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ORIGINAL ARTICLE

Within-Host Virus Models with Periodic Antiviral Therapy

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Abstract This paper investigates the effect of drug treatment on the standard within-host virus model, assuming that therapy occurs periodically. It is shown that eradication is possible under these periodic regimens, and we quantitatively characterize successful drugs or drug combinations, both theoretically and numerically. We also consider certain optimization problems, motivated for instance, by the fact that eradication should be achieved at acceptable toxicity levels to the patient. It turns out that these optimization problems can be simplified considerably, and this makes calculations of the optima a fairly straightforward task. All our results will be illustrated on an HIV model by means of numerical examples based on up-to-date knowledge of parameter values in the model.

Keywords Within-host virus models · HIV · HBV · HCV · Influenza · Malaria · Periodic drug treatment · Optimization

1. Introduction

For the past two decades, within-host virus models describing viral infections have played an important role in the understanding of viruses, and the ways in which they escape not only the immune system, but also the various drugs that have been developed to suppress viral replication. Testing specific hypotheses based on clinical data is often difficult since samples cannot always be taken too frequently from patients, or because detection techniques of the virus may not be accurate. This justifies the central role played by mathematical models in this area of research.

In this paper, we will revisit the standard model of within-host virus infections (Perelson and Nelson, 1999; Nowak and May, 2000) which encompasses several important infections such as HIV (Richman, 2004), hepatitis B (Ganem and Prince, 2004; Locarnini and Lai, 2003) and C (Special issue on virology and clinical advances of HCV infection, 2006), influenza (Earn et al., 2002), and even the malaria parasite *P. falciparum* (Molineaux and Dietz, 2000), and we will explore the consequences of periodic antiviral treatment. We will characterize analytically and numerically the periodic treatment schedules that lead to viral eradication. However, our results should be interpreted with

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a healthy dose of caution. Indeed, in the case of HIV, for example, we know that viral eradication with the currently available drugs is not possible, even when patients adhere to the strict treatment regimens. This means that either the mathematical model does not capture all the relevant dynamics of the interplay of the virus and its host cells, or that the drugs are not potent enough for viral eradication. It seems reasonable to speculate that a mix of both of these factors is to blame, and additional modeling efforts are necessary.

In the case of HIV, several explanations for treatment failure have been proposed, such as the pre-existence of drug-resistant strains (Ribiero and Bonhoeffer, 2000), or the emergence of resistant strains after initiation of drug therapy (Bonhoeffer and Nowak, 1997; Larder et al., 1989; Richman et al., 1994). The ability of the virus to mutate quickly into forms which may be less sensitive to drugs has been, and continues to be, the focus of much attention; see the recent contributions (Ball et al., 2007; De Leenheer and Pilyugin, 2008) that study the behavior of multistrain viral models. According to Siliciano et al. (2003), treatment failure is due to the presence of a latent reservoir of HIV in resting memory CD4+ T cells.

Other research has gravitated around the fact that the periodic regimen in which drugs are taken daily (or more frequently), puts a very high strain on the patient, calling for therapies minimizing the treatment burden on the patient (Kirschner et al., 1997), and also leading to investigations of the use of Structured Treatment Interruptions (STIs) (Bajaria et al., 2004; Krakovska and Wahl, 2007; Ortiz et al., 2001).

Recall that the standard model (Perelson and Nelson, 1999; Nowak and May, 2000) is a three-dimensional nonlinear ODE. In the case of HIV, its state consists of the concentrations of healthy CD4+ T cells (the targets of the HIV), infected T cells, and viral particles. Upon infection of a healthy T cell, one of the first orders of business is to make a copy of the viral RNA, using the enzyme reverse transcriptase. This step, which is error-prone and leads to mutations, can be blocked by a class of drugs called reverse transcriptase (RT) inhibitors. Once the viral copy has been produced, the double stranded viral DNA integrates in the cell's nucleus as provirus. The usual gene expression now does the rest, and viral proteins are produced according to the genetic information encoded in the provirus. These proteins are assembled, mature, and ultimately new viruses bud off from the infected cell's surface which go on to infect other T cells. During the maturation stage, the protease enzyme is used to cleave long protein chains, and the so-called protease (P) inhibitors are drugs that target this step. If effective, they give rise to defective virus.

For other viruses, despite differences in the infection and replication mechanisms, and in the drugs used against them, the standard model is still a popular model for describing the dynamics of the infection. For hepatitis B or C, the target cells are liver cells and some of the drugs used are lamivudine, adefovir and entecavir (for HBV), ribavirin (for HCV) and interferon (for HBV and HCV). The influenza virus infects epithelial cells and is treated with neuraminidase inhibitors (such as oseltamivir and zanamivir) and M2 inhibitors (such as amantadine and rimantadine). Finally, the malaria parasite *P. falciparum* infects erythrocytes (red blood cells) and malaria has commonly been treated by chloroquine.

The purpose of this paper is to assess theoretically and quantitatively what the impact is of periodic drug treatment on the dynamic behavior of the standard model, and in particular to determine what it takes to get rid of the infection. Mathematically, we obtain a nonlinear periodic ODE, for which in general it is difficult to prove global stability

and this explains why much research has traditionally resorted to simulations. Surprisingly though, solutions to the standard model ultimately are bounded by solutions of a monotone system, as pointed out by d'Onofrio (2005), and this allows to conclude global stability for the nonlinear periodic model.

We will first consider a simple case of HIV treatment, where only RT inhibitors are administered, and where it is assumed that the drug is of the bang-bang type, i.e., at each moment during the period of the treatment cycle, the drug is in one of two states: Either it is active at a fixed efficiency level, or it is inactive. The drug is thus characterized by two parameters: its efficiency level when active, and the duration of the activity. A major role in our analysis is played by the spectral radius of a non-negative matrix (namely of the fundamental matrix solution, evaluated over one treatment cycle, of the linearization at the infection-free equilibrium), which is shown to possess expected monotonicity properties in terms of the two parameters that characterize the drug. Specifically, this spectral radius—which also controls the speed of convergence to the infection-free equilibrium—is lower when the drug is more potent or when it is active longer. Equivalently, convergence to the infection-free equilibrium is faster with a more potent drug, or a drug whose activity lasts longer. We will see that these results can be generalized to the case of P inhibitors, or to a mix of both RT and P inhibitors. This latter scenario reflects more closely the standard practice of administering cocktails of drugs to HIV infected patients.

In reality, the efficiency of a drug is not of the bang-bang type. In fact, current research is investigating the effect of including pharmacokinetics into the picture, and has revealed that the efficiency is a periodic signal with an initial steep rise right after drug intake, followed by a slower decay over a period; see the work of Dixit and Perelson (2004), Rong et al. (2007) for detailed models. Therefore, we turn to this more general case, by approximating the efficiency by a more general piecewise constant periodic signal. It turns out that the previous results remain valid.

Finally, we turn to optimization problems that involve either maximizing the speed of convergence to the infection-free equilibrium while making sure that acceptable toxicity levels are not exceeded, or by minimizing toxicity levels, while making sure the speed of convergence does not fall below a certain threshold.

All our results will be illustrated by means of numerical examples of within-host HIV models whose parameters are chosen in accordance with current prevailing knowledge based on clinical data and extensive experimental evidence. Our results have the potential to suggest which drug, or which combination of drugs, are optimal for a given patient. They can also be used to explore the consequences of changing the treatment frequency. The investigation of the impact of periodic treatment cycles on multi-strain models, or the effect of STIs is the subject of ongoing research.

Notation For matrices A and B, $0 \leq A$, $0 < A$ means that A is a (entry-wise) nonnegative, positive matrix, respectively, and $A \leq B$ means that $0 \leq B - A$. A matrix is called quasi-positive if all its off-diagonal entries are nonnegative. The spectral radius of a matrix A is defined as the largest modulus of all eigenvalues of A and will be denoted by $\rho(A)$. We will also use the matrix exponential of a square matrix A, which is defined by the convergent matrix series $\sum_{i=0}^{\infty} \frac{1}{i!} A^i$, and will be denoted by $\mathrm{EXP}[A]$.

2. Within-host virus model with treatment

We briefly recall the well-known standard model (Perelson and Nelson, 1999; Nowak and May, 2000). Let

$$\begin{aligned} \dot{T} &= f(T) - kVT, \\ \dot{T}^* &= kVT - \beta T^*, \\ \dot{V} &= N\beta T^* - \gamma V, \end{aligned} \tag{1}$$

where T, T^*, V denote the concentrations of healthy and infected cells, and virus particles, respectively. The notation T, T^*, V is borrowed from the HIV literature (Perelson and Nelson, 1999; Nowak and May, 2000), where they represent concentrations of CD4+ T-cells, infected T-cells, and HIV virus. But we stress that other virus and parasite infections are described with the same model as explained in the Introduction.

All parameters are assumed to be positive. The parameters β and γ are the death rates of infected cells and virus particles, respectively. The infection is represented by a mass action term kVT, and N is the average number of virus particles budding off an infected cell during its lifetime. The (net) growth rate of the uninfected cell population is given by the smooth function $f(T) : \mathbb{R}_+ \to \mathbb{R}$, which is assumed to satisfy the following:

$$\exists\, T_0 > 0 : f(T)(T - T_0) < 0 \quad \text{for } T \neq T_0, \quad \text{and} \quad f'(T_0) < 0. \tag{2}$$

We have chosen to make the class of allowable $f(T)$'s as large as possible, since the growth rate is hard to determine. In addition, most mathematical results apparently remain valid for this large class. Finally, we notice that the two most popular choices for $f(T)$, namely $a - bT$ for some positive a and b; see Nowak and May (2000) and $s + rT(1 - T/T_{\max})$ for some positive s, r and $T_{\max}$, see Perelson and Nelson (1999) (here, s is a source term modeling cell production—which in the case of HIV occurs in the thymus—and r and $T_{\max}$ are the maximal per capita growth rate and carrying capacity respectively describing logistic growth of cells), satisfy the preceding conditions.

Since continuity of f implies that $f(T_0) = 0$, it follows that

$$E_0 = (T_0, 0, 0),$$

is an equilibrium of (1), and we will refer to it as the infection-free equilibrium.

A second, positive equilibrium (corresponding to an infection) may exist if the following quantities are positive:

$$\bar{T} = \frac{\gamma}{kN}, \qquad \bar{T}^* = \frac{f(\bar{T})}{\beta}, \qquad \bar{V} = \frac{f(\bar{T})}{k\bar{T}}. \tag{3}$$

Note that this is the case iff $f(\frac{\gamma}{kN}) > 0$, or equivalently by (2) that $\bar{T} = \frac{\gamma}{kN} < T_0$. In terms of the basic reproduction number

$$R_0 := \frac{kN}{\gamma} T_0,$$

existence of a positive equilibrium is therefore equivalent with

$$1 < R_0, \tag{4}$$

which will be a standing assumption throughout the rest of this paper. Indeed, if we would assume that $R_0 < 1$, then it would follow from De Leenheer and Smith (2003) that the infection-free equilibrium E_0 is globally asymptotically stable (GAS), and hence in this case the infection would always be cleared without treatment.

We denote the positive equilibrium that corresponds to an infection by $E = (\bar{T}, \bar{T}^*, \bar{V})$. Linearization at E_0 shows that it is unstable, and conditions on $f(T)$ are known that guarantee that E is GAS (excluding of course initial conditions corresponding to a healthy, uninfected individual; these coincide with the T-axis, which is the stable manifold of E_0). However, it is also possible that the model exhibits sustained oscillatory solutions which can be asymptotically stable. Regardless of the dynamical complexity of the solutions of the model, in general, if left untreated, the infection will persist in a patient. All these results follow from De Leenheer and Smith (2003).

Obviously, the purpose of treatment is to clear the infection, hopefully by making E_0 GAS by suitable modifications of model (1) which reflect the effect of drugs. Let us specialize to HIV by examining the effect of RT inhibitors. The effect of using P inhibitors will be considered later. Using monotherapy based on RT inhibitors, model (1) is modified to:

$$\begin{aligned} \dot{T} &= f(T) - k\big(1 - \epsilon(t)\big)VT, \\ \dot{T}^* &= k\big(1 - \epsilon(t)\big)VT - \beta T^*, \\ \dot{V} &= N\beta T^* - \gamma V, \end{aligned} \tag{5}$$

where $\epsilon(t) \in [0, 1]$ is the (time-varying) drug efficiency of the RT inhibitors. The drug is not effective when $\epsilon(t) = 0$ and 100% effective when $\epsilon(t) = 1$. Notice that E_0 is still an equilibrium of the modified model (5), regardless of the drug efficiency.

Assuming that the efficiency is constant over time, we set $\epsilon(t) = e \in (0, 1]$. Then to clear the infection, it suffices to choose e such that the modified basic reproduction number $R_0(\epsilon)$ is less than 1, where

$$R_0(\epsilon) := \frac{k(1-e)N}{\gamma} T_0.$$

Indeed, the results mentioned previously are applicable to this modified model, and they imply that if $R_0(\epsilon) < 1$, then E_0 is GAS for (5). Equivalently, if the efficiency e satisfies

$$e > e_{\text{crit}} := 1 - \frac{1}{R_0}, \tag{6}$$

then treatment will be successful in this case. If the drug would be effective 100% so that $e = 1$, then treatment would always be successful. Current RT inhibitors clearly do not fit this profile. Moreover, in practice, the drug efficiency is not constant through time, and the main purpose of this paper is to investigate the quantitative consequences of this fact.

3. Periodic drug efficiency

We now make the assumption that $\epsilon(t)$ is periodic:

$$\epsilon(t) = \epsilon(t+\tau), \quad \text{for all } t,$$

for some period $\tau > 0$. This is closer to reality where patients ideally adhere to a strict periodic treatment schedule, taking medication daily ($\tau = 1$ day) or twice a day ($\tau = 0.5$ day) for instance.

The shape of $\epsilon(t)$ over one treatment cycle is determined by the pharmacokinetics which will not be modeled here. Roughly speaking, pharmacokinetics describes what happens to a drug after the moment of intake, but before it starts being active at the infection site. The standard model can be coupled with a detailed pharmacokinetics model; see, for instance, the work of Dixit and Perelson (2004), Rong et al. (2007), where it was shown that at least qualitatively, the graph of the periodic function $\epsilon(t)$ is roughly like the one depicted in Fig. 1. It is characterized by a quick rise of the efficiency to a peak value right after drug intake, followed by a slower decay. This is significantly different from the case where the efficiency is constant, the situation we described in the previous section. In pharmacokinetics, the efficiency $\epsilon(t)$ is traditionally defined as

$$\epsilon(t) = \frac{y(t)}{K + y(t)},$$

for some positive constant K, where $y(t)$ is a state component of a compartmental linear system. For our purposes, we do not need to know the details of the pharmacokinetics process, except for the fact that the signal $y(t)$ (and hence also $\epsilon(t)$) converges to a periodic signal with the same period as the treatment schedule.

Thus, we will assume that the efficiency $\epsilon(t)$ is periodic, and we start by linearizing system (5) at the equilibrium E_0:

$$\dot{x} = B(t)x, \tag{7}$$

where

$$B(t) = \begin{pmatrix} f'(T_0) & 0 & -k(1-\epsilon(t))T_0 \\ 0 & -\beta & k(1-\epsilon(t))T_0 \\ 0 & N\beta & -\gamma \end{pmatrix}.$$

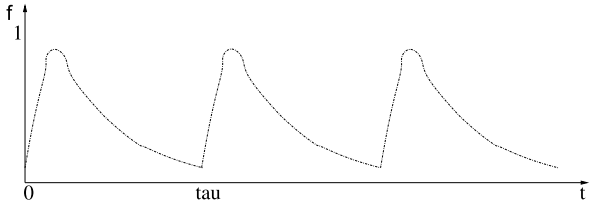

Fig. 1 Periodic drug efficiency $\epsilon(t)$.

It is well known that the stability properties of the origin of (7) (and generically the local stability properties of the equilibrium E_0 for system (5)) are determined by the Floquet multipliers of (7). The block-triangular structure of $B(t)$ implies that these are

$$e^{f'(T_0)\tau} \quad \text{and} \quad \lambda_2, \qquad \lambda_3,$$

where λ_2 and λ_3 are the Floquet multipliers of the planar τ-periodic system:

$$\begin{pmatrix} \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} -\beta & k(1-\epsilon(t))T_0 \\ N\beta & -\gamma \end{pmatrix} \begin{pmatrix} x_2 \\ x_3 \end{pmatrix}. \tag{8}$$

In particular, since $f'(T_0) < 0$ by (2), it follows that the three Floquet multipliers of system (7) are contained in the interior of the unit disk of the complex plane, which in turn implies that E_0 is locally asymptotically stable for system (5)—if $|\lambda_2|, |\lambda_3| < 1$. In fact, by a beautiful argument due to d'Onofrio (2005), it turns out that the same conditions imply the much stronger result of *global* asymptotic stability of E_0 for system (5).

Proposition 1 (d'Onofrio, 2005). *Let the Floquet multipliers of system (7) be contained in the interior of the open unit disk of the complex plane. Then E_0 is GAS for system (5), hence the infection is cleared.*

This result shows how relevant and important it is to determine the Floquet multipliers of system (7). Unfortunately, for general functions $\epsilon(t)$, this is a notoriously difficult task. Therefore, we will consider the simpler case where $\epsilon(t)$ is piecewise constant, bearing in mind that piecewise constant functions are often good approximations to continuous functions. We will start with an even simpler case where $\epsilon(t)$ is of the bang-bang type.

3.1. Periodic drug efficiency of the bang-bang type

We make the following simplifying assumption regarding the shape of the graph of the τ-periodic function $\epsilon(t)$, which is illustrated in Fig. 2:

$$\epsilon(t) = \begin{cases} e, & t \in [0, p], \\ 0, & t \in (p, \tau), \end{cases} \tag{9}$$

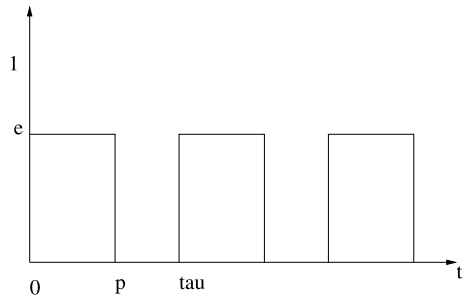

Fig. 2 Periodic drug efficiency $\epsilon(t)$ of the bang-bang type.

where $p \in (0, \tau)$ is the time duration during which the drug is supposed to be active with efficiency $e \in [0, 1]$. During the remaining part of the treatment period the drug is assumed to be totally inefficient. Clearly, this is a very crude way of approximating the more realistic shape of $\epsilon(t)$ depicted in Fig. 1, but some key properties are to be learned from this case, and they carry over to more general cases that describe reality better, as we will discover later.

There are two possible parameters which can be varied in (9), namely e and p, and the purpose of the rest of this subsection is to investigate their effect on the Floquet multipliers of system (8) with (9). These Floquet multipliers are the eigenvalues of the following matrix

$$\Phi(e, p) = \mathrm{EXP}\big[(\tau - p)A(0)\big]\mathrm{EXP}\big[pA(e)\big], \tag{10}$$

where

$$A(e) := \begin{pmatrix} -\beta & k(1-e)T_0 \\ N\beta & -\gamma \end{pmatrix}. \tag{11}$$

Since both $A(e)$ and $A(0)$ are quasi-positive matrices their matrix exponentials are nonnegative matrices.[1] Thus, $\Phi(e, p)$ is a nonnegative matrix and by the Perron–Frobenius theorem (Berman and Plemmons, 1994); its spectral radius $\rho(\Phi(e, p))$ is an eigenvalue of $\Phi(e, p)$. Thus, the Floquet multipliers of system (8) with (9) are contained in the interior of the unit disk of the complex plane if and only if $\rho(\Phi(e, p)) < 1$. This guarantees that the infection is cleared (globally) by Proposition 1.

The following proposition—whose proof is deferred to the Appendix—reveals that $\rho(\Phi(e, p))$ has the expected monotonicity properties: it decreases with e (more efficient treatment) and with p (drug is effective longer).

Proposition 2. *Let $e, e' \in [0, 1]$ and $p, p' \in [0, \tau]$. Then the map $(e, p) \to \rho(\Phi(e, p))$ is continuous,*

$$e < e',\ p \neq 0 \Rightarrow \rho\big(\Phi(e', p)\big) < \rho\big(\Phi(e, p)\big), \tag{12}$$

and

$$p < p',\ e \neq 0 \Rightarrow \rho\big(\Phi(e, p')\big) < \rho\big(\Phi(e, p)\big). \tag{13}$$

Moreover,

$$\rho\big(\Phi(e, 0)\big) = \rho\big(\Phi(0, \tau)\big) = \rho\big(\mathrm{EXP}\big[\tau A(0)\big]\big) > 1$$
$$\text{for all } e \in [0, 1] \text{ and all } p \in [0, \tau] \text{ (no treatment)} \tag{14}$$

and

[1] Proof: Let A be quasi-positive. Then $B = A + \alpha I$ is a nonnegative matrix for all sufficiently large values of α, implying that $\mathrm{EXP}[tB]$ is a nonnegative matrix for all $t \geq 0$. But since $\mathrm{EXP}[tA] = \mathrm{EXP}[-\alpha t]\,\mathrm{EXP}[tB]$, the same conclusion holds for $\mathrm{EXP}[tA]$.

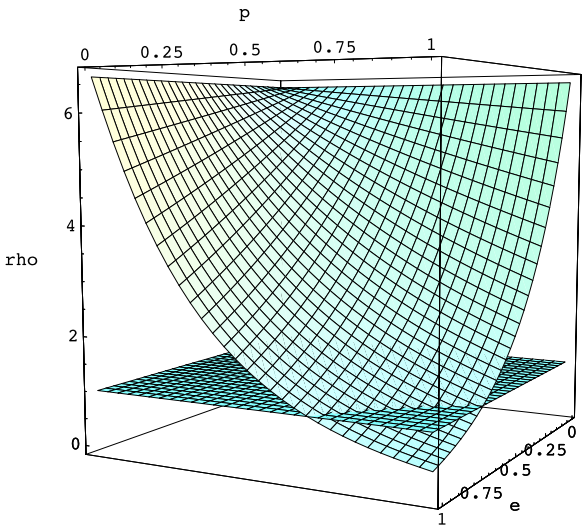

Fig. 3 Spectral radius of $\rho(\Phi(e, p))$ as a function of efficiency e and treatment duration p. The horizontal surface corresponds to $\rho = 1$.

$$\rho\big(\Phi(1,\tau)\big) = \rho\big(\mathrm{EXP}\big[\tau A(1)\big]\big) = \max\big\{\mathrm{EXP}[-\beta\tau], \mathrm{EXP}[-\gamma\tau]\big\} < 1$$
(*constant*, 100% *effective treatment*). (15)

Since $\rho(\Phi(e, p))$ (provided it is less than 1) is a measure of how fast solutions of (5) with (9) approach E_0 (at least locally near E_0), this result may be interpreted as follows: *Let the treatment be periodic, of the bang-bang type, and capable of clearing the infection. If it is more efficient, or lasts longer, then the infection is cleared more quickly.* We illustrate Proposition 2 in Figs. 3 and 4. The parameters used are taken from Rong et al. (2007), and they are as follows: $f(T) = a - bT$ with $a = 10^4$ ml^{-1} day^{-1} and $b = 0.01$ day^{-1} (which implies that $T_0 = 10^6$ ml^{-1}), $k = 2.4 \times 10^{-8}$ ml day^{-1}, $\beta = 1$ day^{-1}, $N = 3000$, $\gamma = 23$ day^{-1}. The period of the treatment τ is 1 day.

In Rong et al. (2007), for a related model, it is argued that the average drug efficiency,

$$\frac{1}{\tau}\int_0^\tau \epsilon(t)\,dt = \frac{ep}{\tau},$$

is a good indicator to assess the success or failure of periodic treatment regimens, in the sense that the outcome of constant (nonperiodic) treatment with drug efficiency at a level equal to the average drug efficiency of the periodic regimen, will predict the outcome of the periodic regimen.

We show in Figs. 5 and 6 that this claim should be interpreted with some caution, as it is only approximately true.

Using the same model parameters as before, we see for instance that the level curve $ep = 0.67$ for the average drug efficiency (recall that $\tau = 1$ day) intersects the level

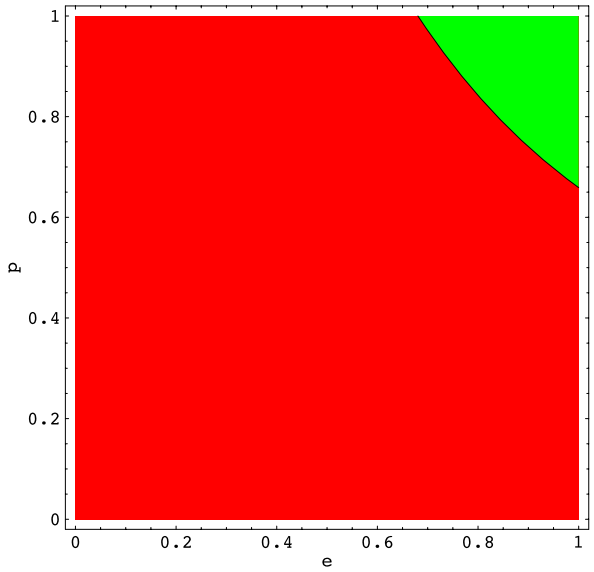

Fig. 4 Contour plot of the spectral radius $\rho(\Phi(e, p))$ as a function of efficiency e and treatment duration p: $\rho(\Phi(e, p)) > 1$ in red (dark) region and < 1 in green (light) region.

curve $\rho(\Phi(e, p)) = 1$. Thus, all points on this level curve and above (below) the curve $\rho(\Phi(e, p)) = 1$ correspond to treatment success (failure). One particular point for which treatment fails is the point $(e, p) = (0.67, 1)$ which corresponds to a constant (nonperiodic) treatment regimen. Recalling (6), we notice that treatment failure for this particular point could also have been concluded from the fact that

$$0.67 < e_{\text{crit}} = 1 - \frac{1}{R_0} \approx 0.681.$$

We can in fact generalize this conclusion, and determine numerically all level curves for the average drug efficiency which contain points corresponding to both treatment failure and success; see Fig. 6. These are the level curves $ep = c$, where $c \in (0.659, 0.681)$, since they intersect the curve $\rho(\Phi(e, p)) = 1$. Points on these level curves that are below (above) the latter curve correspond to treatment failure (success). The efficiency levels $e = 0.659$ and $e = e_{\text{crit}} \approx 0.681$ constitute an interval of

$$\frac{e_{\text{crit}} - 0.659}{e_{\text{crit}}} \approx 3.3\%$$

near e_{crit} for which caution should be exerted in claiming that the average drug efficiency is a good measure for treatment failure or success. Fortunately, this is only a small interval for this example, and thus the average drug efficiency is approximately a good measure for treatment success or failure.

For completeness, we also present in Figs. 7 and 8 the results of a simulation run that illustrate what happens when both a periodic drug treatment regimen, and its corresponding constant (nonperiodic) treatment regimen with the same average drug efficiency fail.

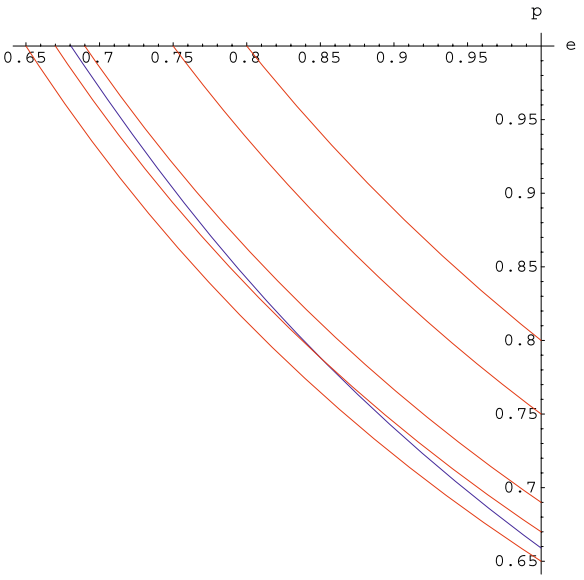

Fig. 5 Level curves for average drug efficiency $ep = c$ in red ($c = 0.65, 0.67, 0.69, 0.75, 0.8$, c increasing in NE direction). Level curve $\rho(\Phi(e, p)) = 1$ in blue: has second lowest intersection with vertical axis.

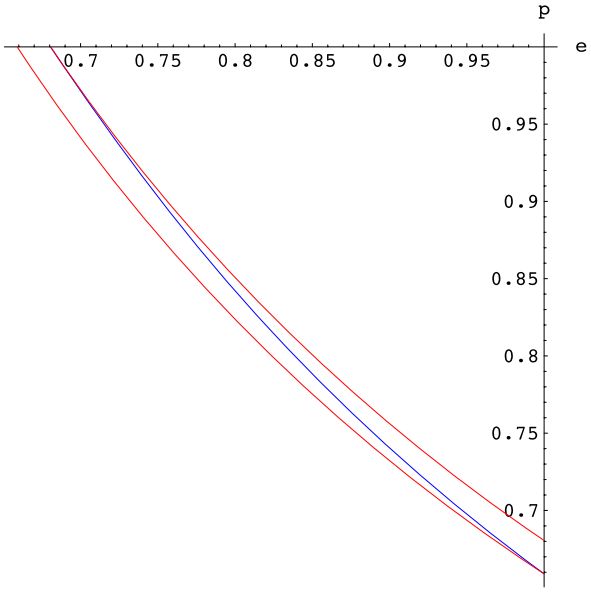

Fig. 6 Level curves for average drug efficiency $ep = c$ in red ($c = 0.659, 0.681$, c increasing in NE direction). Level curve $\rho(\Phi(e, p)) = 1$ in blue: lies between the two level curves of the average drug efficiency. All level curves $ep = c$ with $c \in (0.659, 0.681)$ contain both points of treatment success and treatment failure.

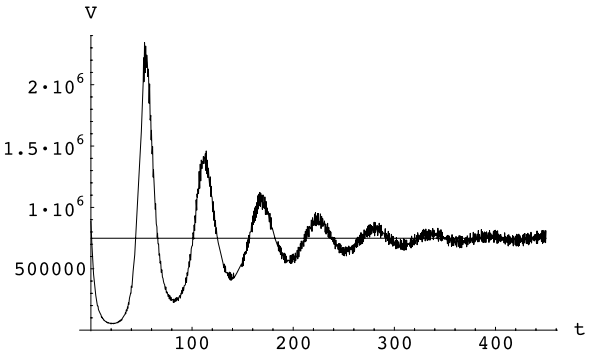

Fig. 7 Plot of the viral load $V(t)$ for system (5) with (9) and $(e, p) = (0.5, 0.5)$. The initial condition is the pretreatment disease steady state $(\bar{T}, \bar{T}^*, \bar{V}) = (319444, 887681, 6806)$; see (3). The horizontal line corresponds to the steady state value of the viral load for the disease steady state of (5) with (9) and $(e, p) = (0.25, 1)$ (that is, a constant, nonperiodic treatment regimen with the same average drug efficiency as the periodic regimen).

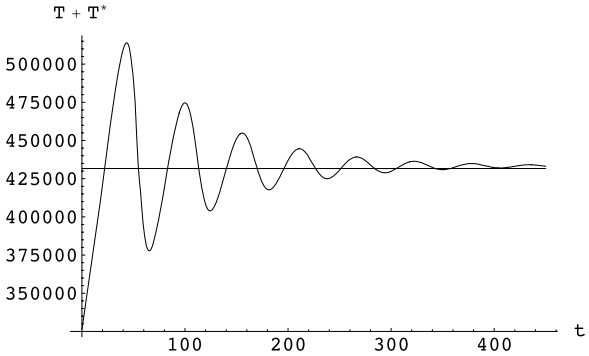

Fig. 8 Plot of the total T-cell load $T(t) + T^*(t)$ for system (5) with (9) and $(e, p) = (0.5, 0.5)$. The initial condition is the pretreatment disease steady state $(\bar{T}, \bar{T}^*, \bar{V}) = (319444, 887681, 6806)$; see (3). The horizontal line corresponds to the steady state value of the total T-cell load for the disease steady state of (5) with (9) and $(e, p) = (0.25, 1)$ (that is, a constant, nonperiodic treatment regimen with the same average drug efficiency as the periodic regimen).

Using the same model parameters as before and using $(e, p) = (0.5, 0.5)$ (so that the average periodic drug efficiency equals $ep/\tau = (0.5)^2/1 = 0.25$), it can be seen that the virus is not eradicated, yet appears to settle down at a periodic cycle. The values of the viral load and total T-cell load at the disease steady state under the constant (nonperiodic) treatment regimen are drawn as horizontal lines.

Remark 1. This result can be modified to the situation in which P inhibitors are used for treatment instead of RT inhibitors. Model (5) is then replaced by

$$\begin{aligned} \dot{T} &= f(T) - kVT, \\ \dot{T}^* &= kVT - \beta T^*, \end{aligned} \tag{16}$$

$$\dot{V} = N\big(1 - \epsilon(t)\big)\beta T^* - \gamma V,$$

and matrix $A(e)$ in (11) by

$$A(e) = \begin{pmatrix} -\beta & kT_0 \\ N(1-e)\beta & -\gamma \end{pmatrix}. \tag{17}$$

With this notation and still using (10), Proposition 2 remains valid.

Remark 2. Similar results can be stated to describe the situation in which combination therapy is used. This is the more commonly found therapy method where patients take a cocktail of both RT and P inhibitors. Model (5) should then be replaced by

$$\begin{aligned} \dot{T} &= f(T) - k\big(1 - \epsilon_{\mathrm{RT}}(t)\big)VT, \\ \dot{T}^* &= k\big(1 - \epsilon_{\mathrm{RT}}(t)\big)VT - \beta T^*, \\ \dot{V} &= N\big(1 - \epsilon_{\mathrm{P}}(t)\big)\beta T^* - \gamma V, \end{aligned} \tag{18}$$

where

$$\epsilon_{\mathrm{RT}}(t) = \begin{cases} e_{\mathrm{RT}}, & t \in [0, p_{\mathrm{RT}}], \\ 0, & t \in (p_{\mathrm{RT}}, \tau), \end{cases} \qquad \epsilon_{\mathrm{P}}(t) = \begin{cases} e_{\mathrm{P}}, & t \in [0, p_{\mathrm{P}}], \\ 0, & t \in (p_{\mathrm{P}}, \tau) \end{cases} \tag{19}$$

denote the piecewise constant efficiencies of the RT and P inhibitors, respectively. Finally, matrix $A(e)$ in (11) is replaced by

$$A(e_{\mathrm{RT}}, e_{\mathrm{P}}) = \begin{pmatrix} -\beta & k(1-e_{\mathrm{RT}})T_0 \\ N(1-e_{\mathrm{P}})\beta & -\gamma \end{pmatrix}. \tag{20}$$

With these notations and assuming without loss of generality that $p_{\mathrm{RT}} < p_{\mathrm{P}}$ (if not, simply swap subscripts RT and P in the expression below), the spectral radius of the following matrix

$$\begin{aligned} &\Phi(e_{\mathrm{RT}}, e_{\mathrm{P}}, p_{\mathrm{RT}}, p_{\mathrm{P}}) \\ &\quad = \mathrm{EXP}\big[(\tau - p_{\mathrm{P}})A(0,0)\big]\,\mathrm{EXP}\big[(p_{\mathrm{P}} - p_{\mathrm{RT}})A(0, e_{\mathrm{P}})\big]\,\mathrm{EXP}\big[p_{\mathrm{RT}}A(e_{\mathrm{RT}}, e_{\mathrm{P}})\big] \end{aligned}$$

is the key quantity. As expected, the spectral radius is decreasing in each of its arguments $e_{\mathrm{RT}}, e_{\mathrm{P}}, p_{\mathrm{RT}}, p_{\mathrm{P}}$. We omit the proofs of these results as they are straightforward modifications of the proof of Proposition 2.

3.2. General piecewise constant periodic drug efficiencies

As mentioned earlier, in practice, the graph of the drug efficiency is not as shown in Fig. 2, but rather as the dashed-dotted line in Fig. 9, which can be approximated by a piecewise constant and τ-periodic efficiency with several constant drug level efficiencies $e_1 > e_2 > \cdots > e_m > e_{m+1}$ during the respective intervals $[p_0, p_1), [p_1, p_2), \ldots, [p_{m-1}, p_m)$, $[p_m - p_{m+1})$, where $p_0 := 0$ and $p_{m+1} := \tau$ for some $m \geq 1$.

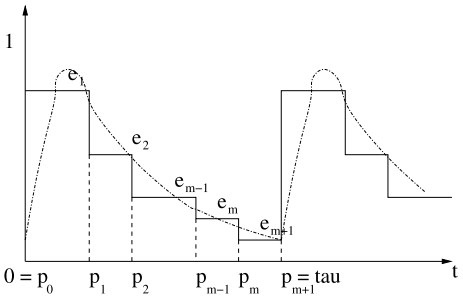

Fig. 9 τ-periodic drug efficiency $\epsilon(t)$ (dashed-dotted line) and a piecewise constant approximation.

Define $(E, P) := (e_1, \ldots, e_{m+1}, p_1, \ldots, p_m)$ and let

$$\Phi(E, P) = \mathrm{EXP}\big[(p_{m+1} - p_m)A(e_{m+1})\big] \ldots \mathrm{EXP}\big[(p_1 - p_0)A(e_1)\big]. \tag{21}$$

Similarly to Proposition 2, we find that the spectral radius of $\Phi(E, P)$ is decreasing in each of its arguments.

Proposition 3. *Let $m \geq 1$, $0 = p_0 < p_1 < p_2 < \cdots < p_m < p_{m+1} = \tau$ and $1 = e_0 \geq e_1 > e_2 > \cdots > e_m > e_{m+1} \geq e_{m+2} = 0$. Then the map $(E, P) \to \rho(\Phi(E, P))$ is continuous. In addition,*

$$i \in \{1, \ldots, m+1\} \text{ and } e_{i+1} < e_i < e_i' < e_{i-1}{}^{2} \Rightarrow \rho\big(\Phi(\tilde{E}_i, P)\big) < \rho\big(\Phi(E, P)\big), \tag{22}$$

and

$$j \in \{1, \ldots, m\} \text{ and } p_{j-1} < p_j < p_j' < p_{j+1} \Rightarrow \rho\big(\Phi(E, \tilde{P}_j)\big) < \rho\big(\Phi(E, P)\big), \tag{23}$$

where

$$\tilde{E}_i = (e_1, e_2, \ldots, e_{i-1}, e_i', e_{i+1}, \ldots, e_{m+1})$$

and

$$\tilde{P}_j = (p_1, p_2, \ldots, p_{j-1}, p_j', p_{j+1}, \ldots, p_m).$$

The proof is deferred to the Appendix.

4. Optimization problems

In this section, we return to the case of periodic efficiencies of the bang-bang type. What follows can easily be generalized to the case of more general, piecewise constant periodic

[2] If $i = 1$, then replace $<$ by $\leq$ in the right most inequality. If $i = m + 1$, replace $<$ by $\leq$ in the left most inequality.

efficiencies. As mentioned earlier, the purpose of treatment is to eradicate the infection by making E_0 GAS for (5) with (9). In practice, however, one would like to achieve this while the burden of drug exposure on the patient is as low as possible. Obviously, there are various ways to measure this burden. Let us list a couple of particular problems, assuming a τ-periodic treatment schedule:

1. Minimize $\rho(\Phi(e, p))$ subject to $(e, p) \in [0, 1] \times [0, \tau]$ and $\int_0^\tau \epsilon(t)\, dt = ep \leq c$, for some fixed $c \in (0, \tau)$.
2. Minimize $\int_0^\tau \epsilon(t)\, dt = ep$, subject to $(e, p) \in [0, 1] \times [0, \tau]$ and $\rho(\Phi(e, p)) \leq \delta$, for some fixed $\delta \in (\rho(\Phi(1, \tau)), 1)$.

In the first problem, the spectral radius of $\Phi(e, p)$ is minimized. As we mentioned before, this spectral radius controls the rate of convergence to E_0 (provided it is less than 1): the smaller the spectral radius, the faster solutions converge. In addition to minimizing the spectral radius, the burden of drug exposure on the patient should not exceed a specified upper bound c. Here, this burden is measured as the area under the graph of the efficiency $\epsilon(t)$ over one treatment cycle. The second problem on the other hand, concerns minimization of the burden, subject to the condition that the spectral radius is less than a given bound δ (assumed to be less than 1 so that convergence to E_0 is guaranteed).

Both problems fit in the larger classes of problems which we describe next. Let the maps $F, G : [0, 1] \times [0, \tau] \to \mathbb{R}$ be continuously differentiable with the following properties:

$$F(0, 0) = G(0, 0) = 0, \quad \text{and} \quad \nabla F,\ \nabla G \geq 0,\ \text{but} \neq 0 \text{ on } [0, 1] \times [0, \tau] \setminus \{(0, 0)\}.$$

Now, consider the more general optimization problems.

Class I. Minimize $\rho(\Phi(e, p))$ subject to $(e, p) \in [0, 1] \times [0, \tau]$ and $F(e, p) \leq c$, for some fixed $c > 0$ satisfying $\{(e, p) | F(e, p) = c\} \cap [0, 1] \times [0, \tau] \neq \emptyset$.

Class II. Minimize $G(e, p)$, subject to $(e, p) \in [0, 1] \times [0, \tau]$ and $\rho(\Phi(e, p)) \leq \delta$, for some fixed $\delta \in (\rho(\Phi(1, \tau)), 1)$.

The first two problems fit in this class for the choices $F(e, p) = G(e, p) = ep$. But it is clear that other choices could be of interest as well, for instance, $F(e, p) = ae^{q_1} + bp^{q_2}$, for some fixed $q_1, q_2 \geq 1$ and $a, b > 0$, or positive linear combinations of several of these functions.

It turns out that both classes of optimization problems can be simplified thanks to Proposition 2. We will see shortly that the optimum appears on the boundary of the constraint set in both cases, which translates into saying that the optimum occurs only if the burden is the maximally allowed one (for problems in the first class), or that the spectral radius takes the largest allowed value (for problems in the second class) implying that convergence to E_0 will be as slow as allowed.

To be more precise, we claim that Class I and II optimization problems are equivalent to Class III and IV problems, respectively, which are defined as follows:

Class III. Minimize $\rho(\Phi(e, p))$ subject to $(e, p) \in [0, 1] \times [0, \tau]$ and $F(e, p) = c$, for some fixed $c > 0$ satisfying that $\{(e, p) | F(e, p) = c\} \cap [0, 1] \times [0, \tau] \neq \emptyset$.

Class IV. Minimize $G(e, p)$, subject to $(e, p) \in [0, 1] \times [0, \tau]$ and $\rho(\Phi(e, p)) = \delta$, for some fixed $\delta \in (\rho(\Phi(1, \tau)), 1)$.

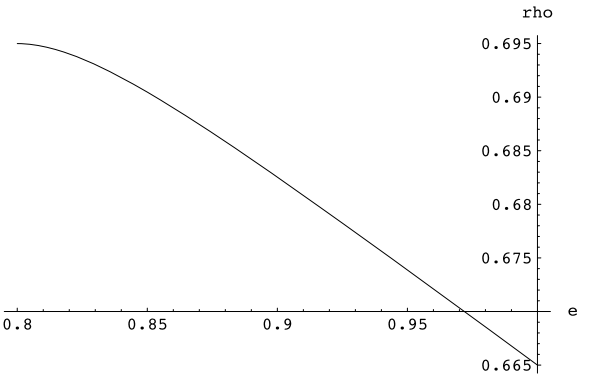

Fig. 10 Graph of $\rho(\Phi(e, p))$ for points (e, p) with $ep = 0.8$ for $e \in [0.8, 1]$. Minimum for ρ is 0.665 and it is achieved for $(e, p) = (1, 0.8)$.

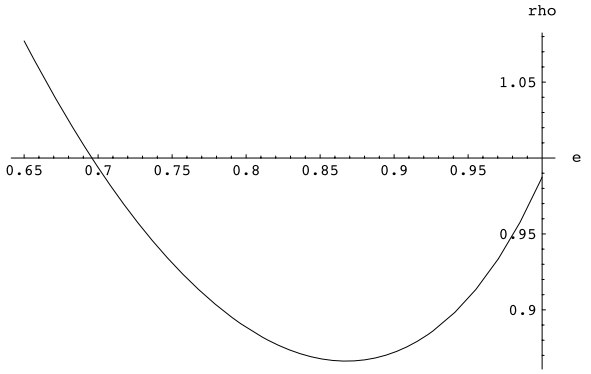

Fig. 11 Graph of $\rho(\Phi(e, p))$ for points (e, p) with $e^2 + p^2 = 1.2^2$ for $e \in [0.65, 1]$. Minimum for ρ is 0.866 and it is achieved for $(e, p) = (0.868, 0.829)$.

Notice that the difference between Class I and III, and Class II and IV is in the constraint only (by replacing the inequality by an equality). In other words, the optimum of Class I and II problems occurs on the boundary of the constraint set. We show this equivalence for Class I and III problems. The argument to show equivalence of Class II and IV problems is very similar and omitted. Suppose that (e^*, p^*) is such that $\rho(\Phi(e^*, p^*))$ is minimal, while $F(e^*, p^*) < c$. Notice that $(e^*, p^*) \neq (0, 0)$ since $c > 0$ and F takes small positive values near $(0, 0)$ in the rectangular region $R := [0, 1] \times [0, \tau]$ and ρ is strictly lower in those points. Also $(e^*, p^*) \neq (1, \tau)$, since otherwise the level set $\{(e, p) | F(e, p) = c\}$ does not intersect R, contrary to our assumption.

If (e^*, p^*) is in the interior of R, then the point $(e', p') := (e^*, p^*) + s\nabla F(e^*, p^*)$ is still in the interior of R with $F(e', p') < c$ for small enough positive s, yet $\rho(\Phi(e', p')) < \rho(\Phi(e^*, p^*))$ by Proposition 2, contradicting minimality. The same argument applies if $(e^*, p^*) = (0, p^*)$ for some $p^* \in (0, \tau)$ or if $(e^*, p^*) = (e^*, 0)$ for some $e^* \in (0, 1)$, since a perturbation of such a point in the direction of $\nabla F(e^*, p^*)$, results in a point which is

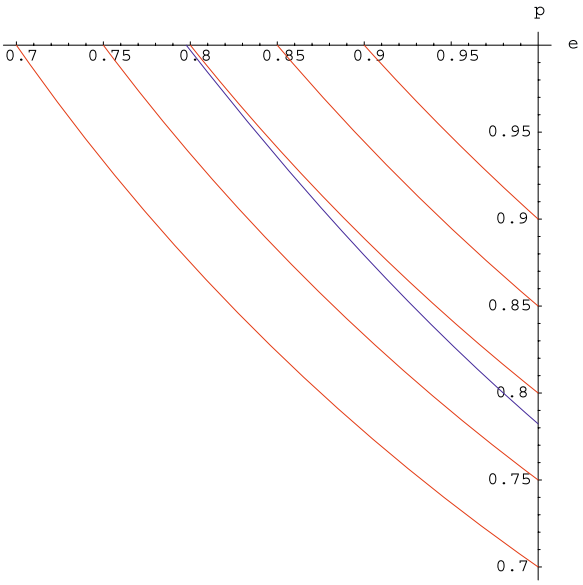

Fig. 12 Level curves $ep = c$ in red ($c = 0.7, 0.75, 0.8, 0.85, 0.9$, c increasing in NE direction). Level curve $\rho(\Phi(e, p)) = 0.7$ in blue: has third lowest intersection with vertical axis.

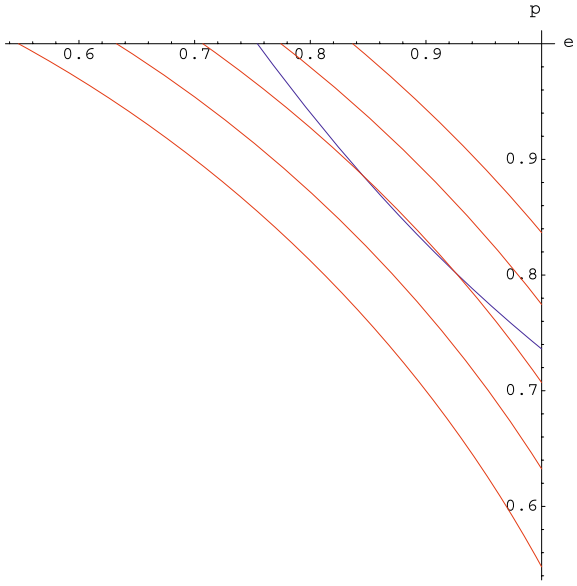

Fig. 13 Level curves $e^2 + p^2 = c$ in red ($c = 1.4, 1.5, 1.6, 1.7, 1.8$, c increasing in NE direction). Level curve $\rho(\Phi(e, p)) = 0.7$ in blue: has fourth lowest intersection with vertical axis.

still in R. If $(e^*, p^*) = (1, p^*)$ for some $p^* \in (0, \tau)$ or if $(e^*, p^*) = (e^*, \tau)$ for some $e^* \in (0, 1)$, then a perturbation in the direction of $\nabla F(e^*, p^*)$ could potentially result in a point outside R. To prevent this, we perturb as follows for the case where $(e^*, p^*) = (1, p^*)$ (the argument when $(e^*, p^*) = (e^*, \tau)$ is similar and omitted): Let $(e', p') = (1, p^*) + (0, s)$. Then for sufficiently small and positive s, (e', p') is still on the boundary of R and $F(e', p') < c$, yet $\rho(\Phi(e', p')) < \rho(\Phi(e, p))$ by Proposition 2, a contradiction to minimality.

5. Numerical examples

Here, we provide some examples of the optimization problems we just discussed. The model parameters used throughout this section are the ones chosen in Section 3.1.

Let us first minimize $\rho(\Phi(e, p))$, see Figs. 3 and 4. The constraint is that the burden of drug exposure on the patient, ep should not exceed 0.8. The minimum is 0.665 (which fortunately implies that with this treatment schedule the infection can be cleared successfully) and it is achieved at $(e, p) = (1, 0.8)$. In other words, the drug should be 100% efficient while it is active. This is illustrated in Fig. 10, which depicts the spectral radius $\rho(\Phi(e, 0.8/e))$.

Let us see what happens when we modify the measure of the burden to $e^2 + p^2$, and demand that it should not exceed 1.2^2. This time the minimal spectral radius is 0.866 (again implying that this therapy will clear the infection) and it is achieved at $(e, p) = (0.868, 0.829)$. This is illustrated in Fig. 11, which depicts the spectral radius $\rho(\Phi(e, \sqrt{1.2^2 - e^2}))$. A striking difference between this schedule and the previous one, is that now the minimum is achieved in the interior of the rectangular parameter space $[0, 1] \times [0, 1]$, while previously it was achieved on the boundary. When the drug is active, it should therefore not be 100% efficient as before.

Let us now consider minimization problems in which the burden is minimized subject to a constraint on the spectral radius, or equivalently, on the speed of convergence to the infection-free equilibrium. If the burden is measured by ep, and if the spectral radius should not exceed 0.7, we find that the minimum is 0.782 and it occurs at $(e, p) = (1, 0.782)$ which is on the boundary of $[0, 1] \times [0, 1]$ and requires that the drug is 100% effective when it is active. This is illustrated in Fig. 12, where we depict a few level curves of ep, and the maximally allowable spectral radius $\rho = 0.7$.

If we modify the measure of the burden to $e^2 + p^2$ (and still assuming the constraint that the spectral radius should not exceed 0.7), then the minimum is 1.493 and it occurs at $(e, p) = (0.884, 0.844)$ which is in the interior of the rectangular region $[0, 1] \times [0, 1]$. This is illustrated in Fig. 13, where we depict a few level curves $e^2 + p^2$, and the maximally allowable spectral radius $\rho = 0.7$.

Acknowledgement

I would like to thank two anonymous reviewers for making several constructive comments and suggestions.

Appendix

Proof of Proposition 2: This proof hinges on the following standard facts:

1. If A is quasi-positive and $A \le B$ but $A \ne B$, then $0 \le \mathrm{EXP}[tA] \le \mathrm{EXP}[tB]$ but $\mathrm{EXP}[tA] \ne \mathrm{EXP}[tB]$ for all $t > 0$.
   To see this, let $\alpha > 0$ be such that $C = A + \alpha I \ge 0$. Then setting $D = B + \alpha I$, we have that $0 \le C \le D$ but $C \ne D$. Then $\mathrm{EXP}[tC] \le \mathrm{EXP}[tD]$, but $\mathrm{EXP}[tC] \ne \mathrm{EXP}[tD]$ for all $t > 0$. It follows that $\mathrm{EXP}[tA] \le \mathrm{EXP}[tB]$ but $\mathrm{EXP}[tA] \ne \mathrm{EXP}[tB]$ for all $t > 0$.
2. For all $t > 0$, $\mathrm{EXP}[tA(e)] > 0$ if $e \ne 1$, while $\mathrm{EXP}[tA(e)] \ge 0$ (but not > 0) if $e = 1$.
3. If $A > 0$ and $B \ge 0$ has no zero row or zero column, then $AB > 0$ and $BA > 0$. This is true in particular when $B = \mathrm{EXP}[tC]$ for $t \ge 0$ and C a quasi-positive matrix because of Fact 1 and the fact that matrix exponentials are invertible.
4. If $0 < A \le B$ but $B \ne A$, then $\rho(A) < \rho(B)$, see Corollary 1.5 in Chap. 2 in Berman and Plemmons (1994).

Continuity of the map $(e, p) \to \rho(\Phi(e, p))$ follows from the definition (10) of ρ and the fact that the spectral radius of any matrix is continuous in terms of its entries.

Let $0 \le e < e' < 1$ and $p \ne 0$. Then

$$
\begin{aligned}
&A(e') \le A(e) \text{ and } A(e') \ne A(e)\\
&\quad\Rightarrow 0 < \mathrm{EXP}\big[pA(e')\big] \le \mathrm{EXP}\big[pA(e)\big] \text{ and } \mathrm{EXP}\big[pA(e')\big] \ne \mathrm{EXP}\big[pA(e)\big]\\
&\qquad\text{by Facts 1 and 2}\\
&\quad\Rightarrow 0 < \mathrm{EXP}\big[(\tau - p)A(0)\big]\mathrm{EXP}\big[pA(e')\big] \le \exp\big[(\tau - p)A(0)\big]\mathrm{EXP}\big[pA(e)\big]\\
&\qquad\text{and}\quad \mathrm{EXP}\big[(\tau - p)A(0)\big]\mathrm{EXP}\big[pA(e')\big] \ne \mathrm{EXP}\big[(\tau - p)A(0)\big]\mathrm{EXP}\big[pA(e)\big]\\
&\qquad\text{by Facts 1 and 3 and invertibility of matrix exponentials}\\
&\quad\Rightarrow 0 < \Phi(e', p) \le \Phi(e, p) \text{ and } \Phi(e', p) \ne \Phi(e, p)\\
&\quad\Rightarrow \rho\big(\Phi(e', p)\big) < \rho\big(\Phi(e, p)\big) \quad \text{by Fact 4.}
\end{aligned}
$$

This result remains valid if $e' = 1$ because $\rho(\Phi(e, p))$ is continuous. This establishes (12).

Let $0 \le p < p' < \tau$ and $e \ne 0$. Then

$$
\begin{aligned}
&A(e) \le A(0) \text{ and } A(e) \ne A(0)\\
&\quad\Rightarrow 0 \le \mathrm{EXP}\big[(p' - p)A(e)\big] \le \mathrm{EXP}\big[(p' - p)A(0)\big]\\
&\qquad\text{and}\quad \mathrm{EXP}\big[(p' - p)A(e)\big] \ne \mathrm{EXP}\big[(p' - p)A(0)\big] \quad \text{by Fact 1}\\
&\quad\Rightarrow 0 \le \mathrm{EXP}\big[(p' - p)A(e)\big]\mathrm{EXP}\big[pA(e)\big] \le \mathrm{EXP}\big[(p' - p)A(0)\big]\mathrm{EXP}\big[pA(e)\big]\\
&\qquad\text{and}\quad \mathrm{EXP}\big[(p' - p)A(e)\big]\mathrm{EXP}\big[pA(e)\big]\\
&\qquad\qquad \ne \mathrm{EXP}\big[(p' - p)A(0)\big]\mathrm{EXP}\big[pA(e)\big] \quad \text{by Fact 1}\\
&\qquad\text{and invertibility of exponentials}\\
&\quad\Rightarrow 0 < \mathrm{EXP}\big[(\tau - p')A(0)\big]\mathrm{EXP}\big[(p' - p)A(e)\big]\mathrm{EXP}\big[pA(e)\big]
\end{aligned}
$$

$$\leq \mathrm{EXP}\big[(\tau - p')A(0)\big]\mathrm{EXP}\big[(p' - p)A(0)\big]\mathrm{EXP}\big[pA(e)\big] \quad \text{and}$$
$$\mathrm{EXP}\big[(\tau - p')A(0)\big]\mathrm{EXP}\big[(p' - p)A(e)\big]\mathrm{EXP}\big[pA(e)\big]$$
$$\neq \mathrm{EXP}\big[(\tau - p')A(0)\big]\mathrm{EXP}\big[(p' - p)A(0)\big]\mathrm{EXP}\big[pA(e)\big]$$
by Fact 2 and invertibility of exponentials
$$\Rightarrow 0 < \Phi(e, p') \leq \Phi(e, p) \text{ and } \Phi(e, p') \neq \Phi(e, p)$$
$$\Rightarrow \rho\big(\Phi(e, p')\big) < \rho\big(\Phi(e, p)\big) \quad \text{by Fact 4.}$$

This remains valid if $p' = \tau$ because $\rho(\Phi(e, p))$ is continuous. This establishes (13).

Finally, it follows from our standing assumption (4), that the determinant of $A(0)$ is negative. Thus, $A(0)$ has a positive eigenvalue which implies (14). Also, (15) is immediate from (11). □

Proof of Proposition 3: The same facts as in the proof of Proposition 2 will be used.

Continuity of the map $(E, P) \to \rho(\Phi(E, P))$ follows from the definition (10) of ρ and the fact that the spectral radius of any matrix is continuous in terms of its entries.

Fix $i \in \{1, \ldots, m+1\}$ and let $e_i < e_i' < 1$. Then

$$A(e_i') \leq A(e_i) \text{ and } A(e_i') \neq A(e_i)$$
$$\Rightarrow 0 < \mathrm{EXP}\big[(p_i - p_{i-1})A(e_i')\big] \leq \mathrm{EXP}\big[(p_i - p_{i-1})A(e_i)\big] \quad \text{and}$$
$$\mathrm{EXP}\big[(p_i - p_{i-1})A(e_i')\big] \neq \mathrm{EXP}\big[(p_i - p_{i-1})A(e_i)\big] \quad \text{by Facts 1 and 2}$$
$$\Rightarrow 0 < \Phi(\tilde{E}_i, P) \leq \Phi(E, P) \text{ and } \Phi(\tilde{E}_i, P) \neq \Phi(E, P) \quad \text{by Facts 1 and 3}$$
and invertibility of matrix exponentials
$$\Rightarrow \rho\big(\Phi(\tilde{E}_i, P)\big) < \rho\big(\Phi(E, P)\big) \quad \text{by Fact 4.}$$

This result remains valid if $i = 1$ and $e_1' = 1$ because $\rho(\Phi(E, P))$ is continuous. This establishes (22).

Fix $j \in \{1, \ldots, m\}$ and let $0 < p_j < p_j' < \tau$. Since $e_{j+1} < e_j$, we have that

$$A(e_j) \leq A(e_{j+1}) \text{ and } A(e_j) \neq A(e_{j+1})$$
$$\Rightarrow 0 \leq \mathrm{EXP}\big[(p_j' - p_j)A(e_j)\big] \leq \mathrm{EXP}\big[(p_j' - p_j)A(e_{j+1})\big] \quad \text{and}$$
$$\mathrm{EXP}\big[(p_j' - p_j)A(e_j)\big] \neq \mathrm{EXP}\big[(p_j' - p_j)A(e_{j+1})\big] \quad \text{by Fact 1}$$
$$\Rightarrow 0 \leq \mathrm{EXP}\big[(p_j' - p_j)A(e_j)\big]\mathrm{EXP}\big[(p_j - p_{j-1})A(e_j)\big]$$
$$\leq \mathrm{EXP}\big[(p_j' - p_j)A(e_{j+1})\big]\mathrm{EXP}\big[(p_j - p_{j-1})A(e_j)\big] \quad \text{and}$$
$$\mathrm{EXP}\big[(p_j' - p_j)A(e_j)\big]\mathrm{EXP}\big[(p_j - p_{j-1})A(e_j)\big]$$
$$\neq \mathrm{EXP}\big[(p_j' - p_j)A(e_{j+1})\big]\mathrm{EXP}\big[(p_j - p_{j-1})A(e_j)\big]$$
by Fact 1 and invertibility of exponentials
$$\Rightarrow 0 < \mathrm{EXP}\big[(p_{j+1} - p_j')A(e_{j+1})\big]\mathrm{EXP}\big[(p_j' - p_{j-1})A(e_j)\big]$$

$$\leq \mathrm{EXP}\big[(p_{j+1}-p_j)A(e_{j+1})\big]\mathrm{EXP}\big[(p_j-p_{j-1})A(e_j)\big] \quad \text{and}$$

$$\mathrm{EXP}\big[(p_{j+1}-p'_j)A(e_{j+1})\big]\mathrm{EXP}\big[(p'_j-p_{j-1})A(e_j)\big]$$

$$\neq \mathrm{EXP}\big[(p_{j+1}-p_j)A(e_{j+1})\big]\mathrm{EXP}\big[(p_j-p_{j-1})A(e_j)\big]$$

by Facts 1 and 3 and invertibility of exponentials

$$\Rightarrow 0 < \Phi(E,\tilde{P}_j) \leq \Phi(E,P) \text{ and } \Phi(E,\tilde{P}_j) \neq \Phi(E,P)$$

by Facts 1 and 3 and invertibility of exponentials

$$\Rightarrow \rho\big(\Phi(E,\tilde{P}_j)\big) < \rho\big(\Phi(E,P)\big) \quad \text{by Fact 4.}$$

This establishes (23). □

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