bar{r}_2}\frac{m^2}{1-2m} + \frac{r_1^2 r_2^2}{\bar{r}_1^2 \bar{r}_2^2} \leq \left(\frac{m^2}{1-2m}\right)^2 + \frac{m^2}{1-2m}\left(\frac{r_1^2}{\bar{r}_1^2} + \frac{r_2^2}{\bar{r}_2^2}\right) + \frac{r_1^2 r_2^2}{\bar{r}_1^2 \bar{r}_2^2}, \tag{A.10}$$

$$\left(\frac{m^2}{1-2m} + \frac{r_1 r_2}{\bar{r}_1 \bar{r}_2}\right)^2 \leq \left(\frac{m^2}{1-2m} + \frac{r_1^2}{\bar{r}_1^2}\right)\left(\frac{m^2}{1-2m} + \frac{r_2^2}{\bar{r}_2^2}\right) \tag{A.11}$$

Since $1-2m$ and $\bar{r}_1^2 \bar{r}_2^2$ are positive,

$$\left[m^2 \bar{r}_1 \bar{r}_2 + r_1 r_2 (1-2m)\right]^2 \leq \left[m^2 \bar{r}_1^2 + r_1^2 (1-2m)\right]\left[m^2 \bar{r}_2^2 + r_2^2 (1-2m)\right], \tag{A.12}$$

$$\frac{\left[m^2 \bar{r}_1 \bar{r}_2 + r_1 r_2 (1-2m)\right]^2}{\phi_1^2 \phi_2^2} \leq 1. \tag{A.13}$$

The result follows when we take the square root of both sides. □

Proof of Theorem 1. By Lemmas 2 and 3,

$$G(T) = \left[(1-m)\bar{r}_1 + \bar{d}_2\right]\hat{t}_1 T + \left[(1-m)\bar{r}_2 - \bar{d}_2\right]\hat{t}_2 T + \operatorname{arccosh}[B]$$

is convex in T. Also $G(0) = 0$. Thus, by Lemma 1, $\bar{f} = G(T)/T$ is a monotone increasing function of T. □

B Proof of Theorem 2

Proof. M_i, D_i and F_i are symmetric, so both $Q_1 = M_1 + F_1 - D_1$ and $Q_2 = M_2 + F_2 - D_2$ are symmetric real matrices, and hence, Hermitian. Then, by Corollary 9 from Cohen *et al.* (1982),

$$G(T) = \log \rho\left[e^{t_2 Q_2} e^{t_1 Q_1}\right]$$

must be convex in the pair (t_1, t_2). It follows directly that $G(T)$ is convexity in $T = t_1 + t_2$. Since $G(0) = 0$, we may apply Lemma 1, and conclude that $G(T)/T$ is a monotone increasing function of T. □

C Multi-Strain Examples

The following time-dependent immigration examples were used to generate Figs. 5 and 8.

For Example 1 in Fig. 5 and Fig. 6,

$$Q_1 = \frac{1}{4}\begin{bmatrix} 2 & 3 \\ 0 & 3 \end{bmatrix}, \quad Q_2 = \frac{1}{4}\begin{bmatrix} 3 & 0 \\ 3 & 2 \end{bmatrix}, \tag{C.1}$$

with $\hat{t}_1 = \hat{t}_2 = 1/2$, the asymptotic fitness $\bar{f}$ is monotonically decreasing in T. Of course, choice of equal treatment periods is especially bad in this scenario, since the asymptotic limit $\bar{f} = 3/4$ is recovered by mixing when $\hat{t}_1 = 0$, $\hat{t}_2 = 1$, or $\hat{t}_1 = 1$, $\hat{t}_2 = 0$.

For Example 2 in Fig. 5 and also Fig. 7,

$$Q_1 = \frac{1}{4}\begin{bmatrix} 1 & 0 & 1 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}, \quad Q_2 = \frac{1}{4}\begin{bmatrix} 1 & 0 & 0 \\ 1 & 1 & 0 \\ 0 & 1 & 0 \end{bmatrix} \tag{C.2}$$

with $\hat{t}_1 = \hat{t}_2 = 1/2$. The maximum growth rate occurs at an intermediate value of T before approaching its minimum as $T \to \infty$.

For Example 3, appearing in Fig. 5, has phases

$$Q_1 = \begin{bmatrix} 0.51 & 0.49 \\ 0.49 & 0.51 \end{bmatrix}\begin{bmatrix} 1.95 & 0 \\ 0 & 0.05 \end{bmatrix}, \tag{C.3}$$

$$Q_2 = \begin{bmatrix} 0.95 & 0.05 \\ 0.05 & 0.95 \end{bmatrix}\begin{bmatrix} 1.9 & 0 \\ 0 & 0.1 \end{bmatrix}, \tag{C.4}$$

$$Q_3 = \begin{bmatrix} \frac{2}{3} & \frac{1}{3} \\ \frac{1}{3} & \frac{2}{3} \end{bmatrix}\begin{bmatrix} 0.05 & 0 \\ 0 & 1.95 \end{bmatrix}, \tag{C.5}$$

with phase fractions $\hat{t}_1 = 1/6$, $\hat{t}_2 = 1/3$, and $\hat{t}_3 = 1/2$. In this example, the asymptotic growth rate has a local minimum near $T = 4$, but the global minimum appears to occur in the limit of small period T, when $\hat{t}_1 = 0.49$, $\hat{t}_2 = 0$, and $\hat{t}_3 = 0.51$.

Example 4, appearing in Fig. 8, has phases

$$Q_1 = \begin{bmatrix} -1.0286 & 0.0067 & 0.0916 & 0 & 0 \\ 0.0141 & -0.2820 & 0 & 0.0285 & 0.1764 \\ 0 & 0.0169 & -0.4551 & 0 & 0.1326 \\ 0.0187 & 0 & 0.0363 & -0.0476 & 0.1581 \\ 0.0167 & 0 & 0 & 0.0558 & 2.0608 \end{bmatrix}, \tag{C.6}$$

$$Q_2 = \begin{bmatrix} -0.7692 & 0.2367 & 0 & 0 & 0.0693 \\ 0.1944 & 0.6765 & 0.1024 & 0 & 0 \\ 0 & 0 & 0.0230 & 0.0180 & 0 \\ 0 & 0.2279 & 0.1890 & -0.9240 & 0 \\ 0 & 0 & 0.0796 & 0 & 0.8763 \end{bmatrix}, \tag{C.7}$$

$$Q_3 = \begin{bmatrix} -0.4988 & 0.0081 & 0.3172 & 0 & 0.0053 \\ 0 & 0.0088 & 0.0964 & 0.1788 & 0.0065 \\ 0 & 0.0217 & 1.6094 & 0.1209 & 0 \\ 0.0258 & 0 & 0.1180 & 1.2440 & 0 \\ 0.0074 & 0.0066 & 0 & 0 & -2.2760 \end{bmatrix}. \tag{C.8}$$

Assuming phases occur in the given order, the globally optimal management strategy in this example appears to be a cycling strategy with phase periods $t_1 \approx 0.67$, $t_2 \approx 1.15$, $t_3 \approx 0.69$. The optimal mixing strategy has approximately the same phase fractions as the globally optimal strategy.