A Lyapunov based heuristic to speed up convergence of a feedback optimization framework with experiment batches - application to bioprocess manufacturing

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Abstract: In this work a heuristic to speed up the convergence of a feedback-based optimization scheme, when experiments can be run in batches, is discussed. The proposed approach allows to select the most promising experiment in the batch, as the one maximising the decrease of an associated Lyapunov function, and to define the inputs for the next batch, based on this. We suggest the application of the scheme to a biological setting, with the goal of maximizing the concentration of a product of interest in a bioreactor under a continuous perfusion framework, while at the same time minimizing the yield of a toxic byproduct. The potential of the approach is exposed by means of a simple synthetic example.

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1. INTRODUCTION

Feedback-based optimization is a real-time optimization technique, whose goal is to drive the steady-state output of a given plant, to local optima of an objective function, by taking into account output measurements of the physical system (see Jokic et al. [2009], François et al. [2012], Bernstein et al. [2019] and references therein). This technique is gaining increasing interest in the control community due to its potential application in many practical fields, in particular recently focusing to power systems optimization [Dall’Anese and Simonetto 2016, Hauswirth et al. 2017].

In Hääberle et al. [2021] the authors described a feedback optimization framework in which the input is discretely updated, based on a projected gradient descent scheme. The ease of tuning, the capacity to handle non-convex problems and to consider input and output constraints, make this approach extremely appealing.

In the bioprocessing production context, one crucial aspect is the optimization of feed-flow medium composition, in order to maximize the yield of products of interest, e.g. as monoclonal antibodies [Chotteau 2015, Singh et al. 2017]. In perfusion processes of mammalian cells, the culture medium is continuously renewed at a given flow rate ensuring delivery of substrates and removal of by-products. Steady-state can be established by maintaining the cell concentration at a given level. Typically optimization of these processes can be addressed using the metabolic reaction network. The composition of the medium used in the culture, named feed-flow medium here, is very important for the process, and its optimization is not a trivial problem due to the large number of components; it is not uncommon to have 50–100 components. This type of optimization is typically performed by trial-and-error approach supported by statistical tools. However for these processes the considered models are highly complex and with large uncertainties, making model based optimization prone to provide sub-optimal solutions. For this reason feedback optimization, where process measurements are used directly, seems to be an interesting alternative. In bioprocessing, to setup and run an experiment can be expensive, both in terms of time and resources spent, and it is therefore desirable to converge to the optimal (or nearly-optimal) feed-flow medium composition in as few iterations as possible. A feedback-based optimization scheme, however, might require a quite large number of iterations to converge to an optimality point, due to the choice of small enough step-sizes to ensure convergence. On the other hand it is convenient, and fairly common in bioproduction, to setup multiple experiments that are run in parallel. However this possibility is not generally exploited in feedback based optimization schemes, which relies on a more sequential scheduling of the experiments.

Our goal here is twofold. First of all we would like to formally define a Lyapunov-based heuristic that, given the possibility of running multiple experiments in parallel, can possibly speed up the convergence of the feedback optimization algorithm, still keeping intact the convergence properties. The approach will use the Lyapunov function employed in Hääberle et al. [2021]. Some works in the real-time optimization literature considered the case of parallel
experiments executed on multiple identical units, with the goal of estimating the objective function’s gradient for the optimization [Srinivasan 2007]. Our aim here is different, as we will attempt to get perfect knowledge of the input-output sensitivity and we will exploit multiple identical units to speed up the convergence of the optimization algorithm significantly. Works similar to Srinivasan [2007] considered multiple non-identical units [Woodward et al. 2009], but still not with the goal of speeding up convergence. We show, in simulation, the potential of the proposed scheme, to handle successfully also this more realistic case.

The second goal we have is to propose, through a synthetic example, the possibility of using such a feedback optimization scheme in a bioprocessing framework. We will consider a simple metabolic network and the problem of maximizing the yield of a product of interest, while still not with the goal of speeding up convergence. We remark again that, given the discrete nature of the map, it is assumed that the system reaches a steady-state before the next input is applied. The plant’s input-output map is assumed to be known.

We consider the following optimization problem to be solved at steady-state:

$$\min_{u, y} \Phi(u, y)$$

s.t. $y = h(u), \; u \in U, \; y \in Y$

where $\Phi : \mathbb{R}^p \times \mathbb{R}^m \to \mathbb{R}$ and $h : \mathbb{R}^p \to \mathbb{R}^m$ are continuously differentiable functions, $U \subseteq \mathbb{R}^p$ and $Y \subseteq \mathbb{R}^m$. The following assumptions are made.

**Assumption 1.** The feasible regions $U \subseteq \mathbb{R}^p$ and $Y \subseteq \mathbb{R}^m$ are described by:

$$U = \{ u \in \mathbb{R}^p \mid Au \leq b, \; A \in \mathbb{R}^{q \times p}, \; b \in \mathbb{R}^q \}$$

$$Y = \{ y \in \mathbb{R}^m \mid Cy \leq d, \; C \in \mathbb{R}^{1 \times m}, \; d \in \mathbb{R} \}$$

**Assumption 2.** For (1), $U$ is compact.

**Assumption 3.** The following set:

$$\bar{U} = \{ u \in \mathbb{R}^p \mid Au \leq b, \; Ch(u) \leq d \} = U \cap h^{-1}(Y)$$

is non-empty.

We remark again that, given the discrete nature of the algorithm and the fact that $h$ is the plant’s steady-state input-output map, it is assumed that the system reaches a steady-state before the next input $u^+$ will be applied. In bioprocessing we can consider that each steady-state is carried out during an experiment, with inputs and outputs analysed between experiments. However, in view of today’s technologies, real-time monitoring of key process variables is possible, and sometimes applied in the field. In case this is available, steady-state perfusion cultures allow to carry out different experimental conditions after each other, typically each for a period of 4 to 5 days at steady-state, with a 2 to 3 days period transient. By closing the loop between the plant and the feedback optimization controller, the input $u$ will evolve, in a discrete fashion, according to the following rule:

$$u^+ = u + \alpha \sigma(\alpha, u, y), \; y = h(u)$$

where $u$ is the input previously applied to the plant, $u^+$ is the new input to be applied, $\alpha > 0$ is a fixed step-size and $\sigma(\alpha, u, y)$ is obtained as:

$$\sigma(\alpha, u, y) := \arg \min_{w \in \mathbb{R}^p} ||w + G^{-1}(u)H(u)^T \nabla \Phi(u, y)^T||_2$$

s.t. $A(u + \omega w) \leq b$

$$C(y + \alpha \nabla h(u)w) \leq d$$

where $G(u) : \mathbb{R}^p \to S^p_+$ is a metric defined on $\mathbb{R}^p$, i.e. a map that to any point $u \in \mathbb{R}^p$ associates a semidefinite positive matrix (which can be constant), $H(u)^T = [I^p \nabla h(u)^T]$ and $A, B$ and $C$ are specified in Assumption 1.

The direction determined by (3)–(5) is a projection of the objective function antigradient, in closed loop, into a linearization of the feasible set. It is also noted that, because the map $h$ is unknown, exact constraints on the output $y$ cannot be enforced, hence violations of output constraints are admitted, but these are bounded and can be quantified – as showed in the proof of [Häberle et al. 2021, Lemma 4] – and it is ensured that the solution will converge to a feasible one.

The following assumption is made to ensure the convergence of the algorithm to an optimality point of (1).

**Assumption 4.** For all $u \in U$ the feasible set:

$$\bar{U}_u := \{ w \mid A(u + \omega w) \leq b, \; C(y + \alpha \nabla h(u)w) \leq d \}$$

is non-empty and satisfies Linear Independence Constraint Qualification (LICQ) (see Häberle et al. [2021] for the formal definition), for all $w \in \bar{U}_u$. 

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With the above assumptions, the following theorem, from Häberle et al. [2021], holds:

**Theorem 1.** Let Assumptions 1–4 hold. Let $\nabla \Phi$ and $\nabla h$ be globally Lipschitz on $\mathcal{U}$. Then $\exists \alpha^* > 0$ s.t. for all $0 < \alpha < \alpha^*$

1. the trajectory of $u$, starting from any $u_0 \in \mathcal{U}$, obtained through the updating rule (2)–(5), and $y = h(u)$, converge to the set of first-order optimality points of (1)
2. if $u^*$ is an asymptotically stable equilibrium of (2)–(5), then it is a strict local minimum of $\tilde{\Phi}(u) := \Phi(u, h(u))$, on $\tilde{\mathcal{U}}$.

Theorem 1 guarantees that, if the assumptions are satisfied, by closing the loop between the plant and the feedback optimization controller, with a small enough step-size, the overall system converges to a first-order optimality point of (1). However, a small step-size can make the convergence very slow, sometimes to an unacceptable degree in some applications.

In the following section we propose a Lyapunov based heuristics, to take advantage of experiments executed in batches, to possibly speed up the convergence of the optimization algorithm.

3. **LYAPUNOV BASED HEURISTICS FOR EXPERIMENT BATCHES**

We will assume that each batch consists of $L$ different experiments run in parallel, on $L$ identical units (identical bioreactors in the bioprocessing context), and we will consider the following general approach:

1. Let $\alpha = \{\alpha_1, \ldots, \alpha_L\}$ be a finite set of $L$ different fixed step sizes. Let $u_0$ be an initial feasible input, leading to the measured output $y_0$. Let $k = 1$:
2. At step $k$ choose the following inputs for the $L$ experiments:
   
   $u^*_k = u_{k-1} + \alpha_j \sigma(\alpha_j, u_{k-1}, y_{k-1}), \quad \forall j \in \{1, \ldots, L\}$
   
   where $\sigma(\alpha_j, u, y)$ is the projection operator (3)–(5), for the step-size $\alpha_j$;
3. Measure the outputs $y^1_k, y^2_k, \ldots, y^L_k$ of the $L$ experiments;
4. Choose $u_k$ as one of the inputs $u^1_k, \ldots, u^L_k$ based on some criterion;
5. Increase $k$ and repeat 2–5.

It is clear that the choice of the heuristic criterion in Step (4) is crucial, as on this depend both the convergence property and the effectiveness of the approach. In the following we propose a Lyapunov based criterion which guarantees convergence, while possibly accelerating it.

In Häberle et al. [2021] the following Lyapunov function is considered:

$$V(u) = \Phi(u, h(u)) + \xi \sum_{i=1}^{l} \max\{C_i h(u) - d_i, 0\}$$

where $\xi$ is an upper bound on the Lagrange multipliers associated with output constraints in (5), which exists because of the compactness of $\mathcal{U}$. The authors proved that by choosing a small-enough step-size $\alpha < \alpha^*$, one can guarantee the convergence of the feedback optimization controller to a first-order optimality point of the function $\Phi(u, h(u))$. This result follows from the fact that:

$$V(u + \alpha \sigma(\alpha, u, h(u))) - V(u) \leq 0, \quad \forall \alpha < \alpha^*$$

When we consider batches of experiments, at step $k$, for each of the $L$ experiments performed, we have all the information to evaluate the function (6) for each of the inputs $u^1_k, \ldots, u^L_k$, i.e.:

$$V(u^k_j) = \Phi(u_k^j, y_k^j) + \xi \sum_{i=1}^{l} \max\{C_i y_k^j - d_i, 0\}, \quad \forall j \in \{1, \ldots, L\}$$

In particular we are interested in the differences in the Lyapunov function with respect to the input $u_{k-1}$. In fact, the input $u_k$ – which will be used to determine the inputs for the next batch – will be chosen as the one among $u^1_k, \ldots, u^L_k$, that minimizes the difference in the Lyapunov function, i.e.:

$$u_k = \arg \min_{u_j^k \in \{u^1_k, \ldots, u^L_k\}} \{V(u^k_j) - V(u_{k-1})\}$$

The idea behind this approach is that at each step we choose the $\alpha_i \in \mathcal{A}$ that guarantees the largest decrease in the Lyapunov function. We will now formally prove that the algorithm will converge when the input is updated following the criterion (7). Before proceeding to formally stating the convergence result, we will make the following assumption on the set $\mathcal{A}$.

**Assumption 5.** Let the set of step-sizes $\mathcal{A} = \{\alpha_1, \ldots, \alpha_L\}$ be ordered (w.l.o.g.), i.e. $\alpha_1 \leq \alpha_2 \leq \cdots \leq \alpha_L$. We assume that it exists at least one index $i \in \{1, \ldots, L\}$ such that $\alpha_i < \alpha^*$ where $\alpha^*$ is the step-size below which convergence of the nominal feedback optimization algorithm is guaranteed in Theorem 1 [Häberle et al. 2021].

The above assumption essentially asks that at least one step-size in the set $\mathcal{A}$, is small enough.

**Theorem 2.** Let Assumptions 1, 2, 3, and 5 hold, as well as Assumption 4 for all $\alpha_i \in \mathcal{A}$. Let $\nabla \Phi$ and $\nabla h$ be globally Lipschitz on $\mathcal{U}$. Then

1. the trajectory of $u$, starting from any $u_0 \in \mathcal{U}$, obtained through the update rule
   
   $$u_k = u_{k-1} + \alpha_i \sigma(\alpha_i, u_{k-1}, y_{k-1})$$
   
   $$\alpha_k = \arg \min_{\alpha_i \in \mathcal{A}} \{V(u_{k-1} + \alpha_i \sigma(\alpha_i, u_{k-1}, y_{k-1})) - V(u_{k-1})\}$$
   
   where $\sigma(\alpha_i, u_{k-1}, y_{k-1})$ is obtained by solving (3) – (5) for $\alpha = \alpha_i$, $y_k = h(u_k)$ and $V$ is the Lyapunov function defined in (6), converges to the set of first-order optimality points of (1)
2. if $u^*$ is an asymptotically stable equilibrium of (8) with (3) – (5), then it is a strict local minimum of $\tilde{\Phi}(u) := \Phi(u, h(u))$, on $\tilde{\mathcal{U}}$.

**Proof.** The proof follows a classical Lasalle approach, and it is partially inspired from [Li et al. 2001, Theorem 1]. Let $u_k$ be the solution of (8), at step $k$, starting from $u_0 \in \mathcal{U}$. Because of Assumption 5, it holds:

$$\min_{\alpha_i \in \mathcal{A}} \{V(u_{k-1} + \alpha_i \sigma(\alpha_i, u_{k-1}, y_{k-1}) - V(u_{k-1})\} \leq 0$$

as we can always consider $\alpha_1 < \alpha^*$, by Assumption 5, for which the difference above is non-positive, hence $V$ is a non-increasing Lyapunov function for the map (8). Since $V$ is continuous on the compact set $\mathcal{U}$, it is bounded from below, implying that $\lim_{k \to \infty} V(u_k) = w$. Moreover, the positive limit set $L^+$ of the solution $u_k$ belongs to $\mathcal{U}$, as this is a compact set and, by standard arguments (see e.g. Khalil [2002]), it follows that $V(u) = w$, $\forall u \in L^+$. From the above steps, and the fact that $u_k \in \mathcal{U}$, $\forall k$ and
that \( U \) is compact, it follows that \( u_k \) converges, as \( k \to \infty \), to the largest invariant set contained in:
\[
E = \bigcup_{i=1}^{L} \{ u \mid V(u) = V(u + \alpha_i \sigma(\alpha_i, u, h(u))) \}
\]

By the above steps we know that the Lyapunov function is constant in the positive limit set \( L^+ \) of \( u \), under the update law (8). This fact, together with the fact that \( L^+ \) is invariant under the control law (8), implies that \( \forall u \in L^+ \) there exists \( j \in \{1, \ldots, L\} \) such that:
\[
0 = V(u + \alpha_j \sigma(\alpha_j, u, y)) - V(u)
\leq V(u + \alpha_i \sigma(\alpha_i, u, y)) - V(u), \forall i \in \{1, \ldots, L\}
\]

In particular, because of Assumption 5, it holds that:
\[
V(u + \alpha_1 \sigma(\alpha_1, u, y)) = V(u)
\]
meaning that, for any \( u \) in the positive limit set \( L^+ \), we can always choose \( \alpha_1 < \alpha^* \) in the update rule (8). The proof of Theorem 1, from H"aberle et al. [2021], can be followed from here to conclude the result.

**Remark 1.** Even if we proved convergence of the feedback optimization algorithm, under the heuristics described by the update (8), we remark that this is a heuristic in terms of convergence speed improvement. At present we cannot formally prove it to be optimal in this sense.

**Remark 2.** The described method requires to choose the set \( \mathcal{A} \) of step-sizes such that at least one \( \alpha_i \) is smaller than the \( \alpha^* \) mentioned above, and determine the value \( \xi \) in (6). These two elements are difficult to be formally determined, and a simple rule of thumb would be to have a small \( \alpha_i \) in the set \( \mathcal{A} \) and to choose a relatively large value of \( \xi \).

**Remark 3.** Theorem 2 requires some assumptions which should be studied. Given the polyhedral structure of the feasibility set, following from Assumption 1, Assumptions 2 and 3 are fairly general, with the first one usually holding in practice and the second one necessary to define a consistent optimization problem. On the other hand it is not easy to verify if Assumption 4 is satisfied for all \( \alpha_i \in \mathcal{A} \) and can therefore be restrictive. We are aware of this limitation, which was also remarked in H"aberle et al. [2021], and we aim to determine sufficient conditions for its satisfaction in future works, especially in the bioprocessing context that we are introducing in the next section. However, as also discussed in H"aberle et al. [2021], this assumption is fairly common in the study of this kind of optimization problems, and it is known to hold generically for a large class of perturbed optimization problems [Springarn and Rockafellar 1979]. Regarding the Lipschitzness assumption, on \( U \), of \( \nabla \Phi \) and \( \nabla h \), we note that this is not too restrictive given the compact nature of the set \( U \) and the fact that both \( \Phi \) and \( h \) are continuously differentiable functions.

**Remark 4.** Given the speed concern in the considered context, we remark that the computational overhead in solving (3)–(5) is negligible, compared to the process timescale, as this is a standard QP problem for which efficient solvers are available.

### 4. METABOLIC NETWORK EXAMPLE

To show the validity of the approach we will consider in this section a simple metabolic network consisting of two substrates \( S_1 \) and \( S_2 \), and two products \( P_1 \) and \( P_2 \). These metabolites are connected through the two reactions:
\[
R_1 : S_1 + 2S_2 \xrightarrow{\text{v}_1} P_1, \quad R_2 : S_2 \xrightarrow{\text{v}_2} P_2
\]

which happen, respectively, at rates \( v_1 \) and \( v_2 \).

Despite the simplicity of the considered example, the approach can be easily adapted to larger scale networks, through appropriate macroscopic modelling techniques [Provost and Bastin 2004, Oddsdóttir et al. 2015]. We assume the rates \( v_1 \) and \( v_2 \) to be a function of the metabolites concentrations. By denoting with \([M]\) the concentration of metabolite \( M \) we consider:
\[
v_1([S], [P]) = \theta_1 \frac{[S_1]}{([S]_1 + \theta_2) \cdot (1 + [S]_3 \theta_4)} \cdot \frac{1}{(1 + [P]_7 \theta_5)}
\]
\[
v_2([S], [P]) = \theta_2 \frac{[S_2]}{([S]_2 + \theta_3) \cdot (1 + [S]_6 \theta_4)} \cdot \frac{1}{(1 + [P]_1 \theta_6)}
\]

where \( \theta = [1, 1, 0.5, 1, 2, 1, 0.75, 6, 1, 2, 0.25] \) (11)

We consider here a continuous perfusion bioprocessing setup, in which substrates are continuously fed to the metabolic system, while at the same time metabolites are continuously removed, typically at the same rate as the medium is fed. We denote by \([S_1]^n\) and \([S_2]^n\) the concentrations of the substrates in the feed medium.

This leads to the following dynamical evolution:
\[
[S_1] = -v_1([S], [P]) \cdot X(t) - F[S_1] + F[S_2]^n,
\]
\[
[S_2] = (-2v_1([S], [P]) - v_2([S], [P])) \cdot X(t) - F[S_2] + F[S_2]^n,
\]
\[
[P_1] = v_1([S], [P]) \cdot X(t) - F[P_1],
\]
\[
[P_2] = v_2([S], [P]) \cdot X(t) - F[P_2],
\]

where \( F \) denotes the flow rate of the system and \( X(t) \) denotes the amount of viable cells at time \( t \). By assuming that the amount of viable cells converges to the value \( b \) and by defining \( x = [S_1] [S_2] [P_1] [P_2] \) and \([S_2]^n = [S_1]^n [S_2]^n]^T \) we can describe the system at steady state with the following mass-balance equation:
\[
bAv(x) - F_1 x + F_2 [S_2]^n = 0
\]
with \( v(x) = [v_1(x) v_2(x)]^T \), \( A \) being the adequate stoichiometric matrix, while \( F_1 = F \cdot I^4 \) and \( F_2 = F \cdot [I^2 0^T]^T \).

Our goal is to optimize the medium concentrations \([S_2]^n\) such that the yield of product \( P_1 \) is maximized, while at the same time trying to minimize the yield of product \( P_2 \), which can e.g. be considered as a toxic byproduct. We do this by minimizing the following objective function:
\[
\Phi([P_1], [P_2]) = -\lambda \cdot [P_1] + (1 - \lambda) \cdot [P_2]
\]
where \( \lambda \in [0, 1] \) is a weight defining the importance of maximizing \( P_1 \) with respect to minimizing \( P_2 \). We apply the feedback optimization scheme, described by (8), (3)–(5) by considering:
\[
y = x, \quad u = [S_2]^n, \quad \Phi(u, y) = -\lambda y_3 + (1 - \lambda) y_4,
\]
\[
G(u) = [I^2 \nabla h(u)]^T [I^2 \nabla h(u)]^T
\]
where the sensitivity \( \nabla h(u) \) of the input-output map \( y = h(u) \) is obtained by applying the implicit function theorem to Eq. (12), which brings to:
\[
\nabla h(u) = -(bAV_y(y) - F_1)^{-1} |_{y=h(u)} F_2
\]
where the output \( y \) in the above expression is available through measurement. The particular structure of the implicit metric \( G(u) \) has been presented in Haberle [2020].

We consider \( \lambda = 0.75 \) in the objective function and the following constraints to be satisfied:
\[
[0.5, 0.5] \leq u \leq [3, 3], \quad [S_2] = y_2 \leq 1, \quad y \geq 0
\]
We remark that adding the last non-negativity constraints explicitly to the optimization problem is not necessary, as these will be naturally enforced by the physical system. We assume that for each iteration a batch of \( L = 4 \) experiments can be run, and we will consider the Lyapunov-based heuristics described in Section 3, with the following set of step-sizes \( \mathcal{A} = \{0.1, 5, 10, 25\} \). We consider \( \xi = 50 \) in the Lyapunov function (6). In Figure 1 we show the evolution of the optimized inputs, and corresponding product concentrations, when the Lyapunov based heuristic is applied. The best step-size \( \alpha_i \), chosen at each iteration, is shown as well. We remark that, the input described by (8), and depicted for this example in Figure 1, is a virtual one. In practice, in our example, 4 different units are running with different inputs at each iteration, as described in Section 3. In the case of identical units, a simple consequence of Theorem 2 is that the inputs for all the different units will converge to the same one. This is shown in Figure 2. In Figure 3 the objective function evolution is shown, with the black curve showing the case where the Lyapunov based heuristic is applied, while the colored curves represent the cases where a sequential approach is considered, with the single step-sizes in \( \mathcal{A} \) being used. It is clear how step-sizes that are too small will lead to a slow convergence, while too large step-sizes will lead to instability. The Lyapunov based heuristic exploits the choice among different step-sizes to improve convergence speed without sacrificing stability properties.

4.1 The case of non-identical units

So far we considered the noise-free case with identical units, which we understand to be unrealistic in a bioprocessing context. Feedback optimization uses measurements to correct for incomplete knowledge of the system, hence a certain degree of robustness is expected. To show this point in simulation we considered the previous system, with a 5% noise on measurements. We consider the parameters \( \theta \) in Eq. (11), to be the nominal (and known) ones. However we assume, for each unit, a different set of real parameters, obtained by perturbing the original vector \( \theta \) in a 5% range, at the same time considering an additional, originally unmodelled, contribution to the kinetic (see appendix for more details). We assume, for the feedback optimization, to have only a nominal knowledge of the system. Figure 4 shows in solid lines the evolution of the objective functions, for the 4 units, when feedback optimization with the described heuristic is applied. The thick dashed lines represent the real optimal values of the objective function for the four different units, while the thin dashed lines represent the suboptimal objective functions obtained by applying the nominal optimal input. It is clear, in particular for units 1 and 2, that feedback optimization can drive the inputs to the real optimal values. The oscillating behaviour for unit 4 is due to the fact that this unit always uses the highest step-size in the set \( \mathcal{A} \) at each iteration, which suggest it might be better to use smaller step-sizes in the uncertain context.

The convergence to the real optimal values of the objective function is due to the fact that measurements are used by the optimization algorithm, both in the \( \alpha \) selection of the Lyapunov based heuristic and in the evaluation of the sensitivity \( \nabla h \) through the implicit function theorem. This example does not constitute a formal proof of the approach validity in the presence of noise and non-identical units, but it shows its potential, motivating further researches.

5. CONCLUSIONS AND FURTHER DEVELOPMENTS

In this work we considered a feedback-based optimization framework, in which the steady-state input-output map is unknown and input and output constraints are included, and we gave a heuristic to speed up convergence when experiments are executed in batches. To show the potential applicability of the method, we discussed a bioprocessing example, with the goal of optimizing the products’ concentration profile, in a bioreactor operating in continuous perfusion mode by optimizing the feed-flow medium composition. The high complexity of these systems, together with the difficulties of defining an accurate model, inspire the use of a feedback scheme in which output measurements are directly used and a degree of robustness can be expected. The convergence speed is crucial here, as to every iteration of the optimization algorithm is associated a time-consuming experiment to be performed in the lab, often with a duration of weeks.

Further developments of this work should consider explicitly the effects that an imperfect knowledge of the sensitivity map can have on convergence properties and the overall algorithm’s performance. It is well known how plant-model mismatch is a critical issue in real-time optimization, with necessary adjustments to be made, either by estimating the real plant sensitivity [François et al. 2012] or by modifying the optimization problem appropriately [Marchetti et al. 2016]. From the simulations we showed it seems that the proposed approach guarantees a certain degree of robustness, which should be further investigated. Finally the approach described in Section 4 should be experimentally validated.

6. APPENDIX - EXAMPLE NUMERICAL DETAILS

Viable cells density at steady-state \( b = 3.2 \) and flow rate \( F = 0.25 \). Reaction rates for unit \( k \) in the case of non-identical units:

\[
\begin{align*}
\nu_1^k([S],[P]) &= \frac{\theta_1^k \cdot [S]}{([S] + \theta_1^k)(1 + [S] \theta_1^k)} \cdot \frac{[S]_2}{([S]_2 + \theta_2^k)(1 + [S]_2 \theta_2^k)} \\
&\quad \cdot \frac{[P]_1}{([P]_1 + \eta_1^k(1 + [P] \eta_1^k)} \cdot \frac{[S]_2}{([S]_2 + \theta_2^k)(1 + [S]_2 \theta_2^k)} \\
\nu_2^k([S],[P]) &= \frac{\theta_2^k \cdot [S]}{([S]_1 + \theta_2^k)(1 + [S]_1 \theta_2^k)} \cdot \frac{[S]_2}{([S]_2 + \theta_2^k)(1 + [S]_2 \theta_2^k)} \\
&\quad \cdot \frac{[P]_1}{([P]_1 + \eta_1^k(1 + [P] \eta_1^k)} \cdot \frac{[P]_2}{([P]_2 + \eta_2^k(1 + \theta_2^k \eta_2^k)} \
\end{align*}
\]

where the parameter vector \( \theta^k \) is obtained by perturbing randomly, in a 5% range, the elements of the parameter vector \( \theta \), differently for each unit \( k \), while the parameters \( \eta^k_j \) are randomly generated uniformly in the range \([0, 0.1]\).

REFERENCES


Fig. 1. Evolution of feedflow substrates concentrations, products yield and step sizes chosen at each iteration.

Fig. 2. Input evolution for the four identical units.

Fig. 3. Evolution of the objective function with the Lyapunov based heuristic (black) and with a sequential approach using different step-sizes.

Fig. 4. Objective function evolution with four non-identical units. Feedback optimization with a Lyapunov based heuristic can converge to the real optima (thick dashed lines) with respect to the suboptimal nominal ones (thin dashed lines).

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