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About frame estimation of growth functions and robust prediction in bioprocess modeling

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Abstract

We address the problem of determining functional framing of experimental data points in view of robust time-varying predictions, which is of crucial importance in bioprocess monitoring. We propose a method that provides guaranteed functional bounds, instead of sets of parameters values for growth functions such as the classical Monod or Haldane functions commonly used in bioprocess modeling. We illustrate the applicability of the method with bioreactor simulations in batch and continuous mode. We also present two extensions of the method adding flexibility in its application, and discuss its efficiency in providing guaranteed state estimations.

1 Introduction and motivations

Interval analysis has recently gained a lot of popularity for the robust estimation of state variables in dynamical models. Bioprocesses are typically subject to various kind of variations or disturbances which are not always easy to model [3, 9]. The idea to determine or compute bounds for uncertain systems is not new [37, 23, 49], but a recent renewed focus has been brought to estimate with intervals state variables or parameters from real-time observations, despite uncertainties on the dynamics [17, 18, 40, 21, 46]. In situations for which the usual random representations (based on probability measures, Gaussian processes, white noise...) are not appropriate or cannot be justified for modeling the perturbations, interval observers give a simple and attractive alternative [13]. Instead of (non-robust) single-valued observers or stochastic filters which both provide single estimates expected to represent average values (provided that hypotheses on the randomness are satisfied), interval observers give a set of plausible trajectories and/or parameters [13, 28, 33, 8, 52]. Typically, for a given deterministic model

$$\frac{dX}{dt} = F(t, X), \quad X \in \mathbb{R}^n, \quad (1)$$

where some terms of the map F are badly known or subject to fluctuations, and an observation vector

$$Y(t) = G(t, X(t)) \in \mathbb{R}^p \quad (2)$$

that is assumed to be available at any time t , the interval approach consists in designing two estimators, a “lower” and a “upper” ones, of the form

$$\frac{dX^-}{dt} = F^-(t, X^-, Y(t)), \quad \frac{dX^+}{dt} = F^+(t, X^+, Y(t)), \quad (3)$$

when the dynamics F is monotone [51, 22], or in a coupled form

$$\frac{dX^-}{dt} = F^-(t, X^-, X^+, Y(t)), \quad \frac{dX^+}{dt} = F^+(t, X^-, X^+, Y(t)) \quad (4)$$

when F is non monotone (applying Muller’s Theorem, see [37, 53, 28]). In this formulation, X^- , X^+ are vectors in \mathbb{R}^n which provide a guaranteed framing of the solutions $X(\cdot)$ of (1) in the following sense

$$\begin{aligned} & \{X_i^-(0) \leq X_i(0) \leq X_i^+(0), (i = 1 \dots n)\} \\ & \implies \{X_i^-(t) \leq X_i(t) \leq X_i^+(t), (i = 1 \dots n)\}, \quad t > 0 \end{aligned} \quad (5)$$

This approach is well suited to “slow” processes or dynamics with long transients, such as bioprocesses, because it guarantees bounds during the transients. It has been successfully applied to several models of bioprocesses [13, 5, 15, 42, 31, 41, 27, 10, 24, 6]. A possible drawback of this approach is that it could provide quite conservative bounds that could be then uninformative for practitioners. However, in recent years, much progress has been made to improve the width of the guaranteed intervals, playing with different structures of the systems [39, 26, 14, 55] (there exist also several results for the class of linear dynamics), changes of coordinates [44, 8], considerations of bundles of observers [4, 32] or with the help of purely numerical methods [20, 21, 40, 41, 28] based on interval analysis [35, 18].

In mass balance models for bioprocesses [3, 7], the most critical uncertainty is primarily found on the specific growth functions of the micro-organisms, often denoted by $\mu(\cdot)$. Consider for instance the classical chemostat model [16]

$$\frac{dX}{dt} = F(t, X) := \begin{bmatrix} \mu(t, X)X_1 - D(t)X_1 \\ -\frac{1}{r}\mu(t, X)X_1 + D(t)(X_2^{in} - X_2) \end{bmatrix} \quad (6)$$

where X_1 , X_2 denote the concentrations of biomass and substrate, respectively. The dilution rate $D(\cdot)$, the input substrate concentration X_2^{in} and the yield factor r , are supposed to be known. Several contributions among the ones cited previously have considered that the effective growth functions $\mu(\cdot)$ depends on time and on the substrate concentration $s = X_2$ in an unknown manner, but are bounded by two “extreme” functions $\mu^-(\cdot)$, $\mu^+(\cdot)$ so that the inequalities

$$\mu^-(s) \leq \mu(t, s) \leq \mu^+(s), \quad s \geq 0 \quad (7)$$

are fulfilled at time t , whatever could be the values of the variable s . Robust state estimations can then be derived from the knowledge of $\mu^-(\cdot)$ and $\mu^+(\cdot)$

(instead of $\mu(\cdot)$), designing the maps F^- , F^+ in (3)-(4), as illustrated in [43, 1, 42]. However, one may wonder how to obtain these functional bounds from experimental data. Let us underline that it is particularly relevant to make a good choice of the functions μ^- , μ^+ as it impacts on the width of the frame (5). Take as an example the class of Monod growth functions

$$\mu(s) = \frac{\mu_{max}s}{s + K_s} \quad (8)$$

for which uncertainty is typically on the parameters μ_{max} and K_s . In the context of state or parameter estimation, several studies have focused on developing techniques to improve the computational efficiency when fitting models to measurement data, assuming arbitrary but bounded error distribution [54, 36, 19, 30, 38, 25]. Central of these approaches is overcoming convergence to local optima and inferring joint confidence intervals or regions [54, 12, 38]. It consists then in obtaining either parameter intervals $[\mu_{max}^-, \mu_{max}^+]$, $[K_s^-, K_s^+]$ in \mathbb{R}_+ or a region of $\mathbb{R}_+ \times \mathbb{R}_+$. Differently from these techniques of guaranteed parameters estimations, the approach we propose here revolves around a functional framing. In fact, it is no longer a matter of looking for a set of parameters, but rather ensuring that there would exist functions $\mu(\cdot)$ (depending on time in an unknown way) that guarantee that experimental data can be generated by a functional frame. This amounts to look for functional intervals $[\mu^-(\cdot), \mu^+(\cdot)]$ within a given class of functions. Although we shall consider classes of functions described by parameters, such as μ_{max} and K_s for the Monod functions, we shall simply look for two functions $\mu^-(\cdot)$, $\mu^+(\cdot)$ belonging to this class. Each of them will be characterized by a parameters pair (μ_{max}^-, K_s^-) , (μ_{max}^+, K_s^+) , but this does not mean that we shall consider that the unknown $\mu(\cdot)$ is a Monod function with unknown parameters (μ_{max}, K_s) belonging to a particular subset. We rather state that the unknown growth function is *any* function $\mu(\cdot)$ verifying the condition (7). In particular $\mu(\cdot)$ is not necessarily a Monod function. Moreover, let us underline that the parameters are not necessarily such that $\mu_{max}^+ > \mu_{max}^-$, $K_s^+ > K_s^-$ to obtain inequalities (7) for a given interval of plausible values of s . To our knowledge, the question of determining functional intervals from experimental data in this way has not been yet addressed in the literature. Functional bounds rather than a parameters set appear to be well suited to the method of interval estimators in the context of bioprocesses.

The purpose of the present work is to propose a generic method to fit two models (an “upper” and a “lower” one) that wrap data within lower and upper functions $\mu^-(\cdot)$ and $\mu^+(\cdot)$ instead of a single average $\mu(\cdot)$. To avoid too conservative bounds, we also introduce some flexibility in the application of the method for choosing the framing quality, either considering different upper and lower classes of growth functions, or forcing to have tightened bounds across the data sets, or both. We illustrate our framing method on synthetic data generated by random Monod [34] or Haldane [2] growth functions, this later one including the effect of substrate inhibition. Then, we compute time-varying predictions through numerical simulations of batch and continuous operating mode, providing bounded state estimations. As recalled previously, we mainly target situations for which the usual statistical hypotheses (reproducibility, uniform distribution of samples, unbiased noise...) are not necessarily met to justify the usual identification methods (least-squares, coefficient of determination, confidence intervals, maximum likelihood... see for instance [11, 50]). The approach

we propose is purely geometrical and does not rely on any statistical property, even though there are some similitude with least-square methods in the choice of the fitting criterion.

The paper is organized as follows. In Section 2, we present the method in a general framework and its theoretical justification (Propositions 1 and 2). In Section 3, we provide two extensions of the method while we show its application to growth curves in Section 4. Then, in Section 5, we report numerical data and simulations for two kinds of bioprocesses (batch and continuous) before we come to a conclusion and some perspectives.

2 Presentation of the method

We describe here the method in a general setting of an unknown scalar function $f : x \mapsto y = f(x)$, to be bounded by two functions f^- , f^+ , given a set of n experimental measurements

$$\mathcal{S} := \{(x_i, y_i)\}_{i \in 1 \dots n}.$$

We consider a class \mathcal{C} of functions (also denoted by f for convenience) parameterized by a vector of parameters $p \in P$, where P is a subset of \mathbb{R}^m :

$$\mathcal{C} := \bigcup_{p \in P} \{f(\cdot, p) : \mathbb{R} \mapsto \mathbb{R}\} \quad (9)$$

and require the following regularity conditions.

Assumption 1. *The set P is a compact subset of \mathbb{R}^m . The map f is continuous with respect to (x, p) in $\mathbb{R} \times P$.*

Most of the time, the set P of parameters is simply a cartesian product of intervals.

A *frame* of \mathcal{S} by functions in \mathcal{C} is determined by a pair $(p^-, p^+) \in P^2$ that satisfies the constraints

$$f(x_i, p^-) \leq y_i \leq f(x_i, p^+), \quad i = 1 \dots n. \quad (10)$$

One may look for the tightest frames, considering a *measure* of the frames as

$$D(p^-, p^+) := \sum_{i=1}^n (f(x_i, p^+) - f(x_i, p^-))^2 \quad (11)$$

and the optimization problem

$$\min\{D(p^-, p^+); (p^-, p^+) \in P^2 \text{ satisfying (10)}\}. \quad (12)$$

This is a nonlinear optimization problem with $2n$ nonlinear constraints. Such problems are classically addressed considering $2n$ Karush-Kuhn-Tucker multipliers $\lambda_i^- \geq 0$, $\lambda_i^+ \geq 0$ ($i = 1 \dots n$) and the objective function

$$D(p^-, p^+) + \sum_{i=1}^n \lambda_i^- (f(x_i, p^-) - y_i) + \sum_{i=1}^n \lambda_i^+ (y_i - f(x_i, p^+))$$

(see for instance [48]). Let us underline that n is large in many experimental contexts. The determination of $2n$ multipliers could be then computationally heavy. We propose here another approach.

For each $p \in P$, we define the non-negative functions

$$L(p) = \sum_{i=1}^n \min(y_i - f(x_i, p), 0)^2, \quad U(p) = \sum_{i=1}^n \max(y_i - f(x_i, p), 0)^2. \quad (13)$$

Note that $L(p) = 0$ amounts to say that the graph of the function $f(\cdot, p)$ is below \mathcal{S} . Similarly $U(p) = 0$ amounts to say that the graph of the function $f(\cdot, p)$ is above \mathcal{S} . For a pair (p^-, p^+) , the sum $L(p^-) + U(p^+)$ measures the quality of the framing of the set \mathcal{S} by the graphs of the functions $f(\cdot, p^-)$ and $f(\cdot, p^+)$, in the following sense. If a pair (p^-, p^+) satisfies

$$L(p^-) + U(p^+) \leq \epsilon^2 \quad (14)$$

with $\epsilon \geq 0$, then one has

$$f(x_i, p^-) - \epsilon \leq y_i \leq f(x_i, p^+) + \epsilon, \quad i = 1 \cdots n. \quad (15)$$

For $\epsilon = 0$, the constraint (10) is satisfied and we shall say that the frame is exact. For $\epsilon > 0$, we shall say that the frame is ϵ -approximate. In practice, one may be satisfied by an ϵ -approximate frame, providing that ϵ is small enough. For a given $\epsilon > 0$, one looks for the best ϵ -approximate frames minimizing the function D , given by pairs $(p^{*-}, p^{*+}) \in P^2$ such that $D(p^{*-}, p^{*+}) = D_\epsilon^*$ where

$$D_\epsilon^* := \min\{D(p^-, p^+); (p^-, p^+) \in P^2; L(p^-) + U(p^+) \leq \epsilon^2\}. \quad (16)$$

This is again a non-linear constrained optimization problem, that can be addressed with a penalty method, or with Karush-Kuhn-Tucker multipliers [48] (for this nonlinear constraint, one may have also to deal with constraints qualification even when the set P is described by a set of independent inequality constraints). Due to the particular structure of the problem, we propose another approach considering a multiplicative parameter of the cost and not of the constraint, as it is usually made. This brings some properties, as described in next Lemma 1 and Proposition 1, one which our method relies. For a given positive number γ , we then consider the criterion

$$J(p^-, p^+, \gamma) := L(p^-) + U(p^+) + \gamma D(p^-, p^+) \quad (17)$$

and associate the optimization problem

$$(\mathcal{P}_\gamma) : \quad J^*(\gamma) := \min\{J(p^-, p^+, \gamma); (p^-, p^+) \in P^2\}. \quad (18)$$

Note that \mathcal{P}_γ is an unconstrained problem, simpler to solve than problem (16), and we shall consider it for different values of $\gamma > 0$. As the function J is continuous w.r.t. (p^-, p^+) and P is a compact set, the minimum in $J^*(\gamma)$ exists for any γ .

We consider now assumptions guaranteeing the existence of non trivial frames of the data by functions in \mathcal{C} . First, we assume that the class \mathcal{C} is rich enough to wrap all the data.

Assumption 2. *There exists $(p^-, p^+) \in P^2$ such that (15) is fulfilled for $\epsilon = 0$.*

We shall consider cases for which all the data do not belong exactly to the graph of single function in \mathcal{C} (otherwise the classical least-square method would do the job, providing best pairs with $p^{*-} = p^{*+}$).

Assumption 3. *There does not exist $p \in P$ such that one has $y_i = f(x_i, p)$ for any $i \in \{1, \dots, n\}$.*

Let us first show that the optimization problem (18) generalizes the classical least-square method in the following way. Denote the classical least-square criterion by

$$J_{LS}(p) := \sum_{i=1}^n (y_i - f(x_i, p))^2$$

and define the number

$$J_{LS}^* := \min\{J_{LS}(p) ; p \in P\}.$$

Lemma 1. *Under Assumptions (1)-(2)-(3), one has*

$$\lim_{\gamma \rightarrow +\infty} J^*(\gamma) = J_{LS}^* . \quad (19)$$

Proof. Notice that $\gamma \mapsto J^*(\gamma)$ is non decreasing, as the family of functions $(J(\cdot, \cdot, \gamma))$ is non-decreasing w.r.t. γ , and is bounded from above by J_{LQ}^* . Therefore the limit of $J^*(\gamma)$ when γ tends to $+\infty$ exists.

Consider a sequence of optimal pairs (p_n^{*-}, p_n^{*+}) for $\gamma = n$. As P is compact, the sequence converges when $n \rightarrow +\infty$, up to a sub-sequence, to a certain $(p_\infty^{*-}, p_\infty^{*+}) \in P^2$ such that $J(p_\infty^{*-}, p_\infty^{*+}, \infty) = \lim_{\gamma \rightarrow +\infty} J^*(\gamma)$. This implies that one has necessarily $D(p_\infty^{*-}, p_\infty^{*+}) = 0$, that is $f(x_i, p_\infty^{*-}) = f(x_i, p_\infty^{*+})$ for any $i = 1 \dots n$. Consequently, one has $J(p_\infty^{*-}, p_\infty^{*+}, \infty) \geq J_{LS}^*$ and we obtain that equality (19) is verified. \square

Remark 1. *It may happen that the data set \mathcal{S} is too poor or that the class \mathcal{C} is over-parameterized. We shall say that \mathcal{S} is rich enough for \mathcal{C} when the following property is fulfilled.*

$$\{f(x_i, p_a) = f(x_i, p_b); i = 1 \dots n\} \Rightarrow p_a = p_b . \quad (20)$$

Under this last condition, any converging sequence of optimal pairs (p_n^{-}, p_n^{*+}) for γ_n satisfies $p_\infty^{*-} = p_\infty^{*+}$, i.e. the optimal frames converge when $\gamma \rightarrow +\infty$ to single curves, solutions of the least-square optimization.*

We give now properties on which the method we propose to obtain functional framing is based.

Proposition 1. *Under Assumptions 1-2-3, consider for any $\epsilon > 0$ the set*

$$\Gamma_\epsilon := \{\gamma \geq 0 ; Q_\epsilon \neq \emptyset\} \quad (21)$$

where

$$Q_\epsilon(\gamma) := \{(p^-, p^+) \in P^2 ; J^*(\gamma) = J(p^-, p^+, \gamma), L(p^-) + U(p^+) \leq \epsilon^2\} . \quad (22)$$

Then, the following properties are satisfied for any $\epsilon > 0$.

1. Γ_ϵ is a closed interval $[0, \gamma_\epsilon^*]$ with $0 < \gamma_\epsilon^* < +\infty$.

2. For any pair (p^{*-}, p^{*+}) in $Q_\epsilon(\gamma_\epsilon^*)$, one has

$$D(p^{*-}, p^{*+}) \leq D(p^-, p^+), \forall (p^-, p^+) \in Q_\epsilon(\gamma), \forall \gamma < \gamma_\epsilon^*.$$

3. For any pair (p^{*-}, p^{*+}) in $Q_\epsilon(\gamma_\epsilon^*)$, one has the estimate

$$D(p^{*-}, p^{*+}) - D_\epsilon^* \leq \frac{\epsilon^2 - L(p^{*-}) - U(p^{*+})}{\gamma_\epsilon^*}. \quad (23)$$

Moreover, if there exists a unique pair (p^{*-}, p^{*+}) realizing the minimum of $J(p^-, p^+, \gamma)$ among (p^-, p^+) in P^2 , then one has necessarily $D(p^{*-}, p^{*+}) = D_\epsilon^*$ with $L(p^{*-}) + U(p^{*+}) = \epsilon^2$.

Proof. Let γ_1, γ_2 be two positive numbers with $\gamma_1 < \gamma_2$. Consider pairs (p_1^-, p_1^+) , (p_2^-, p_2^+) such that $J^*(\gamma_1) = J(p_1^-, p_1^+, \gamma_1)$ and $J^*(\gamma_2) = J(p_2^-, p_2^+, \gamma_2)$. One can write

$$\begin{aligned} J^*(\gamma_2) = J(p_2^-, p_2^+, \gamma_2) &\leq J(p_1^-, p_1^+, \gamma_2) \\ &= J^*(\gamma_1) + (\gamma_2 - \gamma_1)D(p_1^-, p_1^+) \\ &\leq J(p_2^-, p_2^+, \gamma_1) + (\gamma_2 - \gamma_1)D(p_1^-, p_1^+) \end{aligned}$$

from which one obtains

$$J(p_2^-, p_2^+, \gamma_2) - J(p_2^-, p_2^+, \gamma_1) \leq (\gamma_2 - \gamma_1)D(p_1^-, p_1^+)$$

or equivalently

$$(\gamma_2 - \gamma_1)D(p_2^-, p_2^+) \leq (\gamma_2 - \gamma_1)D(p_1^-, p_1^+).$$

This shows the following property

$$\left. \begin{array}{l} \gamma_1 < \gamma_2 \\ J^*(\gamma_1) = J(p_1^-, p_1^+, \gamma_1) \\ J^*(\gamma_2) = J(p_2^-, p_2^+, \gamma_2) \end{array} \right\} \Rightarrow D(p_1^-, p_1^+) \geq D(p_2^-, p_2^+) \quad (24)$$

that shall be useful in the following.

For convenience, let us define the sub-sets

$$Q_\epsilon := \{(p^-, p^+) \in P^2; L(p^-) + U(p^+) \leq \epsilon^2\}.$$

Thanks to Assumptions 1 and 2, Q_ϵ is a non-empty compact set for any non-negative ϵ (including 0). Then the numbers

$$D_\epsilon^* := \min\{D(p^-, p^+); (p^-, p^+) \in Q_\epsilon\}$$

are well defined. Moreover, by Assumption 3, D_ϵ^* is positive for any $\epsilon \geq 0$.

1. We begin by showing that for any $\epsilon > 0$, the set Γ_ϵ contains at least one positive element. For any $\epsilon > 0$, consider $\gamma = \epsilon^2/D_0^*$ and $(p_0^-, p_0^+) \in Q_0$ (i.e. such that $D(p_0^-, p_0^+) = D_0^*$). One has

$$J^*(\gamma) \leq J(p_0^-, p_0^+, \gamma) = \gamma D_0^* = \epsilon^2$$

and any pair (p^-, p^+) realizing $J^*(\gamma)$ verifies then

$$L(p^-) + U(p^+) + \gamma D(p^-, p^+) \leq \epsilon \quad \Rightarrow \quad L(p^-) + U(p^+) \leq \epsilon^2$$

that is $(p^-, p^+) \in Q_\epsilon(\gamma)$, from which we deduce that γ belongs to Γ_ϵ .

We show now that Γ_ϵ is an interval containing 0. Let $\gamma > 0$ belonging to Γ_ϵ and (p^-, p^+) a pair realizing $J^*(\gamma)$ with $L(p^-) + U(p^+) \leq \epsilon^2$. Take $\gamma' \in [0, \gamma]$ and let (p'^-, p'^+) be a pair realizing $J^*(\gamma')$. One can write

$$\begin{aligned} J^*(\gamma') = L(p'^-) + U(p'^+) + \gamma' D(p'^-, p'^+) &\leq L(p^-) + U(p^+) + \gamma' D(p^-, p^+) \\ &\leq \epsilon^2 + \gamma' D(p^-, p^+) \end{aligned}$$

or equivalently

$$L(p'^-) + U(p'^+) \leq \epsilon^2 + \gamma'(D(p^-, p^+) - D(p'^-, p'^+)).$$

From property (24), we have $D(p^-, p^+) \leq D(p'^-, p'^+)$, which demonstrates that the pair (p'^-, p'^+) belongs to $Q_\epsilon(\gamma')$, that is γ' belongs to Γ_ϵ .

Now we show that the upper bound $\gamma_\epsilon^* = \sup \Gamma_\epsilon$ belongs to Γ_ϵ . Let γ_n be an increasing sequence converging to γ_ϵ^* and (p_n^-, p_n^+) a sequence of pairs in Q_ϵ realizing $J^*(\gamma_n)$. For any $(p^-, p^+) \in P^2$, one has

$$J(p_n^-, p_n^+, \gamma_n) \leq J(p^-, p^+, \gamma_n), \quad \forall n.$$

As Q_ϵ is a compact set, there exists a sub-sequence, also noted (p_n^-, p_n^+) , which converges to a certain (p^{*-}, p^{*+}) in Q_ϵ . By continuity of the function J , one obtains that the inequality

$$J(p^{*-}, p^{*+}, \gamma_\epsilon^*) \leq J(p^-, p^+, \gamma_\epsilon^*)$$

is fulfilled for any $(p^-, p^+) \in P^2$, which shows that the pair (p^{*-}, p^{*+}) realizes $J(\gamma_\epsilon^*)$, and thus γ_ϵ^* belongs to Γ_ϵ . This proves the point 1.

2. The point 2. is a direct consequence of the property (24).

3. Consider a pair $(p_\epsilon^-, p_\epsilon^+)$ in P^2 such that $D(p_\epsilon^-, p_\epsilon^+) = D_\epsilon^*$. One has then

$$J^*(\gamma_\epsilon^*) \leq J(p_\epsilon^-, p_\epsilon^+, \gamma_\epsilon^*) = \epsilon^2 + \gamma_\epsilon^* D_\epsilon^*$$

Therefore, any pair (p^{*-}, p^{*+}) in $Q_\epsilon(\gamma_\epsilon^*)$ verifies

$$L(p^{*-}) + U(p^{*+}) + \gamma_\epsilon^* D(p^{*-}, p^{*+}) \leq \epsilon^2 + \gamma_\epsilon^* D_\epsilon^*$$

or equivalently the inequality (23).

Take a decreasing sequence γ_n converging to γ_ϵ^* , and pairs (p_n^-, p_n^+) in P^2 such that $J^*(\gamma_n) = J(p_n^-, p_n^+, \gamma_n)$ for any n . One has necessarily $L(p_n^-) + U(p_n^+) > \epsilon$ and can write

$$J^*(\gamma_n) = L(p_n^-) + U(p_n^+) + \gamma_n D(p_n^-, p_n^+) \leq J(p_\epsilon^-, p_\epsilon^+, \gamma_n) \leq \epsilon^2 + \gamma_n D_\epsilon^*$$

or equivalently

$$\gamma_n (D(p_n^-, p_n^+) - D_\epsilon^*) \leq \epsilon^2 - (L(p_n^-) + U(p_n^+)) < 0.$$

Therefore, one has $D(p_n^-, p_n^+) < D_\epsilon^*$ for any n . Consider a sub-sequence of (p_n^-, p_n^+) converging to a certain (p^{*-}, p^{*+}) . It necessarily satisfies $L(p^{*-}) + U(p^{*-}) \geq \epsilon^2$ and $D(p^{*-}, p^{*+}) \leq D_\epsilon^*$ by continuity of the functions L , U and D . As previously, one can show that (p^{*-}, p^{*+}) is a maximizer of $J^*(\gamma_\epsilon^*)$. As we know that there exists a maximizer of $J^*(\gamma_\epsilon^*)$ in Q_ϵ , we deduce that when the maximizer of $J^*(\gamma_\epsilon^*)$ is unique, it has to verify $L(p^{*-}) + U(p^{*-}) = \epsilon^2$ and by property (23), it has also to realize $D(p^{*-}, p^{*+}) = D_\epsilon^*$. \square

The properties of the set Γ_ϵ given in Proposition (1) leads to the following method for the search of tight ϵ -approximate frames.

Proposition 2. *Consider that Assumptions 1-2-3 are fulfilled. Take $\epsilon > 0$ such that $\epsilon < \frac{J_{LS}^*}{\sqrt{nM}}$, where $M := \max_{i=1 \dots n} \max_{p \in P} |y_i - f(p, x_i)|$, and define the number*

$$\bar{\gamma}_\epsilon = \frac{1}{2} \frac{J_{LS}^*}{J_{LS}^* - \sqrt{nM}\epsilon} \quad (25)$$

Then the procedure

Algorithm 1 Estimation of γ_ϵ^*

Require: $n > 1$

- 1: $\gamma^- \leftarrow 0, \gamma^+ \leftarrow \bar{\gamma}_\epsilon$
 - 2: **for** $k = 1 \dots n$ **do**
 - 3: $\gamma \leftarrow \frac{\gamma^- + \gamma^+}{2}$
 - 4: let p^-, p^+ be such that $J(p^-, p^+, \gamma) = J^*(\gamma)$
 - 5: **if** $L(p^-) + U(p^+) > \epsilon$ **then**
 - 6: $\gamma^+ \leftarrow \gamma$
 - 7: **else**
 - 8: $\gamma^- \leftarrow \gamma$
 - 9: **end if**
 - 10: **end for**
 - 11: **return** γ^-, γ^+
-

provides an estimation of $\gamma_\epsilon^* \in [\gamma^-, \gamma^+]$ with $\gamma^+ - \gamma^- < 2^{-n}\bar{\gamma}_\epsilon$.

Proof. Let us show that $\bar{\gamma}_\epsilon$ is an upper bound of the number γ_ϵ^* given by Proposition (1). Remark first that having $p^- = p^+ = p$ gives $J(p, p, \gamma) = J_{LS}(p)$ whatever is γ . Let \tilde{p} be a solution of the least-square fitting, that is \tilde{p} satisfying $J_{LS}(\tilde{p}) = J_{LS}^*$. As \mathcal{S} does not belong to the graph of a single function in \mathcal{C} (Assumption 3), one has $J_{LS}^* > 0$. Let $\gamma \in \Gamma_\epsilon$ and $(p^-, p^+) \in Q_\epsilon(\gamma)$. One can write

$$\begin{aligned} J_{LS}^* = J(\tilde{p}, \tilde{p}, \gamma) &\geq J^*(\gamma) = J(p^-, p^+, \gamma) \\ &\geq \gamma D(p^-, p^+) \\ &= \gamma \sum_{i=1}^n \left((f(x_i, p^+) - y_i) + (y_i - f(x_i, p^-)) \right)^2 \\ &= \gamma \sum_{i=1}^n (y_i - f(x_i, p^+))^2 + (y_i - f(x_i, p^-))^2 \\ &\quad + 2(f(x_i, p^+) - y_i)(y_i - f(x_i, p^-)) \end{aligned}$$

and thus

$$\begin{aligned}
J_{LS}^* &\geq \gamma(J_{LS}(p^-) + J_{LS}(p^+)) \\
&\quad + 2\gamma \sum_{i=1}^n (f(x_i, p^+) - y_i) (y_i - f(x_i, p^-)) \\
&\geq 2\gamma \left(J_{LS}^* + \sum_{i=1}^n (f(x_i, p^+) - y_i) (y_i - f(x_i, p^-)) \right).
\end{aligned}$$

In this last summation, consider the subset I of indices i for which

$$(f(x_i, p^+) - y_i) (y_i - f(x_i, p^-)) < 0.$$

For $i \in I$, let $\eta_i = \max(y_i - f(x_i, p^+), 0) + \max(f(x_i, p^-) - y_i, 0)$ and one has then

$$(f(x_i, p^+) - y_i) (y_i - f(x_i, p^-)) > -M\eta_i$$

where the numbers η_i satisfy $\sum_{i \in I} \eta_i^2 \leq \epsilon^2$. One obtains then the lower bound

$$\sum_{i=1}^n (f(x_i, p^+) - y_i) (y_i - f(x_i, p^-)) \geq -M \sum_{i \in I} \eta_i \geq -M\sqrt{n}\epsilon$$

from which one deduces that the number γ has to satisfy the inequality

$$J_{LS}^* \geq 2\gamma(J_{LS}^* - \sqrt{n}M\epsilon)$$

or equivalently $\gamma \leq \bar{\gamma}_\epsilon$.

Finally, due to the property of Γ_ϵ being an interval $[0, \gamma_\epsilon^*]$ (cf Proposition 1), the dichotomous algorithm 1 converges to γ_ϵ^* with a guaranteed lower bound at any iteration step. □

Our method consists then in an iteration of the unconstrained problem \mathcal{P}_γ for different positive values of γ to obtain an approximation of γ_ϵ^* , accordingly to Proposition 2. Note that Proposition 1 guarantees the positivity of γ_ϵ^* only when ϵ is positive. Our method is thus fundamentally based on ϵ -approximate frames (for $\epsilon = 0$, one may have $\gamma_0^* = 0$ and all frames realize $J^*(0) = 0$). In practice, for a small positive value of ϵ , the algorithm starts with an upper bound $\bar{\gamma}_\epsilon$ close to $1/2$ and a few iterations are enough to obtain an accurate approximation of the value of γ_ϵ^* for a reasonably small value of ϵ . For this approximate value of γ_ϵ^* , one then gets from the optimization problem $\mathcal{P}_{\gamma_\epsilon^*}$ a maximizer (p^{*-}, p^{*+}) . If $L(p^{*-}) + U(p^{*+}) = \epsilon^2$, then the frame is optimal (i.e. $D(p^{*-}, p^{*+}) = D_\epsilon^*$), accordingly to Proposition 1. If the optimal solution of $\mathcal{P}_{\gamma_\epsilon^*}$ is not unique, one may have $L(p^{*-}) + U(p^{*+}) < \epsilon^2$ but expression (23) of Proposition 1 gives then an estimation of its sub-optimality. Note that the method is robust with respect to the performances of the optimization technique used to solve the problem \mathcal{P}_γ or the choice of the number of iterations in the algorithm. If it provides a sub-optimal solution (for the value of $D(\cdot)$), it always generate an ϵ -approximate frame. We shall see on concrete cases in Section 5 that this method turns out to be fast and efficient, with a simple implementation.

Remark 2. For any pair (p^-, p^+) in $Q_\epsilon(\gamma_\epsilon^*)$, we can also measure the width of the frame by the area delimited by the graphs of the functions $f(\cdot, p^+)$ and $f(\cdot, p^-)$:

$$A(p^-, p^+) := \int_{\min_i x_i}^{\max_i x_i} (f(x, p^+) - f(x, p^-)) dx. \quad (26)$$

This allows to associate to the class of functions \mathcal{C} an "adequacy" value

$$V_\epsilon(\mathcal{C}) := \min \{A(p^-, p^+) ; (p^-, p^+) \in Q_\epsilon(\gamma_\epsilon^*)\}$$

and to compare the adequacy of each class. For two classes $\mathcal{C}_1, \mathcal{C}_2$ of functions, we shall say that \mathcal{C}_1 gives a better ϵ -approximate framing of the set \mathcal{S} than the class \mathcal{C}_2 when one has $V_\epsilon(\mathcal{C}_1) < V_\epsilon(\mathcal{C}_2)$. This will be illustrated in Section 5.

3 Extensions of the method

The extensions we present here bring some additional flexibility to the method, in terms of choice of the class of functions and width of frames. For simplicity of the presentation, we have not incorporated them in the presentation of the overall method. Both extensions are illustrated in Section 5.

3.1 Framing with different upper and lower classes

There is no a priori reason to impose that upper and lower functions in the frame (10) are sought among the same class of functions. Therefore, we can consider without loss of generality two classes

$$\mathcal{C}^- := \bigcup_{p \in P^-} \{f^-(\cdot, p) : \mathbb{R} \mapsto \mathbb{R}\}, \quad \mathcal{C}^+ := \bigcup_{p \in P^+} \{f^+(\cdot, p) : \mathbb{R} \mapsto \mathbb{R}\}$$

instead of the single class \mathcal{C} considered in (9). Here, P^- and P^+ are two subsets of \mathbb{R}^{m^-} and \mathbb{R}^{m^+} , such that Assumption 1 is fulfilled for $P^-, f^-,$ and P^+, f^+ . The dimension m^- is not necessarily equal to m^+ . In Section 5, we shall see that this allows to consider less parameters altogether.

In short, we do not give here the corresponding assumptions and statement, as its simply consists in replacing $P \times P$ by $P^- \times P^+$ in Assumption 2 and Propositions 1, 2 of Section 2. We shall also consider that Assumption 3 is verified for both P^- and P^+ .

3.2 Relaxing with one or more points out of the frame

In practice, the frames provided by Proposition 1 might be too conservative as it considers all the experimental data. Practitioners might want to have tightened bounds, allowing to have one or several points unwrapped. They could of course choose themselves which point(s) to be withdrawn and relaunch the method on a smaller data set. We show here how to extend in a simple way the method to have this done in a systematic way, i.e. as an automatic method choosing which data point(s) can be forgotten to obtain tightened bounds, depending on the maximal number of points that one accepts to be unwrapped.

For each pair (p^-, p^+) in P^2 (or in $P^- \times P^+$), we define the sub-set of indices

$$O(p^-, p^+) = \{i \in \{1, \dots, n\}, y_i \notin [f(x_i, p^-), f(x_i, p^+)]\}.$$

As an extension of the optimization problem considered in Section 2, we consider the following family of problems

$$\gamma_j^* := \max \{ \gamma \geq 0, \exists (p^-, p^+) \in P^2 \text{ s.t. } J^*(\gamma) = J(p^-, p^+, \gamma), \#O(p^-, p^+) \leq j \}$$

for $j \in \{1, n-1\}$, where $\#O$ denotes the cardinality of a set 0.

Then, for each γ_j^* , there exists a pair (p_j^-, p_j^+) solution of the problem $\mathcal{P}_{\gamma_j^*}$, which provides a frame with at most j unwrapped points. However, notice that the optimization problem with $j > 0$ do not guarantee that the pair (p_j^-, p_j^+) provides the minimal value of $D(p^-, p^+)$ among the pairs that exclude exactly j points (differently to what is proved in Proposition 1 for the set $Q_\epsilon(\gamma_\epsilon^*)$). For this later problem, one has to consider a different criterion which consists in computing the functions L, U are D only for indices out of the subset $O(p^-, p^+)$. This last subset does depend on the pair (p^-, p^+) , which makes the computational optimization much heavier. Instead, we propose here a simpler relaxation approach which simply consists in replacing the condition on line 5 in Algorithm 1 of Proposition 2 by the test

$$\#O(p^-, p^+) > j.$$

The family (p_j^-, p_j^+) provides then a sensitivity of the framing with respect to the number of unwrapped points. This will be illustrated in Section 5.

4 Application to the framing of growth curves

The knowledge of the growth functions is very useful in microbiology to predict the evolution of micro-organisms and the performances of the bioprocesses, with models such as (6):

$$\begin{cases} \dot{x} &= \mu(s)x - Dx \\ \dot{s} &= -\frac{1}{r}\mu(s)x + D(s_{in} - s) \end{cases} \quad (27)$$

where x and s stand here for the biomass and substrate concentrations, respectively. Typically, experiments to determine the unknown growth function $\mu(\cdot)$ are drawn as follows.

- either in batch culture i.e. with $D = 0$. Experiments consist in choosing different values s_i of initial substrate concentration $s(0) = s_i$ and computing the value $\mu_i = \frac{d}{dt} \ln(x(t))|_{x=0}$, measuring the time variation of $x(\cdot)$. Data points (s_i, μ_i) are then expected to belong to the graph of the unknown function $\mu(\cdot)$.
- either in continuous culture i.e. with $D > 0$ (assumed to be constant or slowly varying). Experiments consist in choosing different values D_i of D and wait the system to be at a quasi-steady state (x^*, s^*) . Then, the data point $(s_i, \mu_i) = (s^*, D_i)$ is expected to belong to the graph of the unknown function $\mu(\cdot)$.

With the set of data points (s_i, μ_i) , one usually conducts a non-linear regression to adjust the parameters of a growth model with least-square criterion [47], such as for instance the Monod growth function (8), or the Haldane one

$$\mu(s) = \frac{\bar{\mu}s}{K + s + s^2/K_i}. \quad (28)$$

describing the effect of growth inhibition for large concentrations of substrate. However, it has been underlined that the usual R-squared determination coefficient is not appropriate to measure the quality of the adjustment in this non-linearity context [45]. More importantly, reproducibility and environmental fluctuations (such as pH, temperature, light...) from one experiment to another one are common issues in microbiology.

Here, we shall consider that the experiments have been sufficiently numerous to have faced the various possible kinds of fluctuations, so that future utilization of the micro-organisms might be subject to similar fluctuations or combinations of them occurring at various unknown times (his hypothesis is important to justify the framing approach, that we illustrate on synthetic data in the next section).

Let us now show how one can use the lower and upper functions $\mu^-(\cdot)$, $\mu^+(\cdot)$ to obtain guaranteed predictions of $x(\cdot)$ and $s(\cdot)$. Assume that yield coefficient r , dilution rate D (possibly time-varying) and initial condition (x_0, s_0) of model (27) are known. The, one can easily show that the variable $z(t) = x(t) + rs(t)$ is solution of $\dot{z} = D(rs_{in} - z)$. Therefore, one has

$$z(t) = rs_{in} + (x_0 + rs_0 - rs_{in})e^{-Dt}, \quad t \geq 0. \quad (29)$$

We distinguish now the predictions of $x(t)$ and $s(t)$.

1. Prediction of $x(t)$. From $s(t) = \frac{1}{r}(z(t) - x(t))$, one obtains that $x(\cdot)$ is solution of the (non-autonomous) scalar differential equation:

$$\dot{x} = \mu\left(\frac{1}{r}(z(t) - x)\right)x - Dx$$

Then, following [53, Th. VIII, p. 95], a frame $x^-(t) \leq x(t) \leq x^+(t)$ is obtained for any $t \geq 0$ when $x^-(\cdot)$, $x^+(\cdot)$ are solutions of

$$\begin{cases} \dot{x}^- = \mu^-\left(\frac{1}{r}(z(t) - x^-)\right)x^- - Dx^-, & x^-(0) = x_0 \\ \dot{x}^+ = \mu^+\left(\max\left(\frac{1}{r}(z(t) - x^+), 0\right)\right)x^+ - Dx^+, & x^+(0) = x_0 \end{cases} \quad (30)$$

2. Prediction of $s(t)$. Similarly, one has $x(t) = z(t) - rs(t)$ and $s(\cdot)$ solution of the scalar dynamics

$$\dot{s} = -\frac{1}{r}\mu(s)(z(t) - rs(t)) + D(s_{in} - s)$$

which gives a frame $s^-(t) \leq s(t) \leq s^+(t)$ where $s^-(\cdot)$, $s^+(\cdot)$ are solutions of

$$\begin{cases} \dot{s}^- = -\frac{1}{r}\mu^+(s^-)(z(t) - rs^-) + D(s_{in} - s^-), & s^-(0) = s_0 \\ \dot{s}^+ = -\frac{1}{r}\mu^-(s^+)\max(z(t) - rs^+, 0) + D(s_{in} - s^+), & s^+(0) = s_0 \end{cases} \quad (31)$$

Remark that uncertainties on the initial condition $(x_0, s_0) \in [x_0^-, x_0^+] \times [s_0^-, s_0^+]$ can be also incorporated in the framing, considering

$$z^-(t) = rs_{in} + (x_0^- + rs_0^- - rs_{in})e^{-Dt}, \quad z^+(t) = rs_{in} + (x_0^+ + rs_0^+ - rs_{in})e^{-Dt}$$

instead of $z(t)$ in systems (30)-(31) and initialization $x^-(0) = x_0^-$, $x^+(0) = x_0^+$, $s^-(0) = s_0^-$, $s^+(0) = s_0^+$.

5 Numerical illustrations

In the section we illustrate the framing method on synthetic data and its use for predictions as follows.

1. We generate a random set \mathcal{R} of parameters of the growth models Monod or Haldane, from which we generate a set \mathcal{S} of "synthetic" data points (s_i, μ_i) , corrupted by some noise. The set \mathcal{S} is considered to represent a plausible set of experimental data.
2. We apply our framing method to the data set \mathcal{S} for determining the best lower and upper functions $\mu^-(\cdot)$, $\mu^+(\cdot)$ for a given ϵ accuracy (cf Proposition 1), with ϵ small.
3. We use the functions $\mu^-(\cdot)$, $\mu^+(\cdot)$ to compute time varying intervals $[x^-(\cdot), x^+(\cdot)]$, $[s^-(\cdot), s^+(\cdot)]$ for the concentrations $x(\cdot)$, $s(\cdot)$, as solutions of equations (29)-(30)-(31).
4. We simulate the dynamical model (27) where the function $\mu(\cdot)$ changes randomly with time among functions (8) or (28) with parameters within \mathcal{R} , and compare the solution $x(\cdot)$, $s(\cdot)$ during the transients with the lower and upper estimates provided in the previous step.

We have also computed the average growth function and its corresponding trajectory to appreciate its position within the intervals. The optimization problem \mathcal{P}_γ has been solved numerically with the `fmincon` function of `Matlab` software. The algorithm of Proposition 2 has been performed for $\epsilon = 10^{-3}$, starting with an upper bound $\gamma^+ = 1/2$. Twenty iterations we more than enough to obtain a tight framing ($\epsilon = 10^{-6}$ with 40 iterations have tested and have given very similar results).

5.1 Example of a batch process

We have generated randomly ten growth curves (see Fig. 1, left) and one hundred data corrupted with noise (see Fig. 1-right).

We have wrapped all the data points among the class of Monod functions, using the method exposed in Section 2, which gives the functions μ^- , μ^+ whose graphs are depicted on Fig. 3-left. In addition, the graph of the growth curve $\bar{\mu}$ determined by the usual least-square method is plotted in dashed line. To show the convergence of the method, Fig. 2 depicts the frames obtained at each iteration of the algorithm given in Proposition 2. One can see that the frame obtained at the first iteration is close to the least-square solution (in accordance with Lemma 1), and the frames almost no longer change after only 12 iterations.

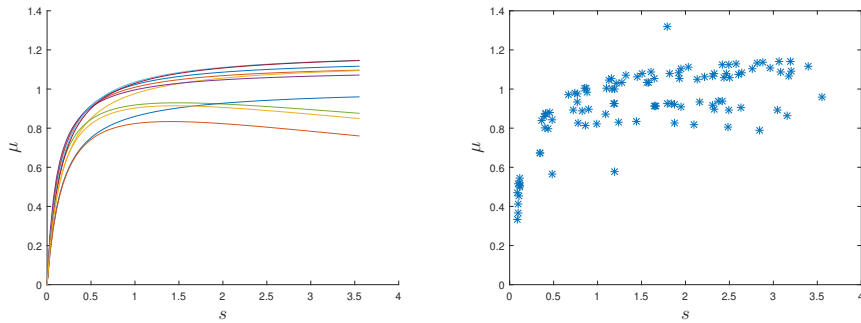


Figure 1: Growth curves randomly generated (left) and random data points (s_i, μ_i) corrupted with noise (right).

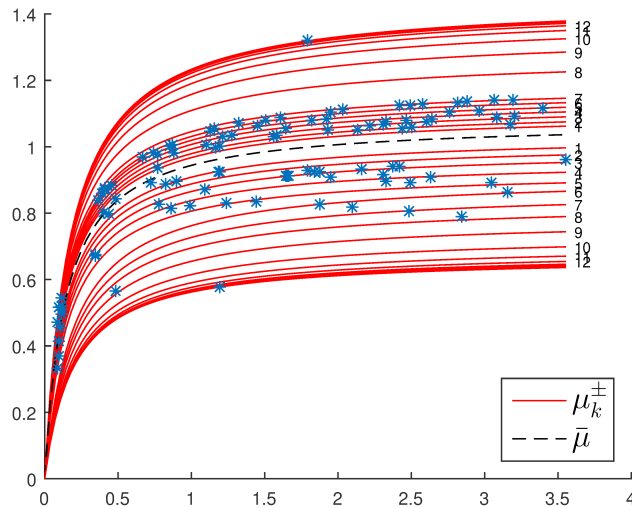


Figure 2: Convergence of the method. Functions μ_k^- , μ_k^+ are obtained with pairs (p_k^-, p_k^+) solutions of problem \mathcal{P}_{γ^+} at the k -th iteration of the algorithm (after 12 iterations, solutions are almost identical).

Indeed, we found that it is enough to stop the algorithm when the upper estimate γ^+ gives a solution (p^-, p^+) of problem \mathcal{P}_{γ^+} with $D(p^-, p^+)$ close to ϵ^2 .

We have then simulated a trajectory of the model (27) in batch mode (i.e. for $D = 0$) with a growth $\mu(\cdot)$ changing randomly with time, along with the solutions of the frame dynamics (30)-(31) (see Fig. 3-right). The value of the yield coefficient r has been kept equal to 0.1. One can notice that the trajectory provided by the average growth $\bar{\mu}$ (in dashed line) is not centered in the trajectories frame. This is due to the non-linearity of the dynamics. This shows the interest of the information provided by the guaranteed interval approach, differently to confidence intervals of the least-square method that are centered on the trajectory generated by the average growth.

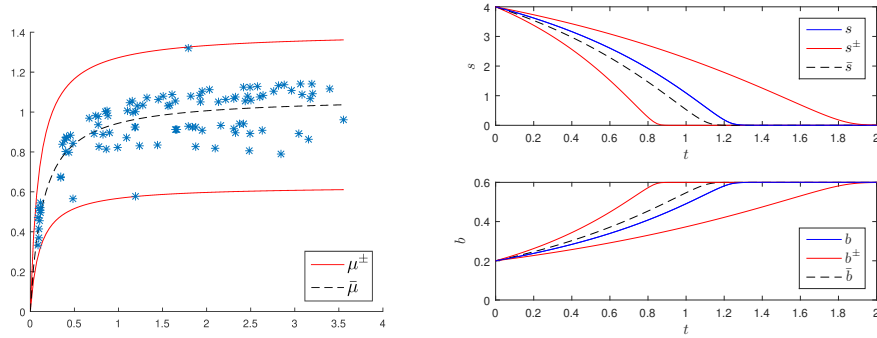


Figure 3: Wrapping of the data (left) and dynamical simulation (right).

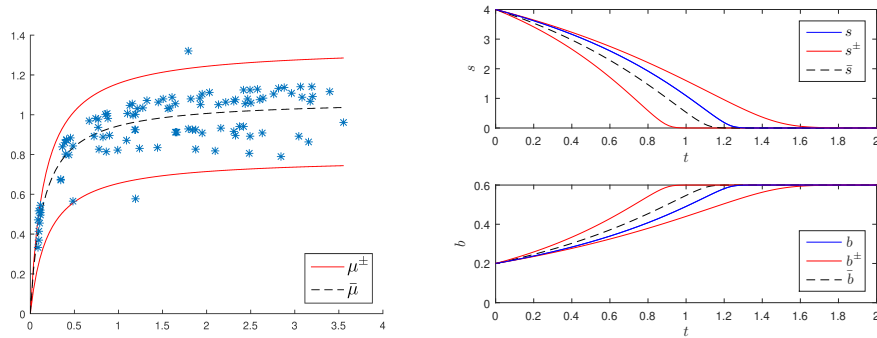


Figure 4: Data wrapping (left) and corresponding simulation (right) allowing two data points to be out of the frame.

One may want to relax the trajectories frame considering that some data points are most probably aberrant. As explained in Section 3, the extension of the method chooses which points to be withdrawn to obtain the growths frame (and this requires less iterations of the algorithm). The algorithm gave the same sequence of frames as depicted on Fig. 2 up to the ninth iteration, which provides a frame that excludes exactly two data points, as shown on Fig. 4-left. Therefore, 9 iterations was enough. On Fig 4-right one can appreciate the impacts on the trajectories frame, allowing only two data points to be unwrapped.

In batch process, the asymptotic value of the biomass x is known, equal to $x_\infty = x_0 + rs_0$ according to (29), but guaranteed intervals allow to estimate the time necessary to reach a given level of production $x_l < x_\infty$, which is of primer utility in industrial applications.

5.2 Example of a continuous process

We have generated another set of random growth curves and random data (see Fig. 5).

As previously, we have wrapped the data points in between the graphs of two functions μ^- , μ^+ among the class of Monod growth functions, depicted on

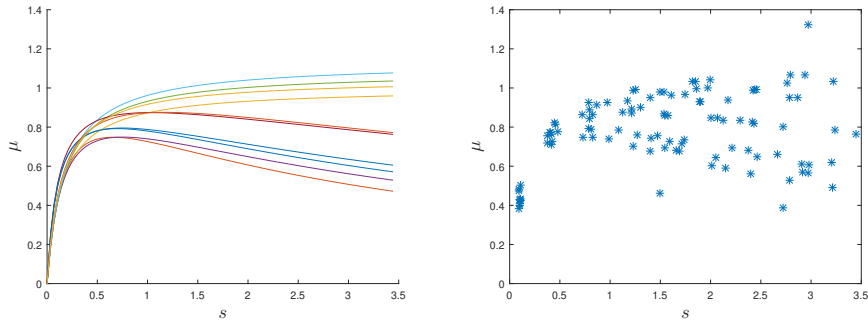


Figure 5: Growth curves randomly generated (left) and random data points (s_i, μ_i) corrupted with noise (right).

Fig. 6-left (the average growth determined by the least-square criterion is plotted in dashed line). We have then considered the model (27) in continuous mode for the input parameters $D = 0.7$ and $s_{in} = 4$ (with the same yield coefficient $r = 0.1$). Fig. 6-right shows a trajectory for a growth $\mu(\cdot)$ changing randomly, lying inside the guaranteed time-varying intervals computed with the functions μ^-, μ^+ .

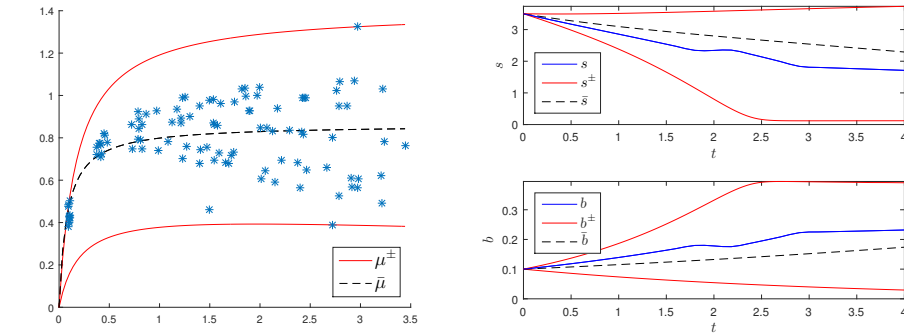


Figure 6: Wrapping with Monod growth functions (left) and associated dynamical simulation (right)

To illustrate the flexibility of the extensions of the method presented in Section 3, we have looked for the upper functions μ^- in the class of Haldane functions (28), allowing thus non monotonic growth curves (see Fig. 7). The area criterion (26) gives an improvement of the fitting (2.66 instead of 3.01). However, this does not impact too much the trajectories frame as this concerns only small values of s . In addition, we have relaxed the framing allowing at most three points to be unwrapped (see Fig. 8), which has then reduced significantly the trajectories frame. Here also, one can see that the interval method is relevant to obtain safe transients estimates, while the use of least-square method is more questionable in the context of unpredictable variations. Of course, better trajectories frames could be obtained over the time when on-line measurements are available, but this was the precise objective of the present work (this is the

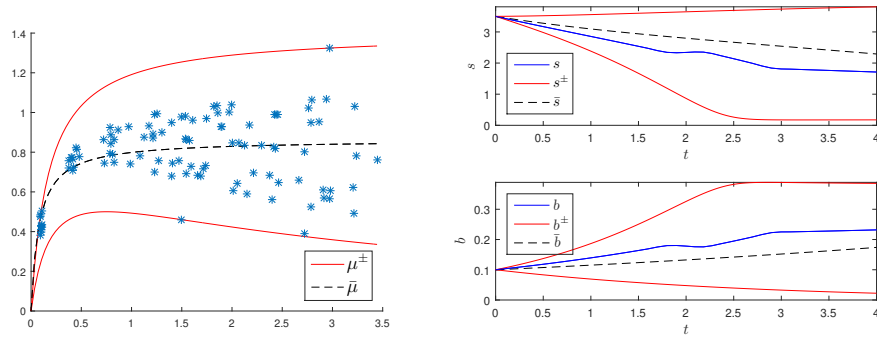


Figure 7: Wrapping with Monod and Haldane growth functions (left) and associated simulation (right)

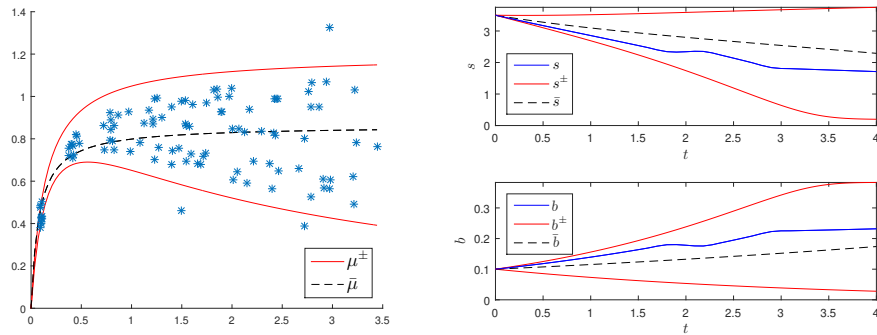


Figure 8: Data wrapping (left) and corresponding simulation (right) requiring three data points to be out of the frame.

matter of the so-called "interval observers" recalled in the introduction).

6 Conclusion and perspectives

We have proposed a geometrical method for the construction of functional frames from experimental data points and applied it to microbial growths, which are often the major source of variability in bioprocesses for robust predictions. Our approach consists in computing a sequence of simple unconstrained optimization problems, allowing flexibility in the choice of upper and lower classes of functions and the number of data points that could be unwrapped. Let us underline that it does not consist in determining a set (or intervals) of parameters values in a class of functions, but rather in wrapping the data in between the graphs of two functions without requiring any particular shape of the unknown growth function (that could moreover change with time). However, the growth functions may depend on other variables, such as biomass concentration in the Contois model, or could be multi-valued, such as in the Droop model where the nutrient uptake function $\rho(\cdot)$ has to be identified concomitantly to the growth

rate function $\mu(\cdot)$. Extensions of the method for these multi-valued contexts might be the matter of a future work.

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