

**NONLINEAR MODEL PREDICTIVE CONTROL
FOR OPTIMAL DISCONTINUOUS DRUG
DELIVERY****Nicolas Hudon * Martin Guay ^{*,1} Michel Perrier **
Denis Dochain ******* Queen's University, Kingston, ON, Canada**** École Polytechnique Montréal, QC, Canada***** Université Catholique de Louvain, Louvain-la-Neuve,
Belgium*

Abstract: This paper exploits a gradient-based model predictive control technique to solve an optimal switching time problem over periodic orbits. Drug delivery scheduling applications, where it is desired to maximize the averaged effect of a drug over time, motivate the study for this type of online optimization problem. The objective is to find the optimal time-switching policy between full treatment and no treatment periods. It is shown, by a numerical application to a simple drug delivery problem, that the resulting predictive algorithm drives the system to the optimal periodic orbit in the state space.

Keywords: Model Predictive Control, Time-switching Control, Optimal Drug Delivery, Periodic Orbits.

1. INTRODUCTION

The usual task of nonlinear model predictive control is to find and track the steady-state optimum of a cost functional, subject to the system dynamics and state constraints. In some applications, however, a steady-state optimization may not be feasible nor optimal with respect to a given measure. For example, as outlined in (Varigonda *et al.*, 2004a; Varigonda *et al.*, 2004b), the steady-state optimization of some drug delivery problems yield optimum conditions that do not lead to therapeutic drug treatments. From a practical point of view, optimal drug delivery problems can be seen as optimal time-switching problems, alternating full treatment periods and no treatment periods. For HIV control, optimal scheduling policies were proposed in (Zurakowski and Teel, 2003; Zurakowski *et al.*, 2004). In (Guay *et al.*, 2005),

differential flatness was used to parameterize the trajectories of the system and to compute, in real-time, optimal periodic trajectories using an extremum-seeking method. Since the problem is periodic by nature, we will study it as an optimal control problem over periodic orbits.

In this paper, the problem of optimal drug delivery by periodic injections is solved as an optimal time-switching control problem. Each control cycle includes periods of treatment, or short input impulses, and periods with no treatment. The control is parameterized by a time-switching parameter that should converge to the optimal time interval length between full treatment periods. This problem was treated in the linear case by (Yastreboff, 1969) and more recently using heuristics in (Grognard and Sepulchre, 2001). Asymptotic stabilization for linear output feedback systems was studied in (Allwright *et al.*, 2005). Gradient-based algorithm to solve an anal-

¹ Corresponding Author guaym@chee.queensu.ca

ogous problem was also presented in (Egerstedt *et al.*, 2003).

In this paper, we use a nonlinear model predictive approach, recently developed in (DeHaan and Guay, 2005) that generalize the approach given by (Magni and Scattolini, 2004). The key idea is to see the optimal control moves (here parameterized by switching-time between two control values) as unknown parameters that can be identified on-line via the model predictive control algorithm. The method relies on discrete transitions of the control action based on real-time evolution of those parameters. We allow maximization calculations throughout the entire sampling interval and update the control parameters at a fixed sampling time. The assumptions needed for this implementation relax the flatness assumption used in (Guay *et al.*, 2005) and (Varigonda *et al.*, 2004b).

The paper is divided as follows. In Section 2, we formulate the optimization problem and parameterize the single input to the system using time at which control switches occur as the control parameter. In Section 3, we present the nonlinear model predictive algorithm based on (DeHaan and Guay, 2005) and discuss stability of the closed loop scheme. Numerical application of the resulting law to the drug delivery problem from (Varigonda *et al.*, 2004b) is presented in Section 4. Conclusions and future investigations are outlined in Section 5

2. CONTROL PROBLEM FORMULATION

We consider a single input nonlinear dynamical system of the form:

$$\dot{x} = f(x, u) \quad (1)$$

where $x \in \mathbb{X} \subset \mathbb{R}^n$ are the states of the system, $u \in \mathbb{U} = \{u_{\min}, u_{\max}\}$ is the control input and $f: \mathbb{X} \times \mathbb{U} \rightarrow \mathbb{R}^n$ is a sufficiently smooth function. We assume that \mathbb{X} is a compact subset of \mathbb{R}^n . We also assume that the user-defined objective functional is a convex differentiable function on \mathbb{X} . The control design objective is to optimize a cost functional given by

$$J = \frac{1}{T} \int_t^{t+T} L(x(\tau)) d\tau \quad (2)$$

with respect to $u(\tau)$ for $\tau \in [t, t+T]$, where T is the fixed period of the system, approximated here as the length of the horizon considered later for the optimization problem. We seek to maximize J subject to the system dynamics (1) and inequality constraints

$$x_{\min} \leq x(\tau) \leq x_{\max}, \quad \tau \in [t, t+T] \quad (3)$$

We consider the problem of finding an optimal switching time between two known values of the control inputs, i.e. u_{\min} and u_{\max} . To represent this type of behavior, we parameterize the control $u(\tau)$ as a finite sum of Heaviside functions $u(\theta)$:

$$u(\theta) = \sum_{i=1}^m [H(\tau - i\theta) - H(\tau - i\theta - \varepsilon)] \quad (4)$$

where θ is the switching time parameter. This parameter will be determined on-line by the optimization algorithm. The parameter ε is the known duration of each full-treatment period. In practice, m would be chosen such that $m \cdot \theta < T$ with a meaningful prediction horizon, T . Other parameterizations could have been considered, however Heaviside functions clearly represent the physical application of discontinuous drug infusion. Another advantage here is that the calculations will be greatly simplified using some elementary properties of Heaviside functions and Dirac delta operator. We now state the following assumption:

Assumption 2.1. The unforced dynamics (1) with $u(t) \equiv u_{\min} \equiv 0$ is stable.

This assumption is needed to ensure stability of the close loop dynamics as discuss in the next Section.

3. NONLINEAR MODEL PREDICTIVE CONTROL

3.1 Interior-Point Method

In order to find the optimal control policy that steers the system (1) to the periodic orbit maximizing the cost functional (2), we have to encode the state constraints (3). We propose log-barrier functions (Nash and Sofer, 1996). The cost functional (2) becomes the following:

$$J_c = \frac{1}{T} \int_t^{t+T} (L(x(\tau))) + R_1(x(\tau)) + R_2(x(\tau)) d\tau \quad (5)$$

where

$$R_1(x(\tau)) = \sum_{j=1}^n \mu_{1,j} \log(x_j(\tau) - x_{j,\max} - \epsilon_{1,j})$$

$$R_2(x(\tau)) = \sum_{j=1}^n \mu_{2,j} \log(x_{j,\min} - x_j(\tau) + \epsilon_{2,j})$$

and $\mu_{.j} > 0$, $\epsilon_{.j} > 0$, $j = 1, \dots, n$, are tuning constants for the barrier functions. Given that the functional is convex with respect to the unknown control parameter θ , we can rely on the first order conditions for optimality, given by

$$\nabla_{\theta} J_c(\theta^*) = 0 \quad (6)$$

where $\nabla_{\theta} J_c(\theta^*)$ is the gradient of the functional J_c with respect to θ evaluated at the minimizer θ^* . From the definition of the cost functional (5), this gradient is expressed as

$$\nabla_{\theta} J_c(\theta) = \frac{1}{T} \int_t^{t+T} \Gamma_1 \frac{\partial x}{\partial u} \frac{\partial u}{\partial \theta} d\tau \quad (7)$$

where Γ_1 is the n -row vector defined by

$$\Gamma_1 = \left(\frac{\partial L}{\partial x} + \frac{\partial R_1}{\partial x} + \frac{\partial R_2}{\partial x} \right)^T \quad (8)$$

with each j^{th} -element, $j = 1, \dots, n$, is given by

$$\Gamma_{1j} = \frac{\partial L}{\partial x_j} + \frac{\mu_{1,j}}{x_j(\tau) - x_{j,\max} - \epsilon_{1,j}} - \frac{\mu_{2,j}}{x_{j,\min} - x(\tau) + \epsilon_{2,j}} \quad (9)$$

The first derivative of x with respect to u can be evaluate along the trajectories of the following tractable dynamics

$$\frac{d}{dt} \left(\frac{\partial x}{\partial u} \right) = \frac{\partial f}{\partial x} \frac{\partial x}{\partial u} + \frac{\partial f}{\partial u} \quad (10)$$

By the parametrization (4) of $u(\theta)$, we have :

$$\frac{\partial u}{\partial \theta} = - \sum_{i=1}^N i \left(\delta(t - i\theta) - \delta(t - i\theta - \varepsilon) \right) \quad (11)$$

where $\delta(\cdot)$ is the Dirac delta function. By definition,

$$\int_{\Lambda} f(x) \delta(x - a) dx = f(a), \quad \text{if } a \in \Lambda \quad (12)$$

Therefore, we can rewrite (7) as

$$\nabla_{\theta} J_c(\theta) = \frac{1}{T} \sum_{i=1}^N i \left[\Gamma_1 \frac{\partial x}{\partial u} \right]_{i\theta}^{i\theta+\varepsilon} \quad (13)$$

where $[F(\cdot)]_a^b = F(b) - F(a)$. Equations (13) shows the dependence of the cost functional J_c on the control parameter θ . We will use this information in the next section to derive a stable updating law for θ . The main advantage of the proposed parametrization is that the cost function gradient to evaluate is now given by a finite sum of trackable terms.

3.2 Parameter Update Law

In this section, we apply the nonlinear model predictive control procedure proposed in (DeHaan and Guay, 2005). The idea is to assume that

we can compute the model prediction instantaneously solving the closed-loop dynamics:

$$\begin{aligned} \dot{x} &= f(x, u(\theta)) \\ \dot{\theta} &= \Psi(t, x) \end{aligned} \quad (14)$$

The continuous update law $\Psi(t, x)$ must be chosen such that $\langle \nabla_{\theta} J_c, \Psi(t, x) \rangle \leq 0$. In (DeHaan and Guay, 2005), one way to achieve this criterion is to use a general descent continuous update law:

$$\Psi(t, x) = \text{Proj}\{\vartheta(t, x)\} \quad (15)$$

$$\vartheta(t, x) = k_{\theta} \Upsilon \nabla_{\theta} J_c \quad (16)$$

In the present paper, Υ is set to I (gradient-based method). The projection algorithm $\text{Proj}(\cdot)$ is designed to ensure that the value of the parameter remains in the convex set

$$\Omega_w = \{\theta \in \mathbb{R} : |\theta| \leq w_m\} \quad (17)$$

This algorithm is given by

$$\dot{\theta} = \text{Proj}\{\theta, \vartheta\} = \begin{cases} \vartheta & \text{if } |\theta| < w_m \\ & \text{or } |\theta| = w_m \\ & \text{and } \nabla \mathcal{P}(\theta) \vartheta \leq 0 \\ \vartheta - \vartheta \frac{\lambda \nabla \mathcal{P}(\theta) \nabla \mathcal{P}(\theta)^T}{\|\nabla \mathcal{P}(\theta)\|_{\lambda}^2} & \text{otherwise} \end{cases} \quad (18)$$

where $\mathcal{P}(\theta) = \theta^2 - w_m \leq 0$, λ is a positive constant gain for the projection algorithm. General properties of this projection algorithm are presented in (Krstic *et al.*, 1995) and (Pomet and Praly, 1992).

3.3 Convergence to the Optimal Cycle

Following the extremum seeking procedure proposed in (Guay and Zhang, 2003), we use the following Lyapunov function:

$$V = \frac{1}{2} |J_c(\theta)|^2 \geq 0 \quad (19)$$

The derivative of V with respect to time is

$$\dot{V} = |J_c(\theta)| \left(\nabla_{\theta} J_c(\theta) \dot{\theta} + \Gamma_1(T+t) - \Gamma_1(t) \right) \quad (20)$$

It is possible to show by a simple Lyapunov argument that the convergence of the algorithm to the optimal cycle is ensured if $\dot{J}_c \rightarrow 0$ as $t \rightarrow \infty$. To achieve stability, the open-loop dynamics must be such that:

$$\frac{\partial \Gamma_1}{\partial x} f(x, 0) < 0 \quad (21)$$

Since by assumption the open-loop dynamics are stable for $u \equiv 0$, the last condition is met for $\frac{\partial \Gamma_1}{\partial x} > 0$. Therefore, the optimum is reached when the cost stabilizes to a constant value, that is

when we reach the optimal closed orbit. Since the dynamic for $\dot{\theta}$ is stable, the algorithm ensures convergence to the optimal periodic orbit whenever θ reaches its optimal value.

3.4 Receding Horizon Implementation

To implement the algorithm derived above in real-time, we need to evaluate on-line sensitivity information of the state trajectories with respect to the control. Moreover, to evaluate the gradient, we need the sensitivity of those equations with respect to time, as expressed in the equations (10). Following ideas presented in (DeHaan and Guay, 2005), the proposed method uses the simulation of the system (1) with u generated by a fixed switching time θ over the receding horizon $\tau \in [t, t + T]$, corresponding to one assumed period of the system. This enables us to generate the gradient information and to update θ according to equation (14). The new value of the parameter θ is changed at the end of the cycle to generate another free dynamic of the system.

To summarize the algorithm:

- (1) Assume fixed switching time θ and prediction horizon T .
- (2) Simulate the system with discontinuous inputs for t to $t + T$.
- (3) Compute the gradient $\nabla_{\theta} J_c(\theta)$ as the finite sum 13.
- (4) At time $t = \theta$, update θ and the horizon T .

Results from (DeHaan and Guay, 2005) show a computational advantage of this method over existing receding horizon techniques. We now turn our attention to a simple numerical example to show the potential of the method.

4. APPLICATION TO DRUG DELIVERY

To illustrate, we apply the algorithm developed in Section 3 to a drug delivery problem studied in (Guay *et al.*, 2005; Varigonda *et al.*, 2004b). The objective is to maximize the time average of some indicator function of the drug concentration, c and the drug antagonist concentration, a :

$$J = \frac{1}{T} \int_0^T I(E(c, a)) d\tau \quad (22)$$

where the indicator function is defined as

$$I(E) = \frac{(E/E_1)^\gamma}{[1 + (E/E_1)^\gamma][1 + (E/E_2)^{2\gamma}]} \quad (23)$$

and the drug effect E is

$$E(c, a) = \frac{c}{(1+c)(1+a/a^*)} \quad (24)$$

where a^* is the relative potency of the antagonist. The prescribed range of the effect of the drug during the therapy is enforced by the parameters E_1 and E_2 in the indicator function. To be effective, the therapy must lie within the interval $[E_1, E_2]$ during the cycle. The parameter γ is used to increase the sensitivity of the indicator to changes in the drug effect. The non-dimensional linear dynamics of the systems are given by

$$\dot{c} = -c + u \quad (25)$$

$$\dot{a} = K_a(c - a) \quad (26)$$

with K_a , the rate constant of the antagonist elimination. We constrain the states with $0 \leq a \leq 1$ and $0 \leq c \leq 1$. In this region, the unforced dynamics converges to the origin. The first derivative of x with respect to u is given by:

$$\frac{d}{dt} \left(\frac{dx}{du} \right) = \begin{pmatrix} -1 & 0 \\ K_a & -K_a \end{pmatrix} \left(\frac{dx}{du} \right) + \begin{pmatrix} 1 \\ 0 \end{pmatrix} \quad (27)$$

Simulations and control parameters are given in Tables 1 and 2 respectively.

Table 1. Drug Delivery Problem Parameters

K_a	0.1
a^*	1
E_1	0.3
E_2	0.6
γ	10
u_{\min}	0
u_{\max}	1
ε	1

Table 2. Control Parameters

κ	0.1
w_m	10
λ	1
T	10
$\mu_{1,2}$	1
$\epsilon_{1,2}$	0.01

Simulation results of the state variable trajectories are given in Figure 1. A phase plane diagram is shown in Figure 2. From that figure, we see how the system is driven to a stable periodic orbit and how this periodic orbit is moved to the optimal one.

The trajectory of the switching-time parameter in Figure 3 shows that the control procedure with the optimal parameter θ .

The cost function value over time is represented in Figure 4. The effect of the drug over time and the value of the indicator function are presented in Figure 5. From this figure, we see that the therapeutic range $[E_1, E_2]$ is reached at each cycle.

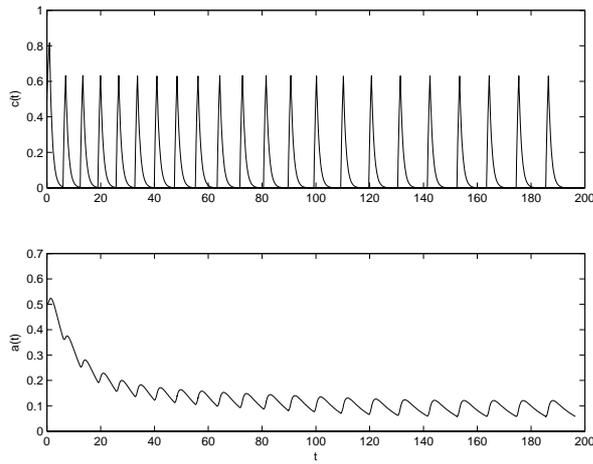


Fig. 1. States trajectories over time

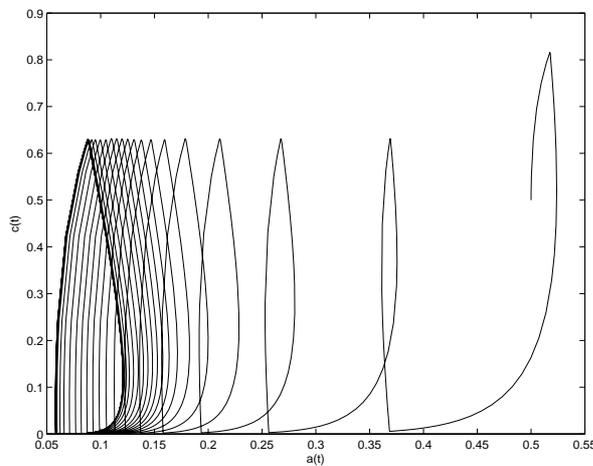


Fig. 2. States in the phase space

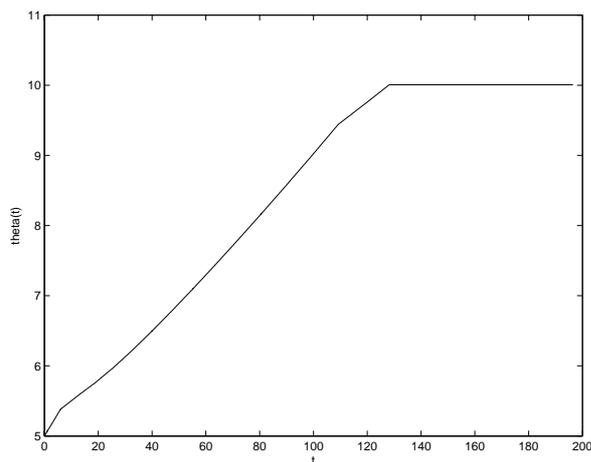


Fig. 3. Evolution of the switching time θ

5. CONCLUSION

In this paper, we posed and solved a single input optimal control problem over periodic orbits using extremum seeking and receding horizon techniques. The method proposed used parametrization of the control as a sequence of time switching.

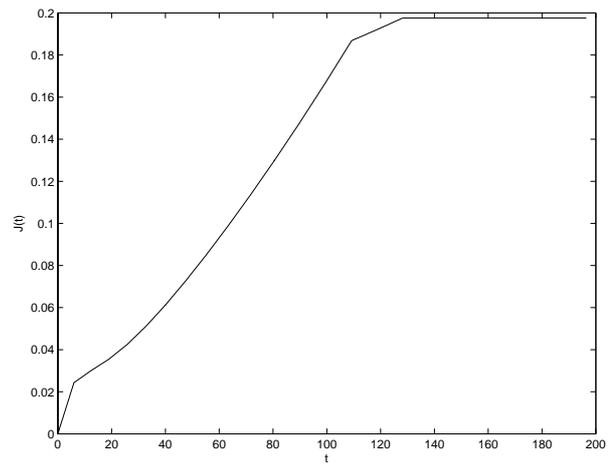


Fig. 4. Cost function over time

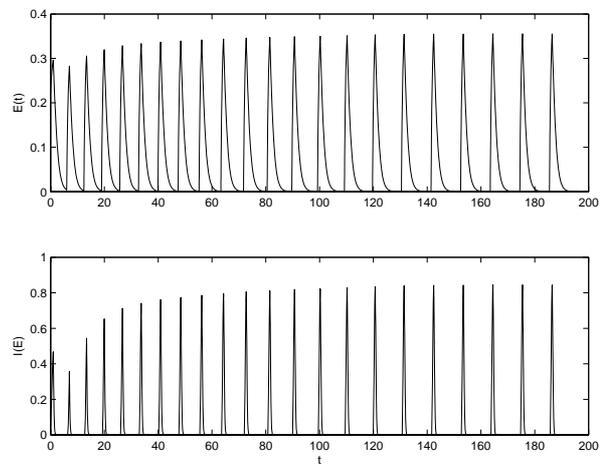


Fig. 5. Drug effect and indicator function over time

Future investigations will focus on adaptive extensions of the method with applications to drug delivery optimal problems with unknown parameters. Other applications with impulse controls can also be considered (see for example the bipedal robot application (Morris and Grizzle, 2005) and the wedge billiard (Sepulchre and Gerard, 2004)).

REFERENCES

- Allwright, J.C., A. Astolfi and H.P. Wong (2005). A Note on Asymptotic Stabilization of Linear Systems by Periodic, Piecewise Constant, Output Feedback. *Automatica* **41**, 339–344.
- DeHaan, D. and M. Guay (2005). A New Real-Time Framework for Nonlinear Model Predictive Control of Continuous-Time Nonlinear Systems. In: *Proceedings of the 44th IEEE Conference on Decision and Control and the European Control Conference*. Seville, Spain. pp. 957–962.
- Egerstedt, M., Y. Wardi and F. Delmotte (2003). Optimal Control of Switching Times in Switched Dynamical Systems. In: *Proceedings*

- of the 42nd IEEE Conference on Decision and Control. Maui, Hawaii. pp. 2138 – 2143.
- Grognard, F. and R. Sepulchre (2001). Global Stability of a Continuous-time Flow which Computes Time-optimal Switchings. In: *Proceedings of the 40th IEEE Conference on Decision and Control*. Orlando, FA. pp. 3826–3831.
- Guay, M. and T. Zhang (2003). Adaptive Extremum Seeking Control of Nonlinear Dynamic Systems with Parametric Uncertainties. *Automatica* **39**, 1283–1293.
- Guay, M., D. Dochain, M. Perrier and N. Hudon (2005). Extremum Control Over Periodic Orbits. In: *Proceedings of the 16th IFAC World Congress*. Prague, Czech Republic.
- Krstic, M., I. Kanellakopoulos and P. Kokotovic (1995). *Nonlinear and Adaptive Control Design*. Wiley and Sons. NY.
- Magni, L. and R. Scattolini (2004). Model Predictive Control of Continuous-time Nonlinear Systems with Piecewise Constant Control. *IEEE Transactions on Automatic Control* **49**(6), 900–906.
- Morris, B. and J.M. Grizzle (2005). A Restricted Poincaré Map for Determining Exponentially Stable Periodic Orbits in Systems with Impulse Effects: Application to Bipedal Robots. In: *Proceedings of the 44th IEEE Conference on Decision and Control and the European Control Conference*. Seville, Spain. pp. 4199–4206.
- Nash, S.G. and A. Sofer (1996). *Linear and Nonlinear Programming*. McGraw-Hill.
- Pomet, J.B. and L. Praly (1992). Adaptive Nonlinear Regulation: Estimation from the Lyapunov Equation. *IEEE Transactions on Automatic Control* **37**(6), 729–740.
- Sepulchre, R. and M. Gerard (2004). Stabilization Through Weak and Occasional Interactions : A Billiard Benchmark. In: *Proceedings of the 6th IFAC Symposium on Nonlinear Control Systems*. Stuttgart, Germany. pp. 75–80.
- Varigonda, S., T.T. Georgiou and P. Daoutidis (2004a). Numerical Solution of the Optimal Periodic Control Problem using Flatness. *IEEE Transactions on Automatic Control* **49**(2), 271–275.
- Varigonda, S., T.T. Georgiou, R.A. Siegel and P. Daoutidis (2004b). Optimal Periodic Control of a Drug Delivery System. In: *Proceedings of IFAC DYCOPS*. Boston, MA.
- Yastreboff, M. (1969). Synthesis of time-optimal control by time interval adjustment. *IEEE Transactions on Automatic Control* **14**(6), 707–710.
- Zurakowski, R. and A.R. Teel (2003). Enhancing Immune Response to HIV Infection Using MPC-Based Treatment Scheduling. In: *Proceedings of the American Control Conference*. Denver, CO.
- Zurakowski, R., A.R. Teel and D. Wodarz (2004). Utilizing Alternate Target Cells in Treating HIV Infection Through Scheduled Treatment Interruptions. In: *Proceedings of the American Control Conference*. Boston, MA.