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On Nonlinear Continuous-time Optimal Control of Penicillin Cultivation

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Abstract— **This paper presents continuous-time optimal control of penicillin production maximizing penicillin concentration at chosen final time. First, control input parametrization is performed and the input is expressed as a piece-wise affine function of continuous time reducing the number of optimizable parameters. Then, iterative numerical gradient optimization with the initial conditions corresponding to the optimal input obtained by projected gradient optimization is used to find the optimal values of the optimized parameters. The proposed approach is compared to both the original gradient method and the traditionally used classical nonlinear feedback controller. All these strategies are tested on a set of numerical experiments for various cultivation lengths and the results are evaluated and discussed. The comparison reveals significant superiority of the proposed algorithm. Together with impressive reduction of memory space needed to store the solution, the results improvement makes the proposed algorithm very attractive from the industrial point of view.**

I. INTRODUCTION

Biotechnological processes (e.g. bakery, beverages fermentation, etc.) have gone along with mankind over ages. Besides the traditional branches such as food production, many new areas have arisen over the last century. According to papers presented at the International Congress Innovation and Technology XXI: Strategies and Policies Towards the XXI Century [1], personalized medicine based on the use of enhanced personally oriented drugs is one of the most emerging technologies - and it is well-known that significant part of medicaments is produced by fermentation which emphasizes the importance of bioprocess control. However, it is not only the economic impact of biotechnologies which makes them interesting from the engineering point of view - being a very illustrative example of a nonlinear system with complicated dynamics, almost every bioprocess can be seen as a challenging test-bed for the modern control theory.

In the industrial medicaments production, traditional control approaches are usually applied - after simple open-loop strategies [2] accompanying on/off [3] or classical PID control strategies, fuzzy-theory-based approaches appeared in the 90s [4] and were revitalized at the beginning of the new millennium [5]. However, none of these approaches is able to exploit the full potential of the modern control theory and reach the top limits of industrial drug productivity. Very promising results can be found in [6]–[8] where the gradient method is shown to be the proper choice for the optimization of the antibiotics production which can be considered as a representative member of the medicament family. Unlike the classical Model Predictive Control (MPC) [9] being another optimization approach exploiting the controlled system model, nonlinear optimization techniques are able to handle the naturally nonlinear dynamics of the cultivation without a need for linearization (either approximate which might degrade the control performance vastly or exact which in many cases does not even exist in the originally-dimensional state space).

Yet another great reserve in the use of the modern control theory for the optimization purposes (not only in the field of bioprocess control but also in a more general scale) can be mentioned - overwhelming majority of its nonlinear applications considers discrete time models - either linear [10], [11] or nonlinear [12]–[14]. Since the earliest ages of the optimal control theory, only very few research attempts have been oriented on the continuous-time optimal control of nonlinear systems. Those few have usually tested their design on two-dimensional systems with a simple nonlinearity [15]–[17]. The lack of continuous-time attempts is the consequence of the fact that one of the crucial aspects of the industrially utilizable optimal control is the trade-off between the optimality of the solution (intuitively improving with shorter sampling period) and the memory and computational demands of the optimization procedure (increasing with shorter period as well). This leads to a very frequent situation in which the engineers sacrifice the optimality to the acceptable complexity of the optimization - either longer sampling periods or shorter control horizons with higher sampling frequency are considered. At the current state-of-art of the industrial actuators, there is no need for such compromises - especially the valves coming into consideration in the case of bioprocess control are able to operate at such high sampling frequencies that they can be considered as continuous-time-working devices. In fact, it is the optimization task that becomes unbearably huge and hardly solvable considering these sampling frequencies - however, performing some kind of input-profile parametrization, the optimization of the continuous-time manipulated variable profile can be computed and the course of dimensionality can be avoided.

In this paper, we follow the suggestions for the future work presented in [18] and bridge the gap between continuous-time control, optimal control and control of nonlinear systems - piece-wise affine continuous-time optimal control for the fed-batch penicillin cultivation is designed with the aim to maximize penicillin concentration at the given final time

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and the results are tested on a set of numerical experiments.

The paper is organized as follows: Section II presents the model of penicillin cultivation used within the optimization routine and briefly explains its basic principles. In Section III, input profile parametrization is introduced and the basic idea of the gradient-search optimization of the corresponding parameters is outlined. The results of the numerical experiments are presented and discussed in Section IV. The proposed approach is compared to the gradient method and to the classical nonlinear feedback controller based on static maximization of the growth/production rate. Section V summarizes the work and concludes the paper.

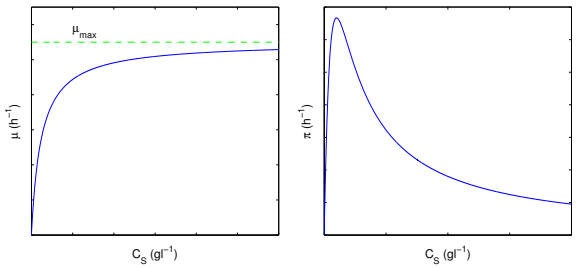
II. MODEL OF PENICILLIN CULTIVATION

For the optimization and simulation purposes, cultivation of the penicillin [19], [9] is considered in this paper.

Biomass X (which can be regarded as the central variable of every bioprocess) represents the „driving engine" of the cultivation - it consumes essential nutrient S and thanks to this „fuel", it ensures its own reproduction at growth rate μ and creates the final product P (the penicillin) at specific production rate π. This is the typical secondary metabolism example - the growth rate increases with higher nutrient concentration while the penicillin production is from critical substrate concentration $C_{S,crit}$ inhibited by the increasing nutrient concentration. This leads to Contois formula for μ and Haldane kinetics for π which are totally different,

$$\mu = \mu_{max}\frac{C_S}{K_X C_X + C_S}, \pi = \pi_{max}\frac{C_S}{K_P + C_S + C_S^2/K_I}.$$

Both rates reach their maxima at different substrate concentrations $C_S = S/V$ (see Fig. 1a and Fig. 1b), which is important for the classical nonlinear controller.



(a) $\mu(C_S)$ (b) $\pi(C_S)$

Fig. 1: Growth and production rate profiles.

The biomass mortality is expressed by the constant death rate K_D at which the amount of biomass decreases. Usual way of complementing the consumed nutrient is pouring the feed with nutrient concentration $C_{S,in}$ into the tank while the feed flow rate u is then the manipulated variable of this control task. Every control action increases the volume level V which naturally decreases due to the vaporization described by the specific vaporization constant K_{vap}. Moreover, penicillin hydrolysis caused by the fact that the cultivation environment is liquid is modeled by its hydrolysis rate K_H. Finally, to follow the bioprocess modeling convention, the „bio-variables" (biomass X, nutrient S and final product P) are considered in the corresponding concentration forms: $C_X = X/V$, $C_S = S/V$, $C_P = P/V$.

The dynamical behavior of this bioprocess can be summarized into a compact model as follows:

$$\begin{aligned}
\dot{x}_1 &= u - K_{vap}x_1,\\
\dot{x}_2 &= \left(\mu_{max}\frac{C_S}{K_X C_X + C_S} - K_D\right)x_2 - \left(\frac{u}{x_1} - K_{vap}\right)x_2,\\
\dot{x}_3 &= -\left(\frac{\mu_{max}}{Y_{X/S}}\frac{C_S}{K_X C_X + C_S} + \frac{\pi_{max}}{Y_{P/S}}\frac{C_S}{K_P + C_S + C_S^2/K_I}\right)x_2 + \frac{C_{S,in}u}{x_1} - \left(\frac{u}{x_1} - K_{vap}\right)x_3,\\
\dot{x}_4 &= \pi_{max}\frac{C_S}{K_P + C_S + C_S^2/K_I}x_2 - K_H x_4 - \left(\frac{u}{x_1} - K_{vap}\right)x_4.
\end{aligned} \tag{1}$$

In this description, states $x = [x_1, \ldots, x_4]^{\mathrm{T}}$ correspond to $[V, C_X, C_S, C_P]$ and input u represents the feed flow rate. Model (1) is further exploited as both the optimization model and the simulation test-bed for the results evaluation.

Values of the system parameters can be found in Table I. Interested readers looking for a more detailed description are referred to [6], [9], [19].

III. PIECE-WISE AFFINE CONTINUOUS-TIME CONTROL

In this section, procedure of design of continuous-time input profile maximizing the penicillin concentration at the final time is explained. First, the input profile is parameterized which brings significant reduction of the optimized parameters. Projected gradient method is used to choose the initial conditions of the parameters. Then, the gradient search using the minimization of spline-approximation is performed and the parameters are searched iteratively.

TABLE I: Model parameters.

Parameter	Value	Parameter	Value
μ_{max}	0.11	$Y_{P/S}$	1.2
π_{max}	0.004	$C_{S,in}$	500
K_P	0.1	K_{vap}	6.23×10^{-4}
$Y_{X/S}$	0.47	K_I	0.1
K_D	0.0136	K_X	0.06
K_H	0.01		

A. Problem formulation

Like in many others branches of industry, maximization of the product is the ultimate goal of the whole process. It can be intuitively expected that the longer is the cultivation, the higher penicillin concentration at final time can be achieved - however, the duration of the cultivation cannot be extended to infinity. Thus, without any loss of objectivity, a set of the admissible final times $\mathbf{T}_{F,admiss}$ can be chosen in advance (in this case, $\mathbf{T}_{F,admiss}(h) = \{100, 200, \ldots, 600\}$) and the maximization of penicillin concentration can be regarded as fixed time optimization task with various length of the optimized time interval.

For the needs of optimization, the whole task can be formulated as follows: we are looking for such a function $u^*(t)$ that the criterion $\mathcal{J}$ is minimized. According to aforementioned, the criterion $\mathcal{J}$ can be formulated as

$$\mathcal{J} = -x_4(T_F), \tag{2}$$

where T_F is the cultivation period, $T_F \in \mathbf{T}_{F,admiss}$. Moreover, the solution must satisfy the given constraints:

$$\begin{aligned} &\dot{x} = f(x,u), \quad x(0) = x_0 = (x_{1,0}, \ldots, x_{4,0})^{\mathrm{T}}, \\ &0 \leq u \leq u_{max}, \end{aligned} \tag{3}$$

with $f(x,u)$ representing the model given by (1). The values of the optimization constraints can be found in Tab. II.

B. Input profile parametrization

In order to reduce the number of optimized parameters, the piece-wise affine continuous-time input profile is considered and parameterized in the time domain.

This idea comes out of the fact that the gradient method can be used to obtain the initial estimates of both the shape of the input profile and the values of the parameters. The gradient method belongs to optimal control methods family and it looks for the optimal input profile v^*_{k+1} as follows:

$$v^*_{k+1} = v^*_k + \alpha \frac{\partial \mathcal{H}}{\partial v}. \tag{4}$$

Here, Hamiltonian $\mathcal{H}$ is constructed as

$$\mathcal{H} = L + p^{\mathrm{T}} f, \tag{5}$$

with L being the integral term of the criterion $\mathcal{J}$ (let us note that in this particular case, $L = 0$), f represents the model (1) and p denotes the costate vector which evolves in time as follows:

$$-\dot{p} = \frac{\partial \mathcal{H}}{\partial x}, \quad p(T_F) = -\left(\frac{\mathrm{d}\phi}{\mathrm{dx}}|_{t=T_F}\right), \tag{6}$$

TABLE II: Optimization constraints.

Parameter	Value
$x_{1,0}$	7.012
$x_{2,0}$	1.5
$x_{3,0}$	6
$x_{4,0}$	0
u_{max}	0.05

ϕ refers to the terminal term of the criterion $\mathcal{J}$. More details on the general properties of the used method can be found in [20], [21] while the routine itself is described in [6].

Let us note that the result of the original gradient method optimization is a vector of discrete values. As the analytical solution of both (1) and (6) is complicated, these two sets of differential equations are solved numerically and the resulting optimized input profile v^* is sampled with the sampling period which corresponds to the sampling period of the Hamiltonian $\mathcal{H}$. In [6], $T_s = 4\,\mathrm{h}$ has been chosen. Considering $\mathbf{T}_{F,admiss}$ as mentioned above, this results in input sequences of 25 to 150 samples (according to the chosen cultivation length T_F). Especially for the longer cultivation periods, the optimization gets more complicated due to the increase of the optimization problem dimension. In [6], a similarity between optimal profiles for various cultivation lengths has been revealed (see Fig. 2) and coming out of this similarity, the following parametrization is suggested:

$$u(t) = \begin{cases} U_1 + dU_1 t & 0 \leq t < T_1, \\ U_2 + dU_2(t - T_1) & T_1 \leq t < T_2, \\ U_3 + dU_3(t - T_2) & T_2 \leq t \leq T_F, \end{cases} \tag{7}$$

with U_i, dU_i, T_j being the optimizable parameters of the input profile, $i \in \{1,2,3\}$, $j \in \{1,2\}$. Let us remind the memory demands reduction - compared to the original input profile which is defined by up to 150 parameters, the continuous-time parameterized profile can be uniquely determined using only these 8 parameters - the number of the parameters is nearly $19\times$ reduced.

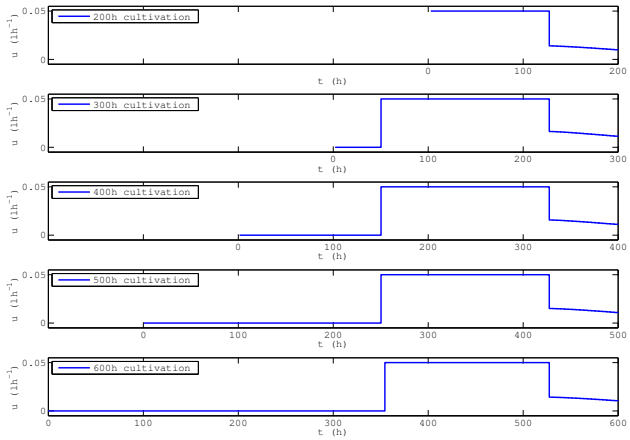


Fig. 2: Original gradient method input profile comparison.

C. Optimization of the input profile parameters

The input parametrization (7) can be expressed in a more compact way as

$$\begin{aligned} u(t) = &(U_1 + dU_1 t)(H(t) - H(t - T_1)) \\ &+ (U_2 + dU_2(t - T_1))(H(t - T_1) - H(t - T_2)) \\ &+ (U_3 + dU_3(t - T_2))H(t - T_2), \end{aligned} \tag{8}$$

$0 \leq t \leq T_F$. $H(\cdot)$ denotes the Heaviside step function. Although this function is derivable with respect to the

parameters, some derivatives include Dirac delta functions which might not be convenient due to the numerical stability. Therefore, we propose an alternative approach.

First, at every iteration, each of the parameters is perturbed in both the positive and negative direction while the others parameters are held fixed and the cost functional values for various values of the particular parameter are obtained. The range of the perturbation is to be chosen. In this paper, we consider the perturbations in the form of $OP_m + \Delta_{OP_m} D_{OP_m}$. Here, $OP_m \in \{U_i, dU_i, T_j\}$ denotes the m-th optimization parameter as mentioned in the previous subsection, $\Delta_{OP_m} \in \{1,2,3,4,50\} \times LPS_m$ refers to the perturbation step, LPS_m stands for the elementary perturbation step of the m-th optimization parameter (tuning this value, the convergence speed can be affected) while $D_{OP_m} \in \{1,-1\}$ is the perturbation direction. To sum up, for each of the eight optimization parameters, 11 values of the optimization criterion $\mathcal{J}$ (together with the unperturbed criterion value) are gathered such that the other parameters are held constant at their values from the previous iteration.

Having gathered these sets of the perturbed cost functional values for all parameters, the second stage of the algorithm can be performed. This step consists in the spline interpolation of each of the gathered sets of the cost functional values. As the explanation of the principles and the practical realization of the spline interpolation is beyond the scope of this paper, interested readers are warmly referred to [22]. Having performed the interpolation, eight splines S_{OP_m} are at disposal and the spline approximation of the optimization criterion is expressed as the function of the particular optimization parameter perturbation,

$$S_{OP_m} \approx \mathcal{J}(\Delta_{OP_m} D_{OP_m}).$$

Here, the piece-wise polynomial character of the splines can be exploited - this feature enables to find the minimum of each spline either analytically or by a simple exhaustive line search. Finally, parameter perturbation values $(\Delta_{OP_m} D_{OP_m})^{min} = \arg\min S(\Delta_{OP_m} D_{OP_m})$ corresponding to the minima of the interpolated splines are lined up to form the numerical gradient which is then used to move along in the eight-dimensional optimization parameter space.

In order to satisfy the input profile constraints, $0 \leq u(t) \leq u_{max}$, the optimal U_i and dU_i parameters are at the o^{th} iteration projected on the admissible intervals,

$$\mathbf{U}_{admiss,i,o} = \langle 0, u_{max} \rangle, \tag{9}$$

$$\mathbf{dU}_{admiss,i,o} = \langle \frac{-U_{i,o}}{T_{i,o} - T_{i-1,o}}, \frac{u_{max} - U_{i,o}}{T_{i,o} - T_{i-1,o}} \rangle. \tag{10}$$

Without any loss of objectivity, $T_0 = 0$ and $T_3 = T_F$ can be assumed. The constraints for the parameters T takes the following form: $T_{i-1,o} \leq T_{i,o}$.

Let us remark that the gradient search for the parameters of the piece-wise affine continuous-time input profile is iterative and the above-described procedure is performed until the difference between k^{th} and the $(k-1)^{\text{st}}$ iteration criterion value $\mathcal{J}^*$ corresponding to the optimal solution at the particular iteration is less than a chosen tolerance.

IV. RESULTS

In this section, the results of the proposed piece-wise affine continuous-time optimal control (PACTOC) algorithm are presented and compared to those obtained by the original gradient method (OGM) and the industrially used classical nonlinear feedback controller (CNFC).

A. Comparison to the original gradient method

First, the proposed PACTOC algorithm has been tested on a set of numerical experiments with satisfactory results and with significant improvement compared to the original OGM approach [6]. Fig. 3 shows the comparison of the penicillin concentration profiles for these two approaches while Tab. III brings the numerical values of both the resulting concentration at final time T_F and number of parameters defining the profile *NP* which is proportional to the memory space needed to store the solution.

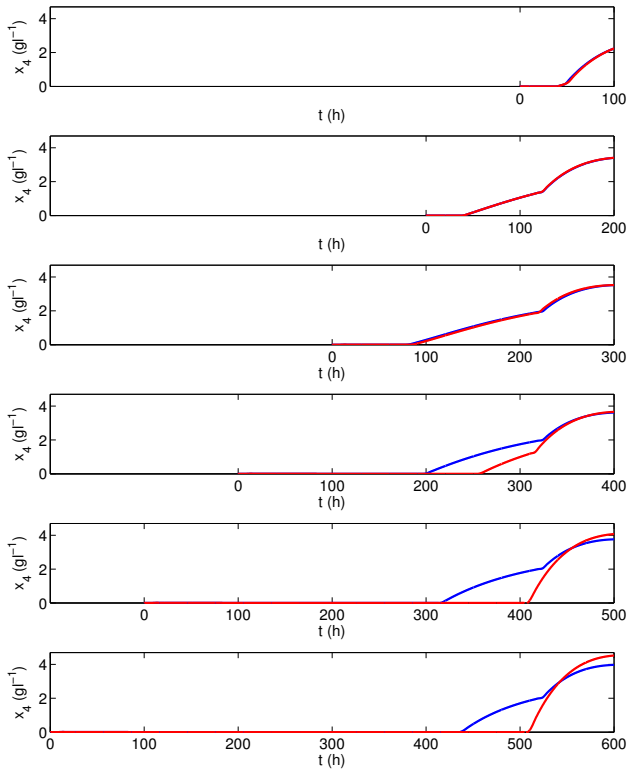


Fig. 3: x_4 profiles comparison (blue - OGM, red - PACTOC).

TABLE III: PACTOC vs. OGM.

T_F (h)	OGM		PACTOC	
	$x_4(T_F)$	*NP* (—)	$x_4(T_F)$	*NP* (—)
100	2.238	25	2.241	8
200	3.405	50	3.410	8
300	3.519	75	3.525	8
400	3.622	100	3.662	8
500	3.761	125	4.074	8
600	3.972	150	4.524	8

It can be seen that the PACTOC algorithm is successful in general and is able to both reduce the memory demands

and improve the resulting concentration at final time. The most impressive is the situation with $T_F = 600\,\text{h}$ where the reduction of the memory requirements is almost 95% while the concentration at the final time increases of almost 14% compared to the OGM approach. In the industrial practice, this improvement together with the memory requirement reduction can be of significant economical impact. It should be noticed that following the assumption that the first two parts of the input profile are constant ($dU_1 = dU_2 = 0$), the number of the optimized parameters can be reduced to 6. Moreover, this assumption can be even extended to $U_1 = 0$, $U_2 = u_{max}$, $dU_1 = dU_2 = 0$ and then, only 4 parameters are left to be optimized. Similarly, for short cultivation periods $T_F \in \{100, 200\}\,\text{h}$ obviously only two piece-wise continuous intervals occur and the *NP* value can be reduced to 3.

For the sake of completeness, Fig. 4 compares the OGM and PACTOC input profiles for various cultivation lengths.

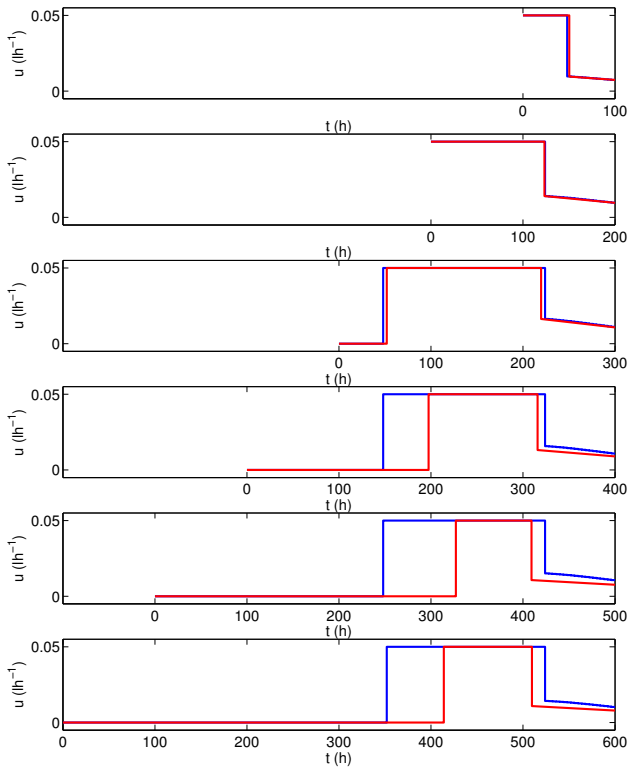


Fig. 4: u profiles comparison (blue - OGM, red - PACTOC).

B. Comparison to the classical nonlinear controller

First, let us briefly introduce the key idea of the classical nonlinear controller. This controller is based on a simple static optimization of the penicillin production and tries to keep the derivative $\dot{x}_4$ as high as possible. It can be seen that the only way to increase the derivative of the x_4 effectively is the maximization of the first term which can be accomplished by the maximization of either the biomass concentration x_2 or the production rate π. This leads to such a strategy that at first, the biomass concentration x_2 is increased maximizing the substrate concentration x_3 which increases its growth rate μ (see Fig. 1a) and then, the penicillin production rate is optimized keeping the x_3 at $C_{S,crit} = 0.1$ (see the model (1) and Fig. 1b). This approach reflects the fact that the penicillin is the secondary metabolite.

It can be shown that the most crucial tuning parameter of the above-mentioned approach is the time point T_{bp} at which the maximization of μ turns into the maximization of π. The input profile is affected by the choice of T_F only through shrinking or extending the interval over which π maximization is performed - in general, the first N hours of the corresponding state and input profiles are identical for various choices of T_F with fixed T_{bp}. Fig. 5 shows the performance of the classical nonlinear controller using a simple exhaustive search tuning of T_{bp}. Cases for different T_{bp} are plotted in different colors, $T_{bp} \in \{0, 10, 20, \ldots, 600\}$, while the dashed lines represent the cultivation periods T_F as mentioned earlier in this section.

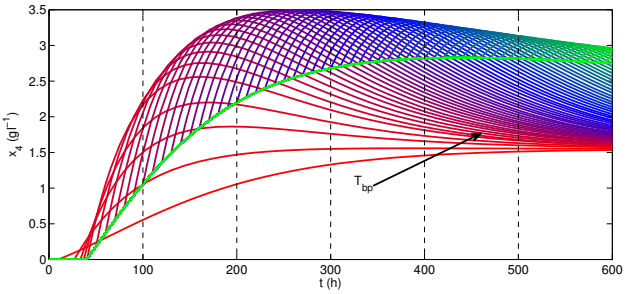


Fig. 5: Classical nonlinear controller performance.

It is obvious that for $T_F > 100\,\text{h}$, the x_4 profiles are often non-monotonic and $x_4(T_F) \neq \max_t(x_4(t))$ for many T_{bp}. Therefore, both $x_4(T_F)$ and $\max_t(x_4(t))$ for particular profiles with the highest reached penicillin concentration should be evaluated. The results for various T_F are listed in Tab. IV. Let us note that in order to obtain higher accuracy, T_{bp} has been chosen from $\{0, 1, \ldots, T_F\}$. In the table, $x_4(T_F)^{max}$ denotes the highest final product concentration reached for various T_{bp},

$$x_4(T_F)^{max} = \max_{T_{bp}}(x_4(T_F)),$$

while $\max_t(x_4(t))^{max}$ refers to the highest product concentration during the whole cultivation period for various T_{bp},

$$\max_t(x_4(t))^{max} = \max_{T_{bp}}(\max_t(x_4(t))).$$

TABLE IV: PACTOC vs. CNFC.

T_F (h)	CNFC		PACTOC
	$x_4(T_F)^{max}$	$\max_t(x_4(t))^{max}$	$x_4(T_F)$
100	2.233	2.233	2.241
200	3.388	3.388	3.410
300	3.481	3.500	3.525
400	3.326	3.500	3.662
500	3.138	3.500	4.074
600	2.963	3.500	4.524

Both Tab. IV and Fig. 6 reveal that although quite admissible for the short cultivation period, the CNFC usually does not fulfill the control requirements - for $T_F > 300$,

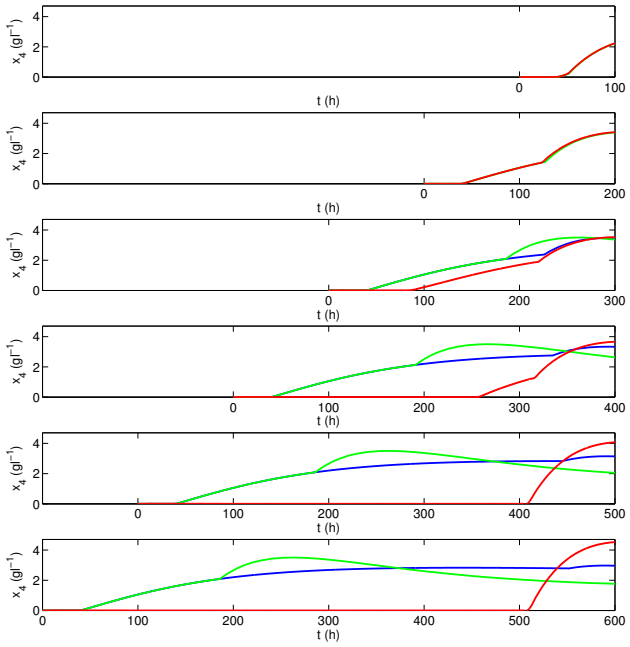


Fig. 6: CNFC vs. PACTOC.

the values of $\max_t(x_4(t))^{max}$ are significantly lower than the results reached by PACTOC (only 77% of the PACTOC results) while $x_4(T_F)^{max}$ are actually quite poor compared to the PACTOC values which is able to reach up to 153% of the CNFC final product concentration. Here, the superiority of the PACTOC algorithm can be fully observed - unlike the commonly used approaches, this approach takes the control goal into account and performs rigorous optimization and outperforms the traditional methods.

V. CONCLUSION

In this paper, continuous-time optimal control algorithm has been introduced and tested on the example of the penicillin production optimization. Taking the advantage of the initial input profile estimate generated by the original gradient method, piece-wise affine parametrization of the input profile has been proposed and successful transformation from higher-dimensional optimization space (from 25 up to 150 dimensions) to significantly lower-dimensional space (8 or less dimensions) has been performed. Besides the problem order reduction, significant results improvement compared to the original gradient method can be observed, especially for the longer cultivation periods (improvement of nearly 14%) for which the optimization dimension reduction is even higher (-95%). In comparison with the traditionally used nonlinear controller, the newly proposed algorithm shows immensely superior results (improvement of up to $+53\%$) which demonstrates its industrial applicability.

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