OPTIMAL PERIODIC CONTROL OF A DRUG DELIVERY SYSTEM

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Abstract: Administration of certain drugs at a steady rate results in a deterioration of the drug effect due to a phenomenon known as tolerance. Periodic drug delivery is an attractive option for maximizing the effect of drugs exhibiting tolerance. In this paper, periodic drug infusion strategies for maximizing an averaged measure of the drug effect are investigated. A simple pharmacokinetic-pharmacodynamic model of a system exhibiting tolerance is considered and optimal periodic control theory is employed. The regions in the parametric space where periodic infusion gives better drug effect than steady infusion are characterized using the so-called π test. The optimal drug delivery strategy obtained using two different computational approaches are presented for a representative set of parameter values and insight is provided into the results. The first method, proposed by the authors, is based on the notion of differential flatness and the second, is based on the standard shooting method for dynamic optimization problems.

1. INTRODUCTION

Periodic delivery of drugs has been observed to be more efficient than a steady delivery in the case of hormonal therapy or when the drug exhibits *tolerance* (Siegel 1997). In many studies on hormonal therapy, it has been observed that if a hormone or a drug that promotes the production of a hormone is administered periodically to match the natural rhythm of the hormone release in the body, it has a better effect. A drug is effective when its concentration is between the levels of a minimum effective concentration (MEC) and a mean toxic concentration (MTC). These limits do not change with time of exposure to the drug for normal drugs. However, for drugs that exhibit tolerance, MEC increases with increasing exposure and may even increase beyond MTC thus making the drug totally ineffective. Thus a periodic infusion of the drug is more suitable for drugs with tolerance. Some recent work on the design of periodic drug delivery systems can be found in (Siegel 1997, Zou and Siegel 1999, Leroux and Siegel 1999).

In this paper, a simple pharmaco-kinetic, pharmaco-dynamic model of a drug is considered and the question whether periodic drug infusion is more effective in a time-averaged sense is investigated. The problem is formulated as an optimal periodic control (OPC) problem so that the powerful analytical and computational techniques developed for OPC problems can be employed (Bittanti and Guardabassi 1986, Bernstein and Gilbert 1980, Maurer *et al.* 1998, Varigonda *et al.* 2004). In particular, the so-called π-test is used to assess when small periodic variations around the optimal steady state (OSS) can improve the OSS performance, a situation known as *local properness*. The region in a two dimensional parameter space

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where the problem is locally proper is computed. Since the π-test is local and only concerns small sinusoidal inputs, more elaborate computations using dynamic optimization methods are required to obtain a solution to the OPC problem. Due to the periodicity of the constraints on the state and the unknown period, the OPC problem is computationally harder than other dynamic optimization problems. The solution to the OPC problem is obtained using two computational methods, both of which produce a consistent solution. The first method is based on flatness as described in (Varigonda *et al.* 2004) and the other, a shooting method provided by a commercially available software tool, gPROMS (PSE n.d.).

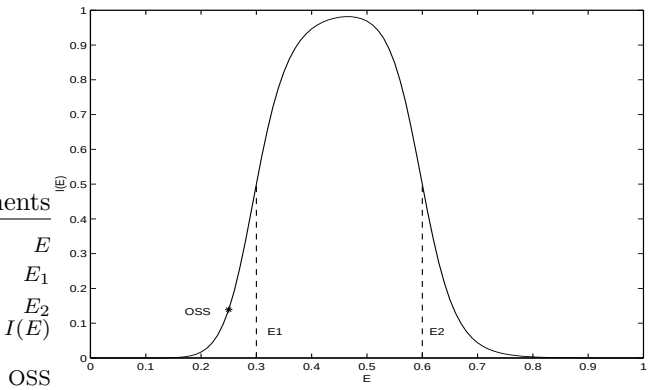


Fig. 1. Plot of the indicator function $I(E)$. The OSS value and the desired interval of the effect E are marked.

2. DRUG DELIVERY SYSTEM MODEL AND FORMULATION OF THE OPC PROBLEM

Here, a variation of the model for tolerance proposed in (Porchet *et al.* 1988) is considered for the cardio-accelerating effect of nicotine. It is demonstrated that periodic delivery gives better performance than steady delivery. The model accounts for tolerance of the drug through the action of a hypothetical metabolite produced by the drug. The metabolite acts as an antagonist and reduces the drug effect. The system consists of a two compartment pharmacokinetic model that describes the time evolution of the drug concentration, c and the antagonist concentration, a and a pharmacodynamic model that describes the effect of the drug in terms of c and a.

The non-dimensionalized dynamics are linear and are given by

$$\dot{c} = -c + u \tag{1}$$

$$\dot{a} = K_a(c - a) \tag{2}$$

where u is the drug infusion rate and K_a is the rate constant for antagonist elimination. The drug effect is described by

$$E(c, a) = \frac{c}{(1 + c)(1 + a/a^*)} \tag{3}$$

where a^* is a measure of the relative potency of the antagonist. The variables c, a and u are all constrained to be positive. In addition there is an upper bound on u reflecting the maximal rate at which the drug can be delivered.

The objective considered is to keep E in a prescribed interval $[E_1, E_2]$ which can be interpreted for the nicotine system as the desired interval for the heart rate. To represent this objective as a maximization, a smooth indicator function is employed. The indicator is close to unity when $E \in [E_1, E_2]$ and close to zero otherwise. The following indicator function is used:

$$I(E) = \frac{(E/E_1)^\gamma}{[1 + (E/E_1)^\gamma][1 + (E/E_2)^{2\gamma}]}.$$

A plot of $I(E)$ is shown in Fig 1.

The objective is to optimize the drug effect indicator, I with respect to the drug infusion rate, u. Both steady and periodic profiles for u are considered. When u is steady, equilibrium solutions of the system in Eqs 1–2 are sought where the objective $J = I(E)$ is maximized. This results in an optimum steady state (OSS) problem. When u is periodic, the time average of the indicator over one time period, given by

$$J = \frac{1}{T} \int_0^T I(E) dt$$

is taken as the objective function for maximization. The period T is unknown and needs to be determined from optimization. In order to be able to repeat the periodic delivery strategy, the states of the system are required to be periodic as well, with the same period. This results in an optimal periodic control (OPC) problem.

3. ANALYSIS USING THE π TEST

A periodically varying u may provide better average drug effect than the OSS solution and in that case, the OPC problem is said to be *proper*. If performance improvements can be obtained by small sinusoidal perturbations of the input around the OSS, then the OPC problem is said to be *locally proper*. Local properness implies properness but the converse is not true. The so-called π-test

can be used to determine local properness of an OPC problem (Bittanti *et al.* 1973, Bernstein and Gilbert 1980).

Consider the OPC problem of minimizing $J = g(y)$ over the inputs, $u(\cdot)$ and the period, T for dynamical system described by $\dot{x} = f(x,u)$ with averaged outputs $y = \frac{1}{T}\int_0^T \phi(x,u)\,dt$. Define the Hamiltonian of the system as

$$H(x,u,y,\lambda,\mu) = g(y) + \lambda' f(x,u) + \mu'(\phi(x,u) - y)$$

where $\lambda(\cdot), \mu$ are the Lagrange multipliers. Notice that the sign of μ is different from that of (Bernstein and Gilbert 1980). This definition ensures consistency of the OSS and OPC Hamiltonians. Let prime denote the transpose and an overbar denote the OSS value. Let $G(s)$ be the transfer function corresponding to the linearized dynamics at the OSS *i.e.*, $G(s) = (sI - \bar{f}_x)^{-1}\bar{f}_u$. The π-test for the local properness of OSS requires that the self-adjoint matrix $\pi(\omega)$ defined by

$$\begin{aligned}\pi(\omega) = {} & G'(-j\omega)\bar{H}_{xx}G(j\omega) + \bar{H}_{ux}G(j\omega) \\ & + G'(-j\omega)\bar{H}_{xu} + \bar{H}_{uu}\end{aligned}$$

be partially negative for some frequency, $\omega > 0$ (Bernstein and Gilbert 1980). The π-test can be used to readily determine if small sinusoidal perturbations of the input u around the OSS value $\bar{u}$ give any improvement in the performance.

The steady state of the system for any given u is given by $c = a = u$ and the optimum steady state (OSS) can be computed by maximizing $I(E)$ which gives $c = a = u = \sqrt{a^*}$ and $E = \frac{\sqrt{a^*}}{(1+\sqrt{a^*})^2}$. The nominal parameter values for the problem are $K_a = 0.1$, $a^* = 1$, $E_1 = 0.3$, $E_2 = 0.6$ and $\gamma = 10$. The optimum steady state (OSS) is at $c = a = u = 1$ and the OSS drug effect is $E_s = 0.25$. The indicator function at OSS is $I(E_s) = 0.1390$. The bounds on the input are taken as $u_{min} = 0$ and $u_{max} = 10$. The optimum steady state (OSS) is at $c = a = u = 1$ and the OSS drug effect is $E_s = 0.25$. The value of the indicator function at OSS is $I(E_s) = 0.1390$.

Since the drug effect E at the OSS is below E_1, steady state operation does not adequately fulfill the requirement that E be in the interval $[E_1, E_2]$. The π test is applied to determine the local properness. A plot of $\pi(\omega)$ *vs.* the frequency, ω is shown in Fig 2. Negative values of the π function over some frequency range indicates that the system is proper and periodic operation can improve the drug effect.

In order to understand the influence of the parameter values K_a and a^* on the local properness,

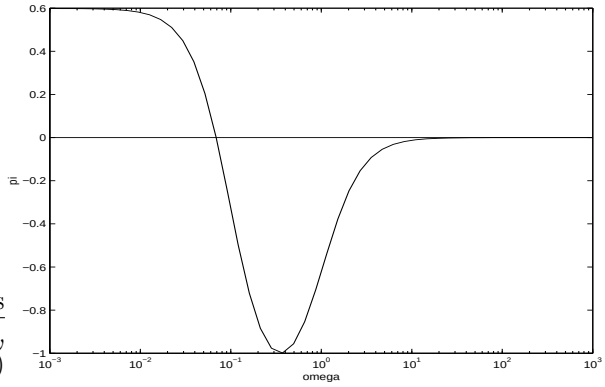


Fig. 2. Result of the π test for the drug effect model with $K_a = 0.1$ and $a^* = 1$

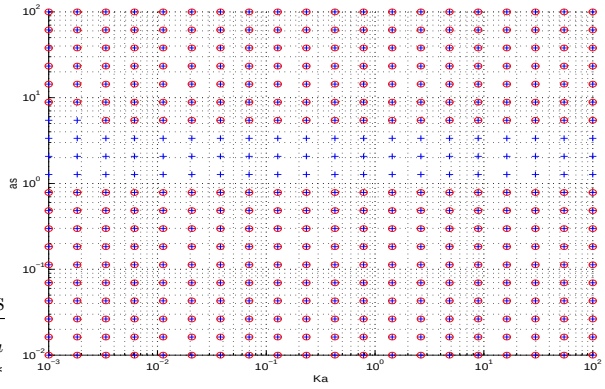
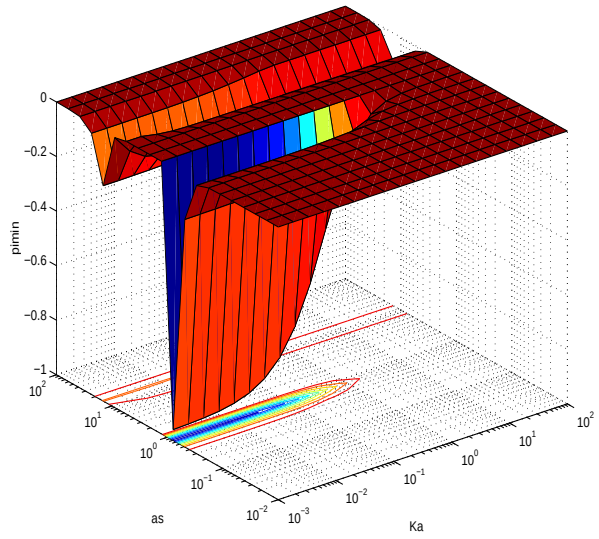


Fig. 3. Grid points in the K_a-a^* space (log-log scale) where the π test is applied (marked by +). Circled points indicate local properness, that is, the superiority of small amplitude periodic delivery over steady delivery.

the π-test is applied for several combinations of K_a and a^*. Fig 3 shows the region in the K_a-a^* space (in log-log scale) where the system is locally proper. It can be seen that the region over which the system is locally proper and small amplitude periodic drug delivery is superior to steady delivery is rather large. The surface plot of $\min_\omega \pi(\omega)$ in Fig 4 shows the extent of improvement that can be obtained with small amplitude periodic inputs in the K_a-a^* parameter space.

4. COMPUTATION OF THE OPTIMAL PERIODIC DRUG DELIVERY STRATEGY

Since the π-test is only local in nature, one cannot determine the exact shape of the periodic control signal that maximizes the drug effect from this test. Computational methods for dynamic optimization, with some modifications, need to be employed for this purpose (Bryson 1999, Maurer *et al.* 1998). It should be emphasized that the computation for the OPC problem is, in general, much harder than a regular optimal control problem due



rag replacements
K_a
a^*

Fig. 4. Surface plot of $\min_\omega \pi(\omega)$ as a function of K_a and a^*. Large negative values of $\min \pi$ indicate stronger gains from periodic delivery.

to the fact that the constraints on the state are periodic and the time period is also unknown.

First, the method based on differential flatness described in (Varigonda *et al.* 2004) to obtain the optimal periodic drug infusion strategy is applied. Differential flatness (or simply, flatness), is the property of a dynamical system that is related to the concepts of absolute equivalence and dynamic feedback linearizability (van Nieuwstadt *et al.* 1998, Martin *et al.* 2003). The system described by $\dot{x} = f(x,u)$ is *differentially flat* if there exist outputs $\xi \in R^m$ depending on x, u and a finite number of time derivatives of u (*i.e.,* $\xi = h(x,u,\dot{u},\ldots,u^{(\rho)})$) such that x, u can be expressed solely as functions of ξ and its derivatives upto order κ (Fliess and *et al.* 1995). The vector ξ must be of the same dimension as u and is called the flat output of the system. An optimal control problem on a flat system can be reformulated as a static optimization problem for efficient computation (Kansal *et al.* 2000, Oldenburg and Marquardt 2000, Mahadevan *et al.* 2000). The need for integration of differential equations is removed by restating the problem in terms of the so-called flat outputs. A computational method for OPC problems using flatness has been presented in (Varigonda *et al.* 2004) and this approach has been used for the current drug delivery problem to compute the OPC solution.

The objective to be maximized in the OPC problem is the time average of the indicator given by

$$J(u,x(0),T) = \frac{1}{T}\int_0^T I(E(c,a))dt.$$

The dynamics in (1)–(2) are linear and flat with the output $\xi = a$. The states and input can be determined from $\Xi := [\xi, \dot{\xi}, \ddot{\xi}]$ using the relations

$$\begin{aligned} a &= \xi \\ c &= \frac{\dot{\xi}}{K_a} + \xi \\ u &= \frac{\ddot{\xi}}{K_a} + (1 + \frac{1}{K_a})\dot{\xi} + \xi. \end{aligned}$$

The highest order derivative of the flat output is parametrized using $2N+1$ Fourier basis functions as:

$$\xi^{(\kappa)}(t,\alpha) = \alpha_1 + \sum_{i=1}^{N} [\alpha_{2i}\sin(i\omega t) \quad (4)$$

$$+\alpha_{2i+1}\cos(i\omega t)] \quad (5)$$

where $\omega = 2\pi/T$ and $\alpha = (\alpha_1, \alpha_2, \ldots, \alpha_N)$. Then, the lower order derivatives $\xi^{(\kappa-1)}, \ldots, \xi$ are obtained by successively integrating Eq. 5 (*e.g.* using quadrature or Simpson's rule), κ times, with an integration constant β_j introduced during the j^{th} integration. Imposing the periodicity constraints on the states one obtains $\alpha_1 = 0$ and $\beta_j = 0$ for all $j = 1, \ldots, \kappa - 1$ since these coefficients lead to polynomial terms in $\xi(t)$. Thus there are only $2N + 2$ unknown parameters, namely, T, α_2, $\ldots$, α_{2N+1} and β_κ to be determined by optimization. Let

$$\theta := [T, \alpha_2, \ldots, \alpha_{2N+1}, \beta_\kappa].$$

The constraints placed on the time period T and the drug infusion rate u are $10^{-2} \le T \le 10^2$ and $0 \le u \le 10$ respectively. In the approximation of $\ddot{\xi}$, 20 Fourier harmonics are employed (*i.e.,* $N = 20$). The solution obtained is shown in Fig 5. It should be noted that there are other locally optimal solutions also for this problem and the one selected is the one that gives the maximum improvement in the objective. The initial guess used and the final solution obtained for the optimization parameter θ are

$$\theta_0 = \begin{bmatrix} 18 \\ 0.01 \\ 0.03 \\ 0 \\ \vdots \\ 0 \\ 0.76 \end{bmatrix}, \qquad \theta = \begin{bmatrix} 17.8138 \\ 0.0051 \\ 0.0295 \\ -0.0058 \\ \vdots \\ 0.0023 \\ 0.7444 \end{bmatrix}$$

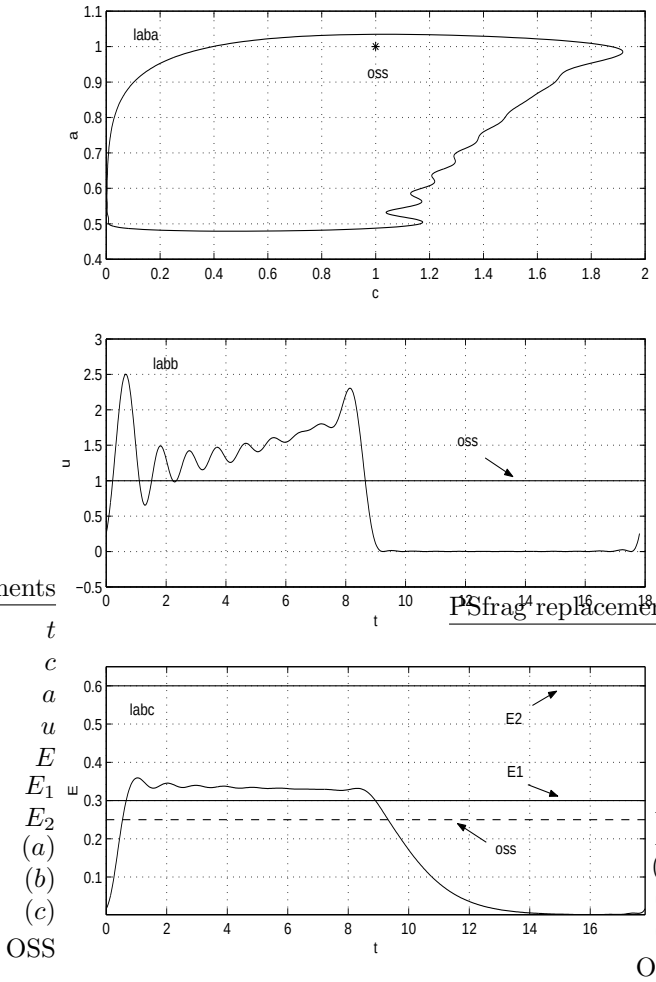


Fig. 5. Optimal periodic drug infusion strategy computed using the flatness method: (a) state space, (b) infusion rate and (c) the effect

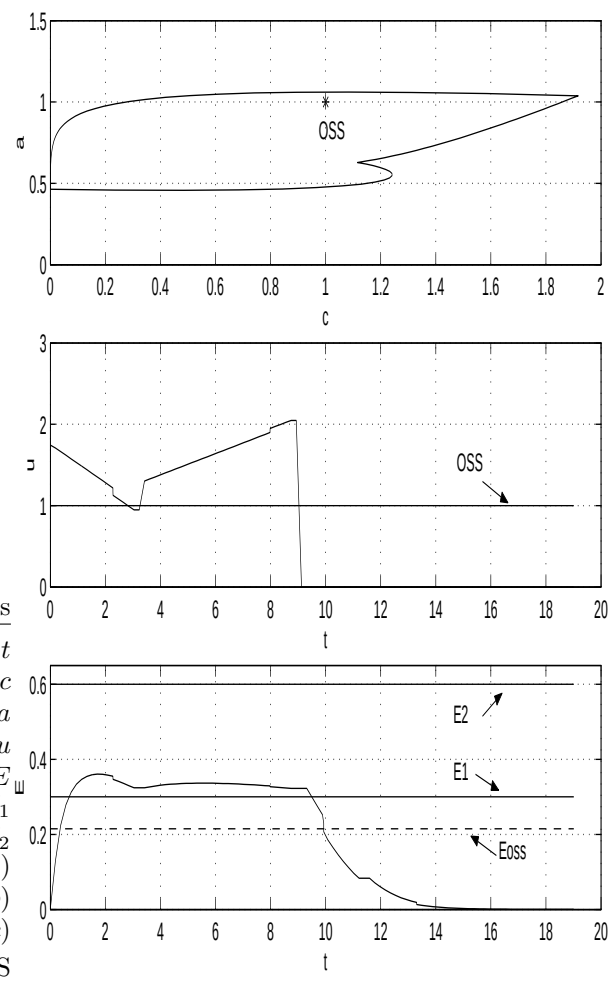


Fig. 6. Optimal periodic drug infusion strategy computed using gPROMS: (a) state space, (b) infusion rate and (c) the effect

where the first element of θ_0 is the time period T and the subsequent terms are the coefficients of the Fourier expansion of $\ddot{\xi}$. The final term is the integration constant β_2 that appears in ξ. The average of the indicator under periodic operation is approximately 0.3537 and the improvement over OSS is 0.2147.

Secondly, the same OPC problem is solved using the dynamic optimization feature of the commercial modeling software, gPROMS (PSE n.d.). Two solvers based on control vector parametrization (CVP) are provided in gPROMS for dynamic optimization. These are CVP_SS (single shooting) and CVP_MS (multiple shooting). CVP refers to the fact that the control signals u are assumed to be of certain shape (*e.g.,* piecewise linear and piecewise constant) and are represented in terms of a few parameters. In order to be able to solve the OPC problem using gPROMS, the problem was reformulated as a fixed time optimal control problem by rescaling time. Thus, the simulation time was fixed at unity while the actual time period T became an optimization parameter appearing on the right hand side of the differential equations. This enabled the objective function J to be correctly evaluated. The solution obtained using the CVP_SS method with 5 piecewise linear segments for u is shown in Fig 6. The similarities in the shape of the trajectory in state space, the input profile and the shape of the drug effect between Fig 5 and Fig 6 are obvious. The differences near the discontinuities are mainly due to the difference in the choice of basis functions.

The numerical improvement in the indicator $I(E)$ itself is not a significant factor since a higher magnitude of improvement can be obtained by using an indicator function that is steeper around the OSS. However, the qualitative features of the solution merit attention. The solution is not of bang-bang type but conforms to the intuitive idea that in presence of tolerance, the best strategy to administer the drug is to give a dose initially that will pump up the effect, while the antagonist is still building up. Once the effect reaches the

desirable value, there is no more incentive in giving more drug. Hence the goal is to only maintain E at the current value for as long as possible. When the antagonist concentration a rises and starts reducing the drug effect, then u needs to be increased again to compensate for the decreasing effect. Ultimately, the antagonist concentration becomes dominating and then u needs to be shut down until a also goes down sufficiently. The cycle then repeats itself.

5. CONCLUSION

A simple pharmacokinetic, pharmacodynamic model of a drug that exhibits tolerance is proposed and an optimal periodic control problem to determine a periodic drug infusion strategy that improves the drug effect is formulated. The local properness of the OPC problem was established using the π-test. The region in the parameter space where the problem is locally proper was also determined using the π-test. The optimal periodic drug infusion rate as a function of time was computed using two very different methods and a consistent solution was obtained. Future work will focus on a better understanding of the modeling aspects that capture the observed superiority of periodic drug administration.

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