EXTREMUM-SEEKING CONTROL OVER PERIODIC ORBITS [1]

M. Guay * **D. Dochain** *** **M. Perrier** ** **N. Hudon** *

* *Department of Chemical Engineering, Queen's University, Kingston, Ontario, Canada K7L 3N6*
** *Département de Génie Chimique, École Polytechnique de Montréal,Montréal, PQ, Canada*
*** *CESAME, Université Catholique de Louvain, Louvain-la-Neuve*

Abstract: In this paper, an extremum-seeking controller is developed to steer a periodic system to orbits that maximize a functional of interest. The problem is posed as a real-time optimal trajectory generation problem in which the optimal orbit is computed using an extremum-seeking approach. The control algorithm provides tracking of the optimal orbit. A drug delivery system is considered to demonstrate the application of the technique.

Keywords: Periodic systems, extremum-seeking control, real-time optimization

1. INTRODUCTION

The task of extremum-seeking control is to track the steady-state optimum of a cost functional subject to the system dynamics. Most techniques developed focus primarily on real-time steady-state optimization where the objective function is a sufficiently smooth function of the state variables and/or some tuning parameters. In many applications, the search for a steady-state extremum does not provide a viable operating policy. As discussed in (Varigonda *et al.*, 2004*a*) and (Varigonda *et al.*, 2004*b*), this situation arises in the design of drug delivery systems where steady-state optimization leads to conditions that are not therapeutic. The same phenomena was observed in the study of catalytic chemical systems (Bailey and Horn, 1971). In biological systems, the very nature of the problem dictates operating about periodic cycles, circadian or otherwise. Recent results (see (Laroche and Claude, 2004) for example) have shown that it is possible, using knowledge of the system dynamics, to change the cyclic behavior of anomalous biological systems so that they can operate normally.

The techniques employed to date are primarily open-loop optimal trajectory generation approaches that rely on off-line optimization. In (Varigonda *et al.*, 2004*b*), numerical techniques are used to compute trajectories of differentially flat systems which maximize user-specified cost functionals over periodic orbits. The application to flat systems allows one to completely parameterize the trajectories of the system by assigning paths in the so-called flat output space. Thus, the dynamic optimization problem can be transformed to a finite-dimensional nonlinear optimization problem which can be solved readily.

In this paper, we consider the approach proposed in (Guay and Zhang, 2003) to solve dynamic optimization problems in finite dimensional nonlinear systems. As in (Guay and Zhang, 2003), a Lyapunov-based optimization method is proposed which uses knowledge of the model structure and

[1] The authors would like to acknowledge the financial support of NSERC.

of the dynamic cost functional. We exploit the knowledge of the model structure to parameterize the set of admissible trajectories to maximize the prescribed cost functional over a finite dimensional set of parameters. Using a Lyapunov-based technique, the set of parameters is updated in real-time to achieve optimization of the dynamic cost. The optimal trajectories are implemented in real-time using a suitable tracking controller. In this paper, we consider the application of this technique to the solution of real-time dynamic optimization problems in differentially flat nonlinear systems.

The paper is organized as follows. In Section 2, we state and formulate the dynamic optimization problem. The optimization technique and the implementation of the control is discussed in Section 3. Simulation results are discussed in Section 4 which is followed by brief conclusions in Section 5.

2. PROBLEM STATEMENT

In this paper, we consider general nonlinear systems of the form:

$$\dot{x} = f(x) + \sum_{i=1}^{p} g_i(x)u_i(t) \tag{1}$$

where the elements of $f : \mathbb{R}^n \to \mathbb{R}^n$ and $g_i : \mathbb{R}^n \to \mathbb{R}^n$ are C^∞ functions, $x \in \mathbb{R}^n$ are the state variables and $\mathbf{u}(t) = [u_1(t), \ldots, u_p(t)]^T \in \mathbb{R}^p$ is the vector of p input variables.

The control design objective is to steer the nonlinear system (1) to the trajectory which optimizes a cost functional of the form:

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

with respect to $x(\tau)$ for $\tau \in [t, t+T]$ subject to the system dynamics (1) and the inequality constraints,

$$r(x(\tau)) \le 0,\ \tau \in [t, t+T] \tag{3}$$

where $r : \mathbb{R}^n \to \mathbb{R}^m$ is a vector-valued smooth function of the states. The period T, assumed fixed, is taken as the length of the horizon considered for the cost functional.

It is assumed that the trajectories $x(\tau)$ evolve in a compact subset Ω of $\Re^n$. The cost functional $J : \Omega \to \Re^+$ is assumed to be a convex differentiable function on Ω. To solve this problem, we must consider some parametrization of the trajectories of the system (1) over the set Ω. In this paper, we focus on the situation where the model (1) is differentially flat.

2.1 Flat Dynamical Systems

Differential flatness, a notion introduced by Martin (Martin, 1992), refers to the existence of so-called flat or linearizing outputs that summarize the dynamics of a nonlinear system. The system (1) is said to be differentially flat if there exists variables $y = [y_1, ..., y_p]^T$ given by an equation of the form:

$$y = \mathbf{h}(x, u, \dot{u}, ..., u^{(\rho)}) \tag{4}$$

The variables $y = [y_1, ..., y_p]^T$ are referred to as the flat outputs.

The main advantage of differential flatness is that all system trajectories can be trivially defined in the flat output space. In fact, the original system variables $\mathbf{x}(t)$ and $\mathbf{u}(t)$ can be written as functions of these *flat outputs* ($\mathbf{y}(t)$ or $\mathbf{y}(\tau)$) and a finite number of their derivatives:

$$\mathbf{x}(t) = \alpha(\mathbf{y}(t), \mathbf{y}^{(1)}(t), ...\mathbf{y}^{(k)}(t)) \equiv \alpha(\bar{\mathbf{y}}(t)) \tag{5}$$
$$\mathbf{u}(t) = \beta(\mathbf{y}(t), \mathbf{y}^{(1)}(t), ...\mathbf{y}^{(k)}(t)) \equiv \beta(\bar{\mathbf{y}}(t))$$

where $\bar{\mathbf{y}}(t)$ is a vector of derivatives of the flat output of the form

$$\bar{\mathbf{y}}(t) = [\mathbf{y}(t), \mathbf{y}^{(1)}(t), ...\mathbf{y}^{(k)}(t)]^T.$$

Here $\mathbf{y}^{(i)}(t)$ stands for the i^{th} derivative of $\mathbf{y}(t)$ with respect to t and k is the number of derivatives of $\mathbf{y}(t)$ required to represent the system in the form (5).

2.2 Dynamic Optimization using Flatness

Using differential flatness, the set of trajectories can be parameterized by simply choosing a suitable parameterization for the flat outputs. The resulting state and input trajectories can be computed directly from (5). This strategy has been employed in many studies (see, (Varigonda *et al.*, 2004*a*), (Agrawal *et al.*, 1999), (Mahadevan *et al.*, 2000), (Martin, 1992), (Murray *et al.*, 1995), (Oldenburg and Marquardt, 2000), (Rothfuss *et al.*, 1996), (Rouchon *et al.*, 1993) and the references therein). In the current application, we enforce the periodicity by parameterizing the flat output trajectories using Fourier series. In particular, we assign the highest derivative of the flat outputs, $y^k(t)$, as

$$y^{(k)}(t) = \alpha_0 + \sum_{i=1}^{n}(\alpha_{1i}\sin(i\omega t) + \alpha_{2i}\cos(i\omega t)) \tag{6}$$

where $\theta = [\alpha_0, \alpha_{11}, \ldots, \alpha_{1n}, \alpha_{21}, \ldots, \alpha_{2n}]^T$ are the parameters to be assigned and $\omega = 2\pi/T$. The flat outputs and their first $k-1$ derivatives are obtained by integrating (6) successively.

Using this parametrization, the cost function (2) can be written as

$$J = \frac{1}{T}\int_t^{t+T} q(\alpha(\theta^T\phi(\tau),\ldots,\theta^T\phi^k(\tau)))d\tau \quad (7)$$

where

$$\phi(\tau) = \Big[1, \sin(\omega t), \ldots, \sin(n\omega t), \cos(\omega t), \ldots, \cos(n\omega t)\Big]^T$$

and $\phi^k(\tau)$ is its kth time derivative. The constraints can be expressed in the parameterized flat output space as follows

$$r(\alpha(\theta^T\phi(\tau),\ldots,\theta^T\phi^k(\tau))) \leq 0. \quad (8)$$

In the next section, the parametrization (7) is considered in the development of an extremum-seeking controller.

3. EXTREMUM-SEEKING DYNAMIC OPTIMIZATION

The objective of the controller design methodology is to steer the system to the periodic orbit that maximizes the cost function (7) as a function of the parameters θ while meeting all constraints (8).

We consider the maximization of $J(\theta)$ with respect to θ. We propose to encode the constraints using an interior point method using a log-barrier function in the cost. This leads to a modified cost function given by

$$J_{ip} = \frac{1}{T}\int_t^{t+T} \Bigg(q(\alpha(\theta^T\phi(\tau),\ldots,\theta^T\phi^k(\tau))) \quad (9)$$
$$+\sum_{i=1}^{m} \mu_i \log\left(r_i(\alpha(\theta^T\phi(\tau),\ldots,\theta^T\phi^k(\tau)) - \epsilon_i)\right)\Bigg)d\tau$$

where $\mu_i > 0$, $\epsilon_i > 0$ for $i = 1,\ldots,m$ are positive constants that are tuning constants for the log-barrier functions. We first make the following assumption.

Assumption 3.1. The constraint set described by (3), which is convex of the set $\Omega \subset \Re^n$, remains convex over a set Υ in the parameter space in its parameterized form (7).

Assumption 3.1 guarantees that the unconstrained optimization of the modified cost J_{ip} leads to the constrained optimum of $J(\theta)$ as the tuning constants $\mu_i \to 0$. Although this assumption can be restrictive in practice, most applications can be adequately solved using the proposed technique through a suitable *a priori* analysis of the problem. One technique, proposed in this paper, is to solve the optimization problem using an update law that constrains the parameters to a convex set.

3.1 Real-Time Optimization Technique

The basic approach is to formulate the optimization of $J(\theta)$ using a Lyapunov based approach. Given that the functional is convex with respect to θ over a prescribed region Υ, we can rely on the first order conditions for optimality given by

$$\nabla_\theta J_{ip}(\theta^*) = 0 \quad (10)$$

where $\nabla_\theta J_{ip}(\theta^*)$ is the gradient of J_{ip} with respect to θ evaluated at the minimizer θ^*. As in (Guay and Zhang, 2003), we propose the following Lyapunov function,

$$V = \frac{1}{2}\left\|\nabla_\theta J_{ip}(\theta)\right\|^2 \quad (11)$$

Note that the gradient of J_{ip} is now a function of a time-varying set of parameters $\theta(t)$ given by the expression

$$\nabla_\theta J_{ip}(\theta)^T = \nabla_\theta J(\theta)^T + \quad (12)$$
$$\frac{1}{T}\int_t^{t+T}\left(\sum_{i=1}^{m}\frac{\partial r_i}{\partial x}\frac{\partial \alpha}{\partial \theta}\frac{\mu_i}{(r_i(\alpha(\bar{\mathbf{y}})) - \epsilon_i)}\right)d\tau$$

where

$$\nabla_\theta J(\theta)^T = \frac{1}{T}\int_t^{t+T}\frac{\partial q}{\partial x}\frac{\partial \alpha}{\partial \theta}(\tau)d\tau, \quad (13)$$

$$\frac{\partial \alpha}{\partial \theta} = \frac{\partial \alpha}{\partial \bar{\mathbf{y}}(t)}\frac{\partial \bar{\mathbf{y}}(t)}{\partial \theta} \quad (14)$$

and

$$\frac{\partial \bar{\mathbf{y}}(t)}{\partial \theta} = \left[\phi(t),\ldots,\phi(t)^{(k)}\right].$$

The time derivative of V is

$$\dot{V} = \nabla_\theta J_{ip}(\theta(t))(\nabla_\theta{}^2 J_{ip}(\theta(t))\dot{\theta} + \Xi(t+T) - \Xi(t))$$

where

$$\Xi(\tau) = \frac{\partial q}{\partial x}\frac{\partial \alpha}{\partial \theta}(\tau,\theta(t)) + \frac{\partial r_i}{\partial x}\frac{\partial \alpha}{\partial \theta}\frac{\mu_i}{(r_i(\alpha(\bar{\mathbf{y}})) - \epsilon_i)},$$

$\nabla_\theta{}^2 J_{ip}(\theta(t))$ is the Hessian of J_{ip} evaluated at $\theta(t)$ given by

$$\nabla^2_\theta J_{ip}(\theta)^T = \nabla^2_\theta J(\theta)^T \quad (15)$$
$$+\frac{1}{T}\int_t^{t+T}\Bigg(\sum_{i=1}^{m} -\frac{\mu_i}{(r_i(\alpha(\bar{\mathbf{y}})) - \epsilon_i)^2}\frac{\partial r_i}{\partial x}\frac{\partial \alpha}{\partial \theta}$$
$$+\frac{\mu_i}{(r_i(\alpha(\bar{\mathbf{y}})) - \epsilon_i)}\frac{\partial \alpha^T}{\partial \theta}\frac{\partial^2 r_i}{\partial x \partial x^T}\frac{\partial \alpha}{\partial \theta}$$
$$+\frac{\mu_i}{(r_i(\alpha(\bar{\mathbf{y}})) - \epsilon_i)}\frac{\partial r_i}{\partial x}\frac{\partial^2 \alpha}{\partial \theta \partial \theta}\Bigg)d\tau$$

and

$$\nabla_\theta{}^2 J(\theta) = \frac{1}{T}\int_t^{t+T}\left(\frac{\partial q}{\partial x}\frac{\partial^2\alpha}{\partial\theta\partial\theta} + \frac{\partial\alpha^T}{\partial\theta}\frac{\partial^2 q}{\partial x\partial x^T}\frac{\partial\alpha}{\partial\theta}\right)d\tau.$$

By the periodic nature of the choice of trajectory parametrization, it follows that

$$\Xi(t+T) - \Xi(t) = 0.$$

We then obtain the following expression for the derivative of V

$$\dot{V} = \nabla_\theta J_{ip}(\theta(t))\left(\nabla_\theta{}^2 J_{ip}(\theta(t))\dot{\theta}\right). \qquad (16)$$

We propose the following parameter update formula:

$$\dot{\theta} = -k\Gamma^{-1}\nabla_\theta J_{ip}(\theta(t))^T \qquad (17)$$

where $\rho = \left\|\nabla_\theta{}^2 J_{ip}(\theta(t))\right\|_F$ is the Frobenius norm of the Hessian matrix. Clearly, the matrix $\Gamma = \left(\nabla_\theta{}^2 J_{ip}(\theta(t)) - \rho I\right)$ is by construction negative definite such that

$$\dot{J}_{ip} = -\nabla_\theta J_{ip}(\theta(t))\Gamma^{-1}\nabla_\theta J_{ip}(\theta(t))^T \geq 0. \quad (18)$$

The cost functional is constrained to increase as long as the gradient is nonzero. Note that, the rate of change of the Lyapunov function V becomes,

$$\dot{V} = -k\nabla_\theta J_{ip}(\theta(t))\nabla_\theta{}^2 J_{ip}(\theta(t))\Gamma^{-1}\nabla_\theta J_{ip}(\theta(t))^T.$$

The correction of the Hessian renders the rate of change of V indefinite. In order to avoid divergence of the scheme, the value of the parameters is constrained to the convex set

$$\Omega_W = \left\{\theta \in \mathbb{R}^N \mid \|\theta\| \leq w_m\right\}$$

for some $w_m > 0$ through the use of a projection algorithm. This algorithm is given by

$$\dot{\theta} = Proj\,\{\theta, \Psi\} \qquad (19)$$
$$= \begin{cases} \Psi, \text{ if } \|\theta\| < w_m \\ \quad \text{or } (\|\theta\| = w_m \text{ and } \nabla\mathcal{P}(\theta)\Psi \leq 0) \\ \Psi - \Psi\dfrac{\gamma\nabla\mathcal{P}(\theta)\nabla\mathcal{P}(\theta)^T}{\|\nabla\mathcal{P}(\theta)\|_\gamma^2}, \text{otherwise} \end{cases}$$

where

$$\Psi = -k\Gamma^{-1}\nabla_\theta J(\theta(t))^T$$

and $\mathcal{P}(\theta) = \theta^T\theta - w_m \leq 0$, θ is the vector of parameter estimates, γ is a positive definite symmetric matrix and w_m is chosen such that $\|\theta\| \leq w_m$.

The relevant properties of the projection operator, $Proj\{\tau\}$, are given in (Krstić *et al.*, 1995)). The purpose of the projection algorithm is to prevent the divergence of the optimization scheme. Although this can be achieved, it remains to check whether the maximization of the cost J can still proceed when a projection algorithm is employed.

By the properties of the projection algorithm, the parameters are guaranteed to remain in the convex set Ω_W. Furthermore, it is also guaranteed that the rate of change of J_{ip} subject to the projection algorithm (19) given as follows:

$$\dot{J}_{ip}(t) = \nabla_\theta J_{ip}(\theta(t))Proj\,\{\theta, \Psi\} \qquad (20)$$

is such that

$$\dot{J}_{ip}(t) \geq 0.$$

Thus, the projection algorithm plays the role of a trust-region algorithm which limits the domain of the trajectories prescribed by the optimization equation (17) while ensuring that the optimization proceeds at time increases. The restricted update law ensures that a local maximum in J can always be achieved over a convex set in the parameter space.

Note that by the smoothness of the cost J with respect to the decision variables θ, it is guaranteed that there exists an upper bound in the magnitude of the gradient and Hessian of J over the convex Ω_w.

The purpose of the optimization strategy is to generate in real-time a periodic orbit of the nonlinear system (1) that maximizes the cost functional J_{ip}. The optimal periodic orbit provides a reference trajectory that must be implemented by the control system.

3.2 Implementation

The purpose of the optimization strategy proposed in the previous subsection is to generate, in real-time, a periodic orbit of the nonlinear system (1) that maximizes the cost functional J. This periodic provides a reference trajectory that must be implemented by the control system.

Since the differential flat systems can always be put in triangular (strict-feedback) form. Any backstepping design (see (Krstić *et al.*, 1995)) is adequate to design a suitable asymptotic trajectory tracking controller. In this work, a simple Lyapunov based tracking controller was designed to implement the optimal periodic orbit. Assuming that the system has strong relative degree, the tracking error dynamics for the closed-loop system have a globally asymptotically tracking equilibrium at the origin. For more details, the author is referred to (Rothfuss *et al.*, 1996), (Murray *et al.*, 1995) and (Rouchon *et al.*, 1993). For the sake of brevity, the details of the implementation will not be discussed here.

4. SIMULATION RESULTS

The example is taken from (Varigonda *et al.*, 2004*b*). A pharmacokinetic model describes the dynamics of the drug uptake of a drug c in the body. The system dynamics are described by the dimensionless linear system:

$$\dot{c} = -c + u, \ \dot{a} = K_a(c - a) \tag{21}$$

where c is the drug concentration, a is the antagonist concentration, u is the drug infusion rate and K_a is the rate constant for antagonist elimination.

The effect of the drug is monitored using the function

$$E(c, a) = \frac{c}{(1 + c)(1 + a/a^*)}. \tag{22}$$

The goal of the therapy is to keep the effect of the drug within a predetermined interval $[E_1, E_2]$. With the help of a suitable weighting (or indicator) function such as

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

the problem is solved by finding a drug therapy $u(t)$ that maximizes the indicator function $I(E)$.

Since the steady-state optimization solution typically leads to an optimal value of E that lies outside the therapeutic range, a periodic drug treatment $u(t)$ is required. The problem of searching for periodic orbits leads to the maximization of the time-averaged indicator function given by

$$J = \frac{1}{T}\int_0^T I(E(t))dt \tag{24}$$

The optimization problem considered is

$$\begin{aligned} \max_{u(t)} \ J = \frac{1}{T}\int_0^T I(E(t))dt \\ \text{subject to:} \quad & \dot{c} = -c + u(t) \\ & \dot{a} = K_a(c - a) \\ & c \geq 0 \ , a \geq 0 \ , u \geq 0 \end{aligned} \tag{25}$$

The dynamical system (21) is differentially flat with the flat output $y = a$. Differentiating the flat outputs we obtain,

$$y = a, \ \dot{y} = K_a(c - a),$$
$$\ddot{y} = -K_a c + K_a u - Ka^2(c - a).$$

As a result, we obtain the following parametrization of the dynamics,

$$a = y, \ c = \frac{1}{K_a}\dot{y} + y,$$
$$u = \frac{1}{K_a}\ddot{y} + \frac{1}{K_a}\dot{y} + y + K_a\dot{y}.$$

We parameterize the trajectories of the system by assigning the highest order derivative of the flat output. In this case, we let

$$\ddot{\xi} = \theta^T\phi(t) \tag{26}$$

where

$$\theta = [\alpha_0, \alpha_{11}, \ldots, \alpha_{1n}, \alpha_{21}, \ldots, \alpha_{2n}]^T$$

and $\phi(t)$ is chosen as above.

Following the proposed technique, we consider the maximization of the cost (25) as a function of θ subject to,

$$a = \xi, \ c = \frac{1}{K_a}\dot{\xi} + \xi, \ u = \frac{1}{K_a}\ddot{\xi} + \frac{1}{K_a}\dot{\xi} + \xi + K_a\dot{\xi}$$

and the constraints

$$\xi \geq 0, \ 0 \leq (\frac{1}{K_a}\dot{\xi} + \xi) \leq 2,$$
$$\frac{1}{K_a}\ddot{\xi} + \frac{1}{K_a}\dot{\xi} + \xi + K_a\dot{\xi} \geq 0.$$

Using this parametrization, we evaluate the gradient and Hessian of J with respect to θ. The constraints are encoded using log-barrier functions to J_{ip}. As in (Varigonda *et al.*, 2004*b*), the system parameters are given by $K_a = 0.1$, $a^* = 1$, $E_1 = 0.3$, $E_2 = 0.6$ and $\gamma = 10$. We fix the period to $T = 12$ hours. The log-barrier function parameters are set to $\mu_1 = 0.01$ and $\epsilon_1 = 0.001$ for the three inequality constraints. For the approximation, 10 harmonic frequencies were used. The tracking controller for this system is given by,

$$u = \frac{1}{K_a}(K_a + K_a^2(c - a) - $$
$$k_1(y - \xi) - k_2(\dot{y} - \dot{\xi}) + \ddot{\xi})$$

where $k_1 = 1$ and $k_2 = 1$. The search region in the parameter space is limited to the convex set $\Omega_w = \{\theta \in \mathbb{R}^N \mid \|\theta\| \leq 10\}$. The gain in the parameter update law is set to $k = 100$. The initial conditions for the simulation are $a(0) = c(0) = 0.5$ and $\theta(0) = [0.7, \ 0, \ldots, 0]$. The initial estimates of the parameters yield a feasible trajectory.

The simulation results are shown in Figures 1 to 3. A maximum optimal value obtained is $J = 0.3523$ which compares with the results cited in (Varigonda *et al.*, 2004*b*). The state trajectories are shown in Figure 1. The input trajectory is given in Figure 2. The results demonstrate that the optimum is reached and that the state and input constraints are met. Note that the tracking controller proposed does not formally enforce the input and state constraints for the system. In this case, the control system performs well. Figure 3 shows the value of the effect of the drug, E. The periodic drug delivery strategy provides an effective drug treatment that reaches the recommended value of 0.3 at each cycle. The resulting treatment is therefore viable, as predicted.

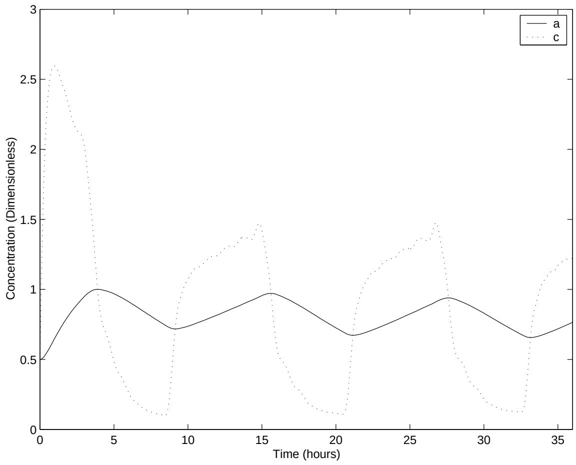

Fig. 1. Closed-loop state variable trajectories, a and c, for the real-time optimization scheme.

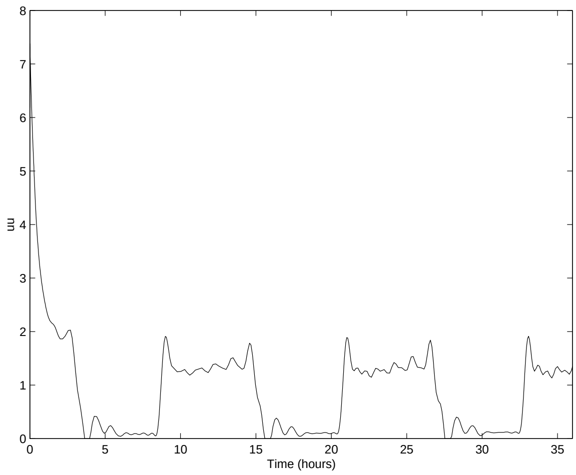

Fig. 2. Control action u for the real-time optimization scheme.

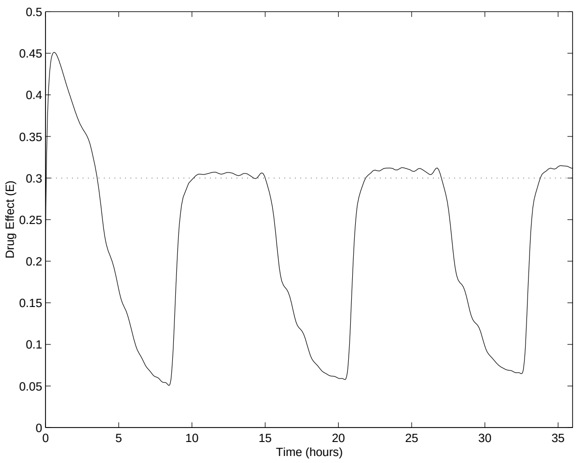

Fig. 3. Drug effect E for the real-time optimization scheme.

5. CONCLUSIONS

In this paper, we proposed and solved an extremum-seeking control problem for a class of nonlinear dynamical control systems. The system provides a real-time optimal trajectory generation system that optimizes cost functionals which are evaluated over periodic orbits of fixed period.

REFERENCES

Agrawal, S.K., N. Faiz and R.M. Murray (1999). Feasible trajectories of linear dynamic with inequality constraints using higher-order representations. In: *Proc. IFAC World Congress*. Beijing,China.

Bailey, J.E. and F.J.M. Horn (1971). Comparison between two sufficient conditions for improvement of an optimal steady-state process by periodic operation. *J. Optim. Theo. Appl.* **7**(5), 378–384.

Guay, M. and T. Zhang (2003). Adaptive extremum-seeking control of nonlinear systems with parametric uncertainties. *Automatica* **30**, 1283–1293.

Krstić, M., I. Kanellakopoulos and P. Kokotović (1995). *Nonlinear and Adaptive Control Design*. John Wiley and Sons. New York.

Laroche, B. and D. Claude (2004). Flatness-based control of per protein oscillations in a drosophilia model. *IEEE Trans. Autom. Contr.* **49**(2), 175–183.

Mahadevan, R., S.K. Agrawal and F.J. Doyle III (2000). A flatness based approach to optimization in fed-batch reactors. In: *Proc. IFAC ADCHEM 2000*. pp. 111–116. Pisa, Italy.

Martin, P. (1992). Contributions à l'étude des systèmes différentiellement plats. PhD thesis. Ecole des mines de Paris, Paris, France.

Murray, R.M., M. Rathinam and W.M. Sluis (1995). Differential flatness of mechanical control systems. In: *Proc. ASME Intern. Cong.and Exp.*

Oldenburg, J. and W. Marquardt (2000). Dynamic optimization based on higher order differential model representations. In: *Proc. IFAC ADCHEM 2000*. pp. 809–814. Pisa, Italy.

Rothfuss, R., R.J. Rudolph and M.Zeitz (1996). Flatness based control of a nonlinear chemical reactor model. *Automatica* **32**, 1433–1439.

Rouchon, P., M. Fliess, J. Lévine and P. Martin (1993). Flatness, motion planning and trailer systems. In: *Proc. 33rd IEEE Conf. Decis. Contr.*. pp. 2700–2705. San Antonio, TX.

Varigonda, S., T.T. Georgiou and P. Daoutidis (2004*a*). Numerical solution of the optimal periodic control using differential flatness. *IEEE Trans. Autom. Contr.* **49**(2), 271–275.

Varigonda, S., T.T. Georgiou, R. A. Siegel and P. Daoutidis (2004*b*). Optimal periodic control of a drug delivery system. In: *Proc. IFAC DYCOPS*. Boston, MA.