TECHNICAL REPORT

DOTcvpSB: application to systems biology problems

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CHAPTER 1

Systems biology

1.1 DRUG DISPLACEMENT PROBLEM

DOTcvp: cdop_DrugDisplacementProblemA, B.m

Consider a drug displacement problem solved e.g. in [2; 3]. The problem consists of the right rate projection of phenylbutazone infusion to minimize the time needed to reach in a patient's bloodstream a desired level of two drugs. The performance index is given by the following equation

$$\min_{u_i, t_i} J_0 = t_F \tag{1.1}$$

subject to

$$\dot{x}_1 = g_4(g_3(0.02 - x_1) + 46.4x_1(u - 2x_2)) \tag{1.2}$$
$$\dot{x}_2 = g_4(g_2(u - 2x_2)) + 46.4(0.02 - x_1) \tag{1.3}$$

with $g_i, i = \overline{1,4}$ defined as follows

$$g_1 = 1 + 0.2(x_1 + x_2) \tag{1.4}$$
$$g_2 = g_1^2 + 232 + 46.4x_2 \tag{1.5}$$
$$g_3 = g_1^2 + 232 + 46.4x_1 \tag{1.6}$$
$$g_4 = \frac{g_1^2}{g_2 g_3 - 2152.96 x_1 x_2} \tag{1.7}$$

where the state variables represent the concentration of warfarin and phenylbutazone drugs. The initial values were set for the process and decisions variables at the value of $x_0 = [0.02; 2.00]$ and $u_0 = [4]$, respectively. The boundaries of the decision variables are as follows: $u \in [0; 8]$.

The equality point constraints on the final amount of displacement drugs are given by

$$x_1(t_F) = 0.02 \tag{1.8}$$
$$x_2(t_F) = 2.00 \tag{1.9}$$

Two scenarios were considered. First one -case A, without and second one -case B with the path constraint defined as follows

$$x_1(t) \leq 0.026 \tag{1.10}$$

where the inequality constraint ensures a maximum allowance level of the warfarin concentration in the patient's bloodstream.

Model Parameters (Reaction Coefficients)			Weighted Coefficients	Initial Values	Desired Values
$k_1 = 0.09$	$k_8 = 32.24$	$K_{15} = 0.16$	$w_1 = 5.0$	$x_1(0) = 0.03966$	$x_1^s = 6.78677$
$k_2 = 2.30066$	$K_9 = 29.09$	$k_{16} = 4.85$	$w_2 = 5.0$	$x_2(0) = 1.09799$	$x_2^s = 22.65836$
$k_3 = 0.64$	$k_{10} = 5.0$	$K_{17} = 0.05$	$w_3 = 15.0$	$x_3(0) = 0.00142$	$x_3^s = 0.38431$
$K_4 = 0.19$	$K_{11} = 2.67$	$t_F = 22.0$	$w_4 = 25.0$	$x_4(0) = 1.65431$	$x_4^s = 0.28977$
$k_5 = 4.88$	$k_{12} = 0.7$		$w_5 = 50.0$		
$k_6 = 1.18$	$k_{13} = 13.58$		$w_6 = 5.0$		
$k_7 = 2.08$	$k_{14} = 153.0$				

Table 1.1 – The table with the time-fixed parameters, weighted coefficients, initial, and desired values of the state variables for a calcium oscillator problem.

```
________________
Final results [single-optimization; case A]:
 ............ Problem name: DrugDisplacementProblemA
 ...... NLP or MINLP solver: IPOPT
 . Number of time intervals: 5
 ... IVP relative tolerance: 1.000000e-008
 ... IVP absolute tolerance: 1.000000e-008
 . Sens. absolute tolerance: 1.000000e-008
 ........... NLP tolerance: 1.000000e-005
 ....... Final state values: 2.000012e-002 2.000044e+000 2.212415e+002
 ...... 1th optimal control: ...
 ..... Final size of the dt: 1.000999e-002 1.000999e-002 1.000998e-002 1.888941e+002 3.231729e+001
 ..... Final time [sum(dt)]: 2.212415e+002
________________
 ........... Final CPUtime: ... seconds
 . Cost function [min(J_0)]: 221.24146626

________________
Final results [stochastic part - hybrid-strategy; case B]:
 ............ Problem name: DrugDisplacementProblemB
 ...... NLP or MINLP solver: DE
 . Number of time intervals: 10
 ... IVP relative tolerance: 1.000000e-005
 ... IVP absolute tolerance: 1.000000e-005
 . Sens. absolute tolerance: none
 ........... NLP tolerance: 1.000000e-003
 ....... Final state values: 2.024236e-002 2.002572e+000 2.660897e+002
 ...... 1th optimal control: ...
 ..... Final size of the dt: 2.494448e+001 1.456665e+001 1.030967e+001 1.819885e+001 2.766473e+001 1.751853e+001 4.522449e+001
                             9.229657e+000 6.555467e+001 3.287798e+001
 ..... Final time [sum(dt)]: 2.660897e+002
 . 1th inequality constrain violation [without the penalty coefficient]: 1.883506e-008
________________
 ........... Final CPUtime: ... seconds
 . Cost function [min(J_0)]: 0.84353360

________________
Final results [deterministic part - hybrid-strategy; case B]:
 ............ Problem name: DrugDisplacementProblemB
 ...... NLP or MINLP solver: MISQP
 . Number of time intervals: 10
 ... IVP relative tolerance: 1.000000e-007
 ... IVP absolute tolerance: 1.000000e-007
 . Sens. absolute tolerance: 1.000000e-007
 ........... NLP tolerance: 1.000000e-005
 ....... Final state values: 1.999999e-002 2.000000e+000 2.660897e+002
 ...... 1th optimal control: ...
 ..... Final size of the dt: 2.494448e+001 1.456665e+001 1.030967e+001 1.819885e+001 2.766473e+001 1.751853e+001 4.522449e+001
                             9.229657e+000 6.555467e+001 3.287798e+001
 ..... Final time [sum(dt)]: 2.660897e+002
 . 1th inequality constrain violation [without the penalty coefficient]: 2.318316e-009
________________
 ........... Final CPUtime: ... seconds
 . Cost function [min(J_0)]: 0.79850272
```

1.2 PHASE RESETTING OF A CALCIUM OSCILLATOR PROBLEM

The state oscillations are possible to observe in the systems biology very frequently. This behaviour is caused by instabilities of the steady-states. These oscillations can be removed temporarily with the help of the external stimuli, usually binaries. The strength and timing of these control variables have a smoothing effect on the behavior of the system. Without further influences of the stimuli the oscillations occur again. It appears from this that we can talk about the phase reseting.

For the demonstrative purposes of our toolbox with the CVP approach, the calcium oscillator model describing intracellular calcium spiking in hepatocytes induced by an extracellular increase in adenosine triphosphate

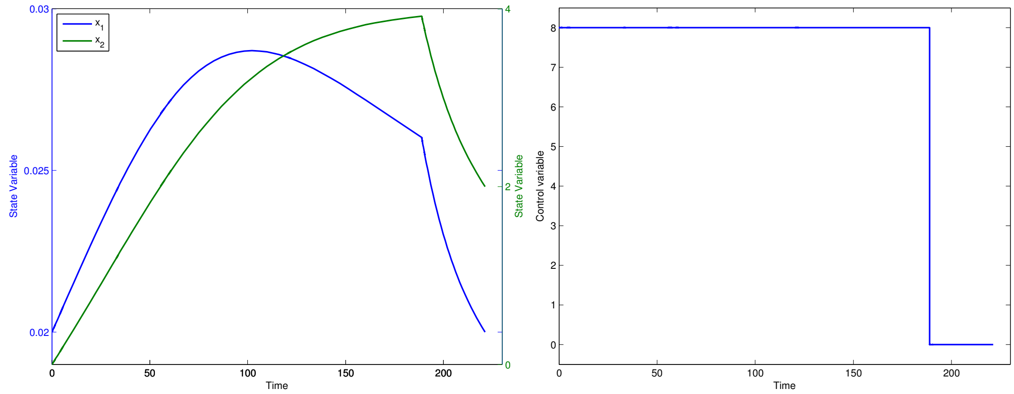

Figure 1.1 – Optimal state trajectories (left) and the control profile (right) for the drug displacement problem without the path constraint.

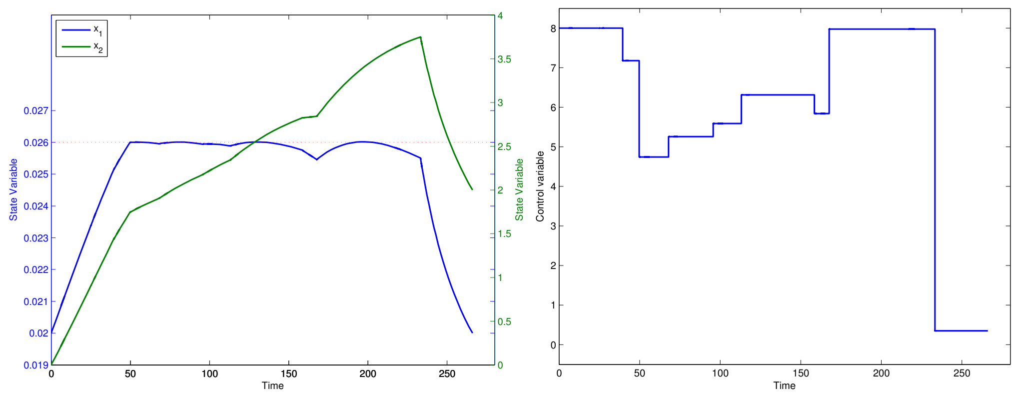

Figure 1.2 – Optimal state trajectories (left) and the control profile (right) for the drug displacement problem with the path constraint.

(ATP) concentration originally proposed in [1] and later slightly modified and solved in [4] is investigated. We have skipped the path constraints added in [4], because on the basis of the system behavior, these constraints were never violated. The aim of the optimization is to minimize the intracellular oscillations behavior with the help of two binary control variables. The values of these variables and the time of the switching from one mode to another together with the time-independent parameter are decision variables. Afterwards, the problem is formulated as minimization of the state variables deviations from the desired values (see Table 1.1) over the whole time interval

$$\min_{x,u_i,p} J_0 = \int_0^{t_F} \left(\sum_{j=1}^{4} w_j \left(x_j(t) - x_j^s \right)^2 + w_5 u_1 + w_6 u_2 \right) \mathrm{d}t \tag{1.11}$$

subject to

$$\dot{x}_1 = k_1 + k_2 x_1 - \frac{k_3 x_1 x_2}{x_1 + K_4} - \frac{k_5 x_1 x_3}{x_1 + K_6} \tag{1.12}$$

$$\dot{x}_2 = (1 - u_2) k_7 x_1 - \frac{k_8 x_2}{x_2 + K_9} \tag{1.13}$$

$$\dot{x}_3 = \frac{k_{10} x_2 x_3 x_4}{x_4 + K_{11}} + k_{12} x_2 + k_{13} x_1 - \frac{k_{16} x_3}{x_3 + K_{17}} + \frac{x_4}{10} - u_1 \frac{k_{14} x_3}{p_1 x_3 + K_{15}} - (1 - u_1) \frac{k_{14} x_3}{x_3 + K_{15}} \tag{1.14}$$

$$\dot{x}_4 = -\frac{k_{10} x_2 x_3 x_4}{x_4 + K_{11}} + \frac{k_{16} x_3}{x_3 + K_{17}} - \frac{x_4}{10} \tag{1.15}$$

and the time-independent parameter

$$1 \leq p_1 \leq 1.3 \tag{1.16}$$

where state variables represent the concentration of activated G-protein (x_1), active phospholipase C (x_2), intracellular calcium (x_3), and intra-ER calcium (x_4). The time-fixed parameters $p = (k_1, \ldots, K_{17})$ together with the initial concentrations, desired values of the state variables and weighted coefficients are described in detail in the Table 1.1. As the control variables are chosen binaries (u_1, u_2), which have an impact on the concentration of an uncompetitive inhibitor of the PMCA (plasma membrane Ca^{2+}) ion pump and on the inhibitor of PLC activation by the G-protein. The influence of the first inhibitor is modeled according to Michaelis-Menten kinetics and of the second inhibitor with the help of the term $(1 - u_2)$, where $u_2 = 1$ corresponds with the maximum amount of the inhibitor.

For testing the toolbox applicability two cases were chosen: (i) scenario with 6 free time intervals and one control variable, second one is set at the value of zero all the time; (ii) scenario with 5 free time intervals and two control variables. One additional equality constraint was added to retain the total time at the fixed value (t_F). All results presented later were obtained with the help of MITS solver implemented directly into the toolbox. The cost function in all scenarios neglects all weight parameters and therms: u_1, u_2 if those exist.

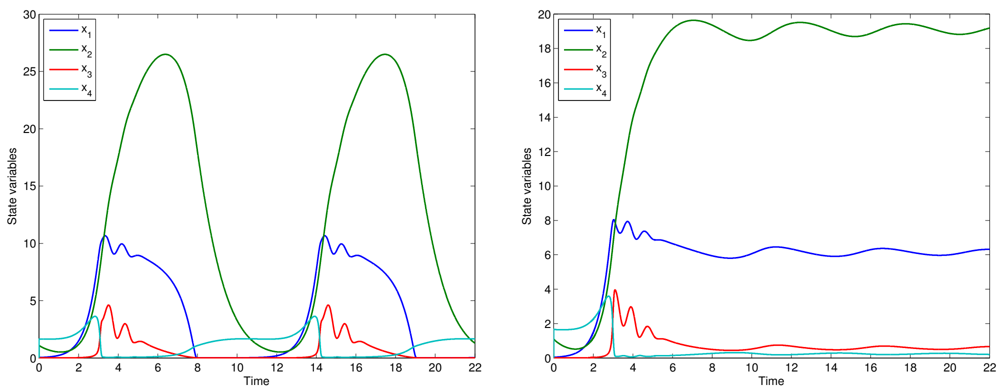

Figure 1.3 – Simulation of the system with no inhibition (left) and with the constant maximum inhibition of the PMCA (right) for the calcium oscillator problem.

The complex oscillations of the state variables are shown in the Figures 1.3 where two cases were investigated. The first one, on the left side where no inhibition is considered $(u_1 = 0, u_2 = 0, p_1 = 1)$ and the second one, on the right side, where full inhibition of the PMCA and no channel blocking is considered ($u_1 = 1$, $u_2 = 0$, $p_1 = 1.3$) during the whole simulation time. These figures are obtained directly with the help of the simulation module implemented in our toolbox.

1.2.1 The scenario with free transition times and one control variable

DOTcvp: midop_PhaseResettingOfCalciumOscillationsA.m

In the paper [4] the author reported that the system is extremely sensitive to the small perturbations in the stimulus. Previous authors used the multiple shooting method for solving this problem. For the first scenario with one control variable the value of the cost function 1604.13 was reported. We obtained a solution of 1620.55 which is slightly worse that the one presented in the literature.

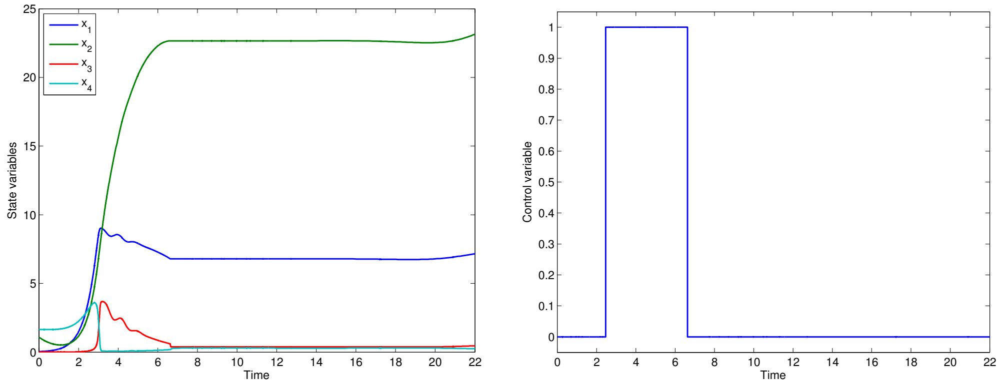

Figure 1.4 – Optimal state trajectories (left) with corresponding control profile (right) for the calcium oscillator problem.

The optimal trajectories are shown in the Figure 1.4 and the final value of the time-independent parameter is 1.14601340. Following the figures it is possible to say that the impact of the PMCA inhibitor is significant and smooths the state trajectories considerably.

1.2.2 The scenario with free transition times and two control variables

DOTcvp: midop_PhaseResettingOfCalciumOscillationsB.m

For the second scenario, where two control variables are active, the cost function value of 1538.00 was reported from the afore mentioned literature. Our value is 1542.50 what is comparable but the total time of the use of the first and the second inhibitor is during the simulation 13.3 % less. As well not only the total time of the stimuli with the inhibitor is lower but also the amount of the inhibition of the PMCA ion pump. This improvement has an influence on the total inhibitor price.

The appropriate optimal trajectories are shown in the Figure 1.5 where oscillations are smoothed considerably. The dotted red lines always indicate the desired states. The optimal value of the time-independent parameter is 1.02430397. In the case that the stimuli will stop, the oscillations appear again (see Figure 1.6) due to the instability of the steady states.

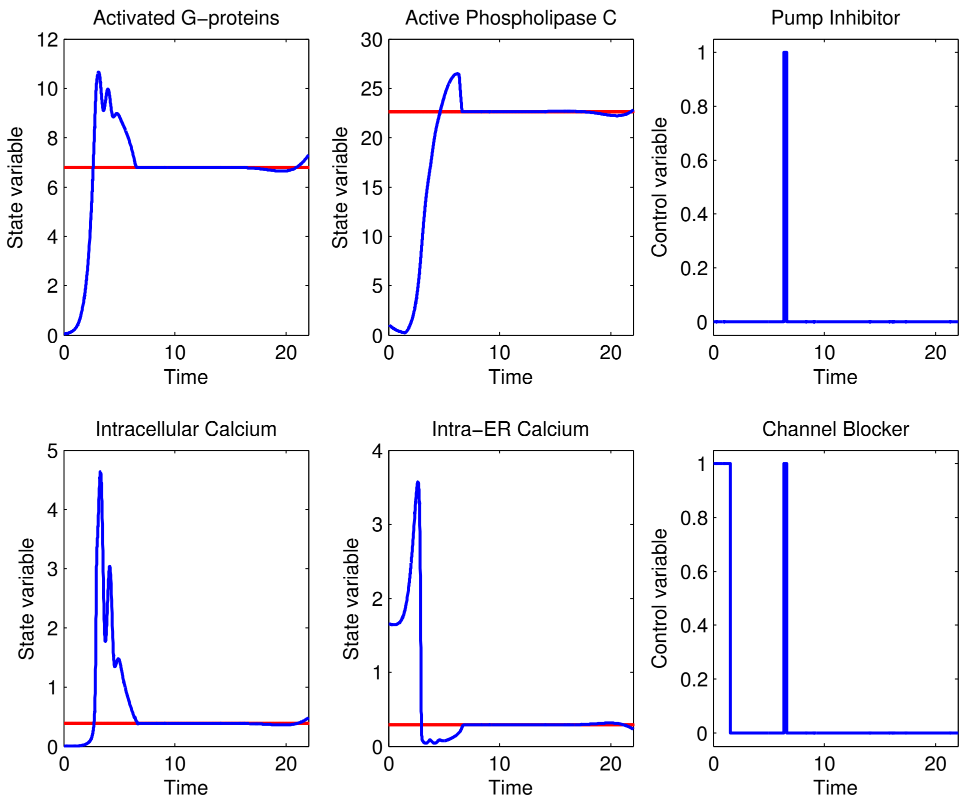

Figure 1.5 – Optimal state and control trajectories for the calcium oscillator problem.

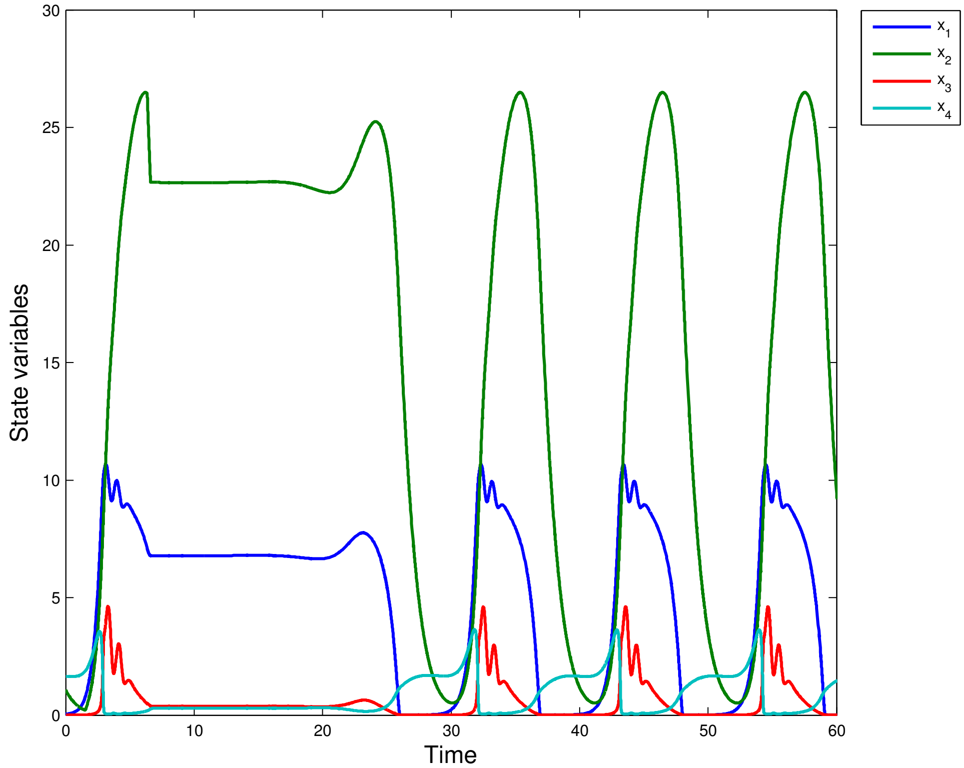

Figure 1.6 – The problem simulation to longer times ($t_F = 60$) without more stimuli for the calcium oscillator problem.

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