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Mixed-integer non-linear optimal control in systems biology and biotechnology: numerical methods and a software toolbox

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Abstract: Here we consider the problem of optimal manipulation of biological or biotechnological systems, formulated as a class of mixed-integer optimal control problems. We describe the current state of the art regarding the numerical solution of these problems, and a software implementation developed in our group (DOTcvp toolbox, based on Matlab).
DOTcvp combines the control vector parameterization approach with a number of local deterministic and global stochastic and hybrid (mixed-integer) non-linear programming solvers and suitable dynamic process simulation methods so as to cover the solution of a wide class of problems. The performance of DOTcvp is illustrated considering representative set of benchmark problems, including the problem of drug displacement in a patient, the optimal operation of a fed-batch bioreactor, and the optimal control of intracellular calcium oscillations.
The DOTcvp toolbox is freely available to academic users.

Keywords: Dynamic optimization, nonlinear optimal control, systems biology, MATLAB toolbox

1. INTRODUCTION

The open-loop optimal control problem (OCP), also called dynamic optimization (DO), considers the computation of the best operating policies for processes or systems so as to maximize a pre-defined performance index (usually involving quality, productivity and/or cost criterions).

The solution of this type of problems has received a great deal of attention during the last two decades. This has particularly been the case for the DO of biochemical and biological systems. An overview of optimization in the context of computational systems biology was given by Mendes and Kell (1998) and more recently by Banga (2008), the latter highlighting the need of robust and efficient dynamic optimization methods.

These problems can be very challenging due to the highly non-linear nature of the systems dynamics, plus the usual presence of path constraints. In this sense, a review of the recent literature reveals a significant number of works, including advanced local optimization methods (for example, Balsa-Canto et al. (2000); Wächter and Biegler (2006)) which are able to handle large scale constrained dynamic optimization problems, and the use of global optimization methods, either deterministic (e.g., Esposito and Floudas (2000)), or stochastic and hybrid methods (e.g., Banga et al. (2005); Balsa-Canto et al. (2005)), in order to handle the non-convexity of many of these problems.

In addition, in recent years, there has also been a growing interest in problems that incorporate discrete –binary or integer– decisions to represent the inclusion or exclusion of elements in a design, discontinuities in a process model, or temporal sequencing decisions. This gives rise to the mixed-integer dynamic optimization (MIDO) problems.

The numerical solution of such problems often relies on the combination of the control vector parameterization approach, based on a piecewise approximation of the control functions, with a suitable mixed-integer non-linear programming solver (MINLP) and an initial value problem solver to deal with the system dynamics.

Recently, Bansal et al. (2003) and Chachuat et al. (2006) have reviewed numerical methods to solve these MIDO/MINLPs. They argue that since most of the MIDO problems of interest are non-convex, there is a distinct need global optimization methods to guarantee proper (globally optimal) solutions.

Many of the proposed numerical methods to solve (MI)DO problems have been successful in dealing with small benchmark problems, or even with several more realistic cases. However, the absence, in most of the cases, of easy-to-use and friendly software tools, suitable for non-expert users, has precluded the widespread application of these methodologies. In this context, and although there are a relatively large number of software packages for dynamic optimization, very few packages can handle MIDO problems: to the best of our knowledge, only gPROMS (Barton and Pantelides (1993); Bansal et al. (2003)) and ABACUSS-II (Clabaugh et al. (1999)).

This work presents a MATLAB toolbox, DOTcvp (Dynamic Optimization Toolbox with Control Vector Parameterization approach) which, based on the CVP approach, is able to handle general (MI)DO problems. DOTcvp offers a number of advantages:

- It is able to handle non-convex problems through a number of stochastic and hybrid NLP and MINLP global solvers.
- It incorporates a number of state of the art local NLP and MINLP solvers and computes exact gradients so as to enhance their convergence properties.
- It has been fully implemented in MATLAB, with ease of use in mind, and with a user friendly graphical interface. Moreover, and with the aim of maximizing the computational efficiency, most of the computations can be automatically performed via compiled Fortran code if needed.
- It can import SBML models, a de facto standard in systems biology.

This contribution is organized as follows, Section 2 formulates the general class of MIDO problems considered and presents the basics about the numerical methods used; Section 3 describes DOTcvp toolbox in detail and Section 4 presents the application of the toolbox to a representative set of DO and MIDO problems from the domain of systems biology.

2. THEORY AND BACKGROUND

2.1 Mixed-Integer Optimal Control Problem

The mixed-integer optimal control problem, also called mixed-integer dynamic optimization (MIDO) problem, considers the computation of time dependent operating conditions (controls), discrete –binary or integer– decisions and time-independent parameters so as to minimize (or maximize) a performance index (production cost, process productivity, etc) while keeping a set of constraints coming from safety and/or quality demands and environmental regulations. This may be mathematically formulated as follows:

Find $\mathbf{u}(t)$, $\mathbf{i}(t)$, $\mathbf{p}$ and t_f so as to minimize (or maximize):

$$J = G_{t_f}(\mathbf{x}, \mathbf{u}, \mathbf{i}, \mathbf{p}, t_f) + \int_{t_0}^{t_f} F(\mathbf{x}(t), \mathbf{u}(t), \mathbf{i}(t), \mathbf{p}, t)\mathrm{d}t \quad (1)$$

subject to:

$$\mathbf{f}(\dot{\mathbf{x}}(t), \mathbf{x}(t), \mathbf{u}(t), \mathbf{i}(t), \mathbf{p}, t) = 0, \qquad \mathbf{x}(t_0) = \mathbf{x}_0 \quad (2)$$

$$\mathbf{g}(\mathbf{x}(t), \mathbf{u}(t), \mathbf{i}(t), \mathbf{p}, t) \le 0, \qquad l = \overline{1, m_e + m_i} \quad (3)$$

$$\mathbf{u}_L \le \mathbf{u}(t) \le \mathbf{u}_U, \quad (4)$$

$$\mathbf{i}_L \le \mathbf{i}(t) \le \mathbf{i}_U, \quad (5)$$

$$\mathbf{p}_L \le \mathbf{i}(t) \le \mathbf{p}_U, \quad (6)$$

where $\mathbf{x}(t) \in X \subseteq \mathrm{R}^{n_x}$ is the vector of state variables, $\mathbf{u}(t) \in U \subseteq \mathrm{R}^{n_u}$ is the vector of real valued control variables, $\mathbf{i}(t) \in I \in \mathrm{Z}^{n_i}$ is the vector of integer control variables, $\mathbf{p} \in P \subseteq \mathrm{R}^{n_p}$ is the vector of time-independent parameters, t_f is the final time of the process, m_e, m_i represent the number of equality and inequality constraints, respectively and $\mathbf{g}$ collects all state constraints, pathway, pointwise and final time constraints and $\mathbf{u}_L$, $\mathbf{i}_L$, $\mathbf{p}_L$, $\mathbf{u}_U$, $\mathbf{i}_U$, $\mathbf{p}_U$ correspond to the lower and upper bounds for the control variables and the time-independent parameters.

2.2 Control Vector Parameterization

The CVP method proceeds dividing the control variables ($\mathbf{u}(t)$ and $\mathbf{i}(t)$) into a number of elements and then approximating each element by means of different basic functions, usually constant polynomials, in such a way that the control variables are parameterized using $\mathbf{w}_u \in \mathrm{R}^\rho$ and $\mathbf{w}_i \in \mathrm{Z}^\rho$ which become decision variables.

This parameterization transforms the original problem into a finite dimension (mixed-integer) non-linear programming problem that may be solved by a suitable MINLP solver. Note that the evaluation of the objective function and constraints requires the solution of the system dynamics by an initial value problem (IVP) solver.

If the outer (MI)NLP problem is convex, deterministic (gradient-based) local methods seem to be the best alternatives to efficiently solve it. In this regard, (mixed-integer) sequential quadratic programming methods, such as MISQP (Exler and Schittkowski (2007)), are considered the state-of-the-art.

Nevertheless, in presence of non-convexities, local methods may present convergence to local minima, calling for the use of global optimization methods. In this concern, several possibilities exist that may be classified in two major groups: deterministic and stochastic. Deterministic global methods ensure global optimality, at least for particular classes of problems, although in many situations the computational cost is excessive. They have been recently applied for the solution of MIDO problems (Chachuat et al. (2006)).

Regarding stochastic global methods, several authors (see the review in Banga et al. (2005)), have illustrated their great potential in the context of DO and, more recently (Exler et al. (2008)), also for MIDO. This type of methods may locate the vicinity of global solutions with relative efficiency, but the cost to pay is that global optimality can not be guaranteed. Alternatives such as global-local hybrid methods have been suggested for DO Balsa-Canto et al. (2005) and MIDO Schlüter et al. (2009) as ways of significantly enhancing the efficiency of the optimization convergence.

Many of these optimization methods require the computation of gradients of the objective and/or constraints with respect to the decision variables. Vassiliadis (1993) proposed the use of first order parametric sensitivities to compute such information in the context of CVP. The sensitivity equations result from a chain rule differentiation applied to the system defined in Eqns. 2 with respect to the decision variables and may be solved in combination with the original system. In this concern, the use of BDF

(Backward Differentiation Formula) methods may be quite attractive since they are able to exploit the fact that the original system and the sensitivities share the Jacobian.

3. DOTCVP DESCRIPTION

DOTcvp is a MATLAB (www.mathworks.com) toolbox particularly oriented to the solution of (mixed-integer) dynamic optimization problems related to non-linear processes, with the presence of non-linear constraints on control and state variables. DOTcvp is based on the CVP approach, therefore the solution of the original dynamic optimization problem is approximated by solving a main MINLP problem with an inner IVP embedded.

3.1 Key Features

- Handles a wide class of (mixed-integer) dynamic optimization problems, including constrained, unconstrained, fixed, and free terminal time problems described by ordinary differential equations (ODEs).
- The inner initial value problem (IVP) is solved using the state-of-the-art methods available in SUNDIALS (Hindmarsh et al. (2005)), which have been specially designed to deal with non-stiff, stiff, and large scale systems.
- Symbolically calculates exact gradients through the derivation of first order parametric sensitivities that are simultaneously solved with the system dynamics.
- The outer MINLP problem can be solved using a number of advanced solvers, including local deterministic methods, stochastic global optimization methods, and hybrid metaheuristics.
- In addition to the traditional single optimization approach, the toolbox also offers more sophisticated strategies, like multistart, sucessive re-optimization (Balsa-Canto et al. (2000)), and sequential hybrid strategies (Balsa-Canto et al. (2005)).
- Ease of use: it can be used from the command line, by defining a simple structure of input data, or via a graphical user interface (GUI), which makes the definition and edition of a problem easier for novel users.
- It offers many output options for the format of the results, including detailed figures.

3.2 Numerical Methods

Regarding the solution of the (MI)NLP problems, DOTcvp incorporates several possibilities:

- local deterministic
  (1) IPOPT (Wächter and Biegler (2006)), Interior Point OPTimizer, implements a primal-dual interior point method, and uses line searches based on Filter methods;
  (2) FMINCON (Coleman et al. (1998)), Find MINimum of CONstrained non-linear multivariable function, belongs to the MATLAB optimization toolbox and uses sequential quadratic programming (SQP);
  (3) MISQP (Exler and Schittkowski (2007)), Mixed-Integer Sequential Quadratic Programming, solves mixed-integer non-linear programming problems by a modified SQP method;
- stochastic global
  (1) DE (Storn and Price (1997), Differential Evolution) uses population based approach for minimizing the performance index;
  (2) SRES (Runarsson and Yao (2000), Stochastic Ranking Evolution Strategy) uses an evolution strategy combined with an approach to balance objective and penalty functions;
- and hybrid metaheuristics
  (1) ACOmi (Schlüter et al. (2009), Ant Colony Optimization for mixed-integer non-linear programming problems) is inspired by ants foraging behavior, using MISQP for the local searches;
  (2) MITS (Exler et al. (2008), Mixed-Integer Tabu Search algorithm) is based on extensions of the metaheuristic Tabu Search, useing MISQP for local searches.

where the deterministic MISQP local solver and all hybrid solvers are able to handle mixed-integer problems directly.

In addition several optimization modules have been implemented for the sake of flexibility in problem solution:

- Single optimization: It consists on solving the master MINLP problem in a single pass (i.e. a single optimization run).
- Multistart: The user may select to perform a multistart of local methods from different initial guesses. This technique allows to identify possible non-convexities.
- Sequential hybrid optimization: Sequential hybrid methods are characterized by the combination of a stochastic global method plus a deterministic local method, which are run in two phases. First phase, uses a global method to locate the vicinity of the global solution and second phase is devoted to the refinement of the solution by using a local method (Balsa-Canto et al. (2005)). The toolbox offers the possibility of combining the available methods into a sequential hybrid approach.
- Sucessive re-optimization: To speed up the convergence for problems where a high control discretization level is desired. This procedure runs several successive single optimizations automatically increasing the control discretization after each run (Balsa-Canto et al. (2000)).

Regarding the solution of the embedded IVP, a modified SUNDIALS tool (Hindmarsh et al. (2005)) is used. Forward integration of the ODE system is ensured by CVODES, part of SUNDIALS, which is also able to perform the simultaneous or staggered sensitivity analysis. The IVP problem can be solved with the Newton or Functional iteration module and with the Adams or BDF linear multistep method. The Adams method is recommended for solving of the non-stiff problems while BDF is recommended for solving of the stiff problems. The sensitivity equations are provided analytically and the error control strategy for the sensitivity variables could be enabled. Detailed information about the settings, methods and procedures of the toolbox can be found in the technical report Hirmajer et al. (2008).

4. ILLUSTRATIVE EXAMPLES

In order to test the different possibilities available in the toolbox we have considered a number of illustrative examples ranging from convex DO to non-convex MIDO problems. This section presents the solution of a collection of representative case studies with different characteristics as summarized in Table 1.

Table 1. Main characteristics of the illustrative examples.

	Brief description	n_x	n_u	n_i	m_e	m_i
P1	minimum time, end-point constrained, DO problem	2	1	0	2	0
P2	fixed transition times, DO problem	7	2	0	0	0
P3	pathway constrained, free transition times, MIDO problem	4	0	2	1	4

P1: Drug Displacement Problem

The problem consists of finding the optimal rate injection of phenylbutazone infusion to minimize the time needed to reach in a patient's bloodstream a desired level of two drugs (Balsa-Canto et al. (2005)). The system dynamics is described by 2 non-linear differential equations where the state variables represent the concentration of warfarin and phenylbutazone drugs that may achieve a desired value at final time (two end-point constraints). Table 2 shows a typical simple input structure to solve this problem with DOTcvp.

The problem was solved for a control discretization level $\rho = 5$ with IPOPT. The optimal solution found corresponds to a minimum time of 221.24 that is in good agreement with the best published result of 221.43 (Banga et al. (2005)). The optimal control profile and the corresponding state trajectories are shown in the Fig. 1.

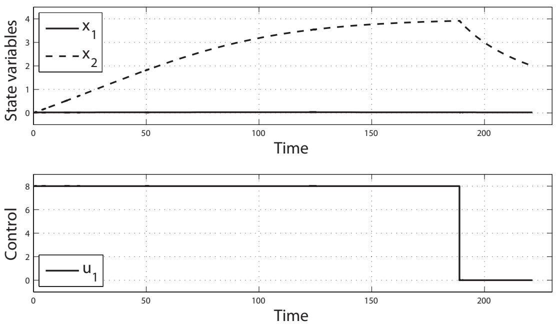

Fig. 1. Optimal state trajectories (top) and the control profile (bottom) for the drug displacement problem.

P2: Lee-Ramirez Bioreactor

This problem considers the optimal control of a fed-batch bioreactor for induced foreign protein production by recombinant bacteria. This problem was first presented by Lee and Ramirez (1994), slightly modified by Tholudur and Ramirez (1997), and later solved using a second order sensitivities approach (Balsa-Canto et al. (2001)). The objective is to maximize the profitability of the process using the nutrient (u_1) and the inducer feeding rates (u_2) subject to 7 non-linear differential equations which represent reactor volume, the cell density, the nutrient concentration, the foreign protein concentration, the inducer concentration, the inducer shock factor on cell growth rate, and the inducer recovery factor on cell growth rate.

The problem was successfully solved using the successive re-optimization strategy from DOTcvp and FMINCON as NLP solver, setting the initial control discretization at $\rho = 15$. The mesh increasing factor and the number of mesh refinements were set at values of 2 and 4, respectively. The results for the increasing ρ values are shown in Fig. 2, which have the following performance index values: 5.64058, 5.72840, 5.75707, and 5.75710. These performance indexes are in very good agreement with those published in the literature.

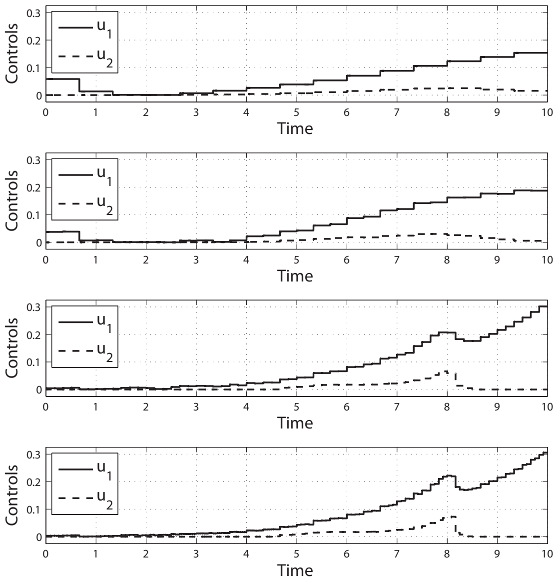

Fig. 2. Optimal trajectories for increasing discretization (15, 30, 60, and 120) for the Lee-Ramirez bioreactor.

P3: Phase Resetting of a Calcium Oscillator Problem

We have considered a calcium oscillator model describing intracellular calcium spiking in hepatocytes induced by an extracellular increase in adenosine triphosphate concentration, as originally proposed by Kummer et al. (2000) and later slightly modified and solved by Sager (2005); Lebiedz et al. (2005). The aim of the optimization is to minimize the intracellular oscillations behavior with the help of two binary control variables (i_1, i_2) and one parameter (p_1). The system is described by 4 non-linear differential equations which represent the activated G-protein, active phospholipase C, intracellular calcium, and intra-ER calcium. The control variables refer to the concentrations of an uncompetitive inhibitor of the PMCA ion pump and the inhibitor of PLC activation by the G-protein. The best performance index reported in Sager (2005) was 1538.00 and authors reported that the system is extremely sensitive to small perturbations in the stimulus.

We first solved this problem using the multistart module of the DOTcvp toolbox, using MISQP as local solver and the control discretization level was set to a value of $\rho = 5$. The

Table 2. DOTcvp typical simple input screen for the drug displacement problem.

```
data.name                  = 'DrugDisplacement';    % name of the problem
data.odes.res(1)           = {'((1+0.2*(y(1)+y(2)))^2/(((1+0.2*(y(1)+y(2)))^2+232+46.4*y(2))*((1+0.2*(y(1)+y(2)))^2
+232+46.4*y(1))-2152.96*y(1)*y(2)))*(((1+0.2*(y(1)+y(2)))^2+232+46.4*y(1))*(0.02-y(1))+46.4*y(1)*(u(1)-2*y(2)))'};
data.odes.res(2)           = {'((1+0.2*(y(1)+y(2)))^2/(((1+0.2*(y(1)+y(2)))^2+232+46.4*y(2))*((1+0.2*(y(1)+y(2)))^2
+232+46.4*y(1))-2152.96*y(1)*y(2)))*(((1+0.2*(y(1)+y(2)))^2+232+46.4*y(2))*(u(1)-2*y(2))+46.4*(0.02-y(1)))'};
data.odes.res(3)           = {'1'};
data.odes.ic               = [0.02 0.0 0.0];        % vector of initial conditions
data.odes.tf               = 500.0;                 % final time
data.odes.NonlinearSolver  = 'Functional';          % ['Newton'|'Functional']
data.odes.RelTol           = 1*10^(-8);             % IVP relative tolerance level
data.odes.AbsTol           = 1*10^(-8);             % IVP absolute tolerance level
data.sens.SensAbsTol       = 1*10^(-8);             % absolute tolerance for sensitivity variables
data.nlp.RHO               = 5;                     % CVP discretization level
data.nlp.J0                = 'y(3)';                % performance index, min-max(performance index)
data.nlp.u0                = 4.0;                   % initial guess for control values
data.nlp.lb                = 0.0;                   % lower bounds for control values
data.nlp.ub                = 8.0;                   % upper bounds for control values
data.nlp.solver            = 'IPOPT';               % ['FMINCON'|'IPOPT'|'FSQP'|'SRES'|'DE'|'ACOMI'|'MISQP'|'MITS']
data.nlp.FreeTime          = 'on';                  % ['on'|'off'] set 'on' if free time is considered
data.nlp.eq.status         = 'on';                  % ['on'|'off'] switch on/off of the equality constraints (ECs)
data.nlp.eq.NEC            = 2;                     % number of active ECs
data.nlp.eq.eq(1)          = {'y(1)-0.02'};         % first equality constraint
data.nlp.eq.eq(2)          = {'y(2)-2.0'};          % second equality constraint
data.nlp.eq.time(1)        = data.nlp.RHO;          % to indicate that it is an end-point constraint
data.nlp.eq.time(2)        = data.nlp.RHO;          % to indicate that it is an end-point constraint
```

multistart number of runs was set to 100, with randomly generated initial values for all the decision variables in each run. The set of solutions found were spread in a quite wide range, a clear sign of multimodality. The histogram of these solutions is shown in Fig. 3, where performance index values worse than 2500.00 are not shown. The best value obtained by the multistart was 1641.03, which is still far from the published solution reported above.

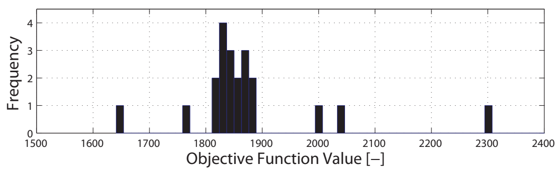

Fig. 3. Histogram of the objective function value for the calcium oscillator problem.

In a second step, we solved this problem using the MITS hybrid strategy. The best solution found by MITS was 1542.50, which is very close to the value reported in Sager (2005). The corresponding optimal trajectories are shown in Fig. 4 and Fig. 5 where it can be seen how the optimal control policies rapidly cancel the oscillations.

5. CONCLUSIONS

In this contribution we presented a MATLAB toolbox, DOTcvp, which is based on the control vector parameterization approach, and is able to handle general mixed-integer dynamic optimization (open loop optimal control) problems. DOTcvp offers a number of advantages over other existing tools:

- It incorporates a number of local and global NLP and MINLP solvers so as to handle a wide range of MIDO problems, including non-convex (multimodal) ones.
- It offers several optimization strategies, including (i) multistart (to detect possible non-convexities); (ii)

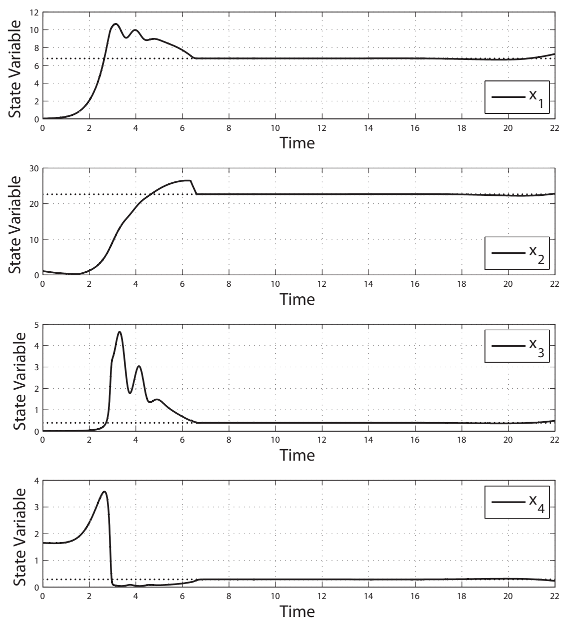

Fig. 4. Optimal state trajectories and desired states (dotted lines) for the calcium oscillator problem.

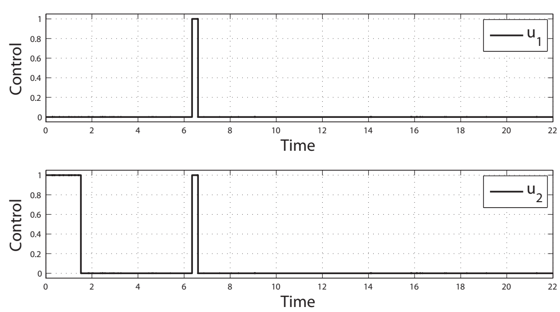

Fig. 5. Optimal control trajectories for the calcium oscillator problem.

sucessive reoptimization (to obtain smoother control profiles); (iii) hybrid sequential methods (to enhance efficiency during the solution of multimodal problems).

In order to illustrate the capabilities of the toolbox, we presented the solution of a collection of problems from the domain of systems biology with quite different characteristics. The software, documentation, and further examples can be obtained from the authors upon request.

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