Asociación Argentina
de Mecánica Computacional

Mecánica Computacional Vol XXXIII, págs. 2023-2036 (artículo completo)
Graciela Bertolino, Mariano Cantero, Mario Storti y Federico Teruel (Eds.)
San Carlos de Bariloche, 23-26 Setiembre 2014

"OPTIMAL DESIGN TECHNIQUES FOR PARAMETER ESTIMATION IN A BACTERIAL GROWTH MODEL

Diana Rubio[a], Nicolas Saintier[b] and María Inés Troparevsky[c]

[a]*Centro de Matemática Aplicada - ECyT, Universidad de Gral. San Martín, B.A., Argentina, drubio@unsam.edu.ar*

[b]*Instituto de Ciencias, Universidad Nacional de Gral. Sarmiento, B.A., Argentina, nsaintie@dm.uba.ar.*

[c] *Departamento de Matemática, Facultad de Ingeniería, Universidad de Buenos Aires, Argentina, Paseo Colón 850 CABA, mariainestro@gmail.com*

Keywords: Optimal design, Parameter estimation, Inverse problem, Sensitivity, Bacterial growth.

Abstract. Mathematical models are fundamental tools to analize and predict the behaviour of dynamical processes arising in different disciplines. To ensure a reliable numerically simulated data we need to choose a model that reflects the dynamics together with a suitable set of parameter values. In this work we focus on experimental design techniques for the parameter estimation of the Baranyi bacterial growth model. We present a new criterion for selecting data leading to an accurate estimation of parameters based on the incremental generalized sensitivity functions. We conduct several numerical experiments to compare the performance when data is uniformly distributed along time with classical *optimal design* methods and the new technique. For each data selection we perform the parameter estimation, calculate relative errors and compute confidence intervals. We show some typical results. The numerical experiments indicate that the new criterion can be used to obtain a good estimation with few measurements.

1 INTRODUCTION

In a series of recent works (Banks et al., 2007, 2010, 2011; Banks and Rehm, 2013b,a), several authors have developed a design framework based on the Fisher information matrix (FIM) for a system of differential equations to determine when and where an experimenter should take samples and what variables to measure in collecting information on a physical or biological process that is modeled by a vector dynamical system. This framework has also been proposed in inverse problem methodologies in the context of dynamical system or mathematical model parameter estimation when a sufficient number of observations of one or more states (variables) are available. Experimental designs using the FIM, based on sensitivity (traditional and generalized) matrices, are described in Banks et al. (2010) for the case of scalar data. In Banks et al. (2011), the authors develop an experimental design theory using the FIM to identify optimal sampling times for experiments on physical processes modeled by an ordinary differencial equation, in which scalar or vector data are taken. The methodology can be readily applied to problems involving ordinary, partial and delay differential equations but requires both a *mathematical model* and a *statistical model*. These ideas were successfully applied in Banks and Rehm (2013b) for an experimentally validated six-compartment HIV model and a thirty-eight dimensional enzyme kinetics model of the Calvin Cycle in spinach. In Banks et al. (2013a) and Banks et al. (2013b) numerical results for a distributed parameter system in a 3D one-layer spherical domain are presented.

The problem of modelling the growth of bacteries is of great interest in microbiology, in particular in relation with microorganisms in food (Buchanan, 1995; Skinner and Larkin, 1994; McMeekin et al., 1997). The logistic and Gompertz models and their variants have been frecuently used for this kind of problem (McMeekin et al., 1993; Peleg, 1997; Vadasz et al., 2001; Verhulst, 1838; Virene, 1968; Zwietering et al., 1990). Among the mathematical models introduced in the literature for bacterial growth problems we can mention Hutchinson model (Hutchinson, 1948), Gibson model (Gibson et al., 1987) and Baranyi's model (Baranyi et al., 1993; Baranyi and Roberts, 1995, 1994). The latter is a dynamical model that combines the logistic and the Michaelis-Menten's models and it approximates the time evolution of bacterial population with great precision (Baranyi et al., 1993). Moreover, it can be easily modified when environmental conditions vary over time (Baranyi et al., 1995). For this reason Baranyi model is widely used to describe this kind of processes (George et al., 1996; McClure et al., 1997).

In this paper we numerically study different data selection methods and their influence on the estimation of the Baranyi modeling parameters. We present a new criterion for collecting data based on the incremental generalized sensitivity functions. We conduct several numerical experiments considering data uniformly distributed along time and classical *optimal design* methods and the new sampling technique. For each data selection we perform the parameter estimation, calculate relative errors and compute confidence intervals. We show typical results and state some conclusions.

2 MATHEMATICAL ASPECTS

2.1 Baranyi bacterial growth model

A well known and widely used mathematical model of the bacterial population growth is the Baranyi model (see Baranyi et al. (1993)). It combines the logistic and the Michaelis-Menten models to obtain an equation for $y(t) = \ln(x(t))$, the logarithm of the cell concentration $x(t)$

(in CFU/ml) at time t, given by

$$y(t) = y_0 + \mu_{max}t + \frac{\ln(e^{-\nu t} + e^{-h_0} - e^{-\nu t - h_0})}{\mu_{max}} - \frac{1}{m}\ln\left(1 + \frac{e^{m\mu_{max}t + \ln(e^{-\nu t} + e^{-h_0} - e^{-\nu t - h_0})/\mu_{max}} - 1}{e^{m(y_{max} - y_0)}}\right), \quad (1)$$

where $y_{max} = \ln(t_{max})$ and $y_0 = \ln(t_0)$, being t_0 and t_{max} the initial and the asymptotic values of cell concentration, respectively; μ_{max} is the maximum specific growth rate, m and ν are the curvature parameters to characterize the transition from and to, respectively, the exponential phase; and h_0 is a dimensionless parameter that indicates the initial physiological state of the cells.

As suggested in Baranyi and Roberts (1995), m and ν are taking to be $\nu = \mu_{max}$ and $m = 1$. The number of modeling parameters is then reduced to four, μ_{max}, h_0, y_0 and y_{max}. Thus, the equation becomes

$$y(t) = y_0 + \mu_{max}t + g(t, h_0, \mu_{max}) - \ln\left(1 + \frac{e^{\mu_{max}t + g(t,h_0,\mu_{max})} - 1}{e^{y_{max} - y_0}}\right), \quad (2)$$

where $g(t, h_0, \mu_{max}) = \frac{\ln(e^{-\mu_{max}t} + e^{-h_0} - e^{-\mu_{max}t - h_0})}{\mu_{max}}$.

We denote by θ the vector of modeling parameters to be estimated in equation (2) , that is, $\theta = (\mu_{max}, h_0, y_0, y_{max}) \in \mathbb{R}^4$.

In Grijspeerdt and Vanrolleghem (1999), identifiably properties of the Baranyi model were investigated. The authors proved that the model is structurally identifiable, which means that noiseless data determine unique parameter values. They also proved that it has acceptable practical identifiably in the presence of realistic data. Using a D-optimal design criterion they showed that there are four optimal sampling regions that provide valuable information in order to perform the estimation.

2.2 Inverse problem formulation

We suppose that there exists a real-valued vector θ_0 such that the equation (2) exactly describes the process and consider the corresponding parameter estimation problem, which consists in estimating the unknown true parameter θ_0 from given data.

Since in real experiments the procedure to collect data contains uncertainty and error, a statistical model is neccesary to study and implement inverse problem techniques properly. Regarding the statistical model, we consider.

$$U(t, \theta_0) = y(t, \theta_0) + \mathcal{E}(t), \quad t \in [0, T],$$

where $\mathcal{E}$ is a vector random process that represents the observation error for the measured variables. The outputs of the system are realizations of this stochastic process and can be written as

$$u(t, \theta_0) = y(t, \theta_0) + \epsilon(t), \quad t \in [0, T].$$

We suppose that the additive noise $\epsilon_1, .., \epsilon_n$ are independent realizations of a centered normal random variable with variance σ^2. In this context the inverse problem consists in the estimation of the unknown parameter θ_0 from

$$u_j(\theta_0) := y(t_j, \theta_0) + \epsilon_j \quad , j = 1, .., n.$$

The parameter value θ_0 may be estimated by a least square (LS) procedure yielding to $\hat{\theta}$, that is,

$$\hat{\theta} = \arg\min_{\theta \in \mathcal{A}} J_\Lambda(\theta), \tag{3}$$

where $\mathcal{A}$ is the set of admissible parameter values, $\Lambda = \{t_1, .., t_n\}$ the set of observation times, and $J_\Lambda(\theta)$ denotes the sum of the square errors between the measured data and the simulated outputs at the observation points, namely

$$J_\Lambda(\theta) = \sum_{j=1}^{n} |y(t_j, \theta) - u_j(\theta_0)|^2. \tag{4}$$

We remark that $\hat{\theta}$ is a realization of a random variable $\hat{\Theta}$ that, under suitable hypothesis, $\hat{\Theta}$ has asymptotically normal distribution (see, for instance, Banks et al. (2014); Seber and Wild (2003))

$$\hat{\Theta} \sim N(\theta_0, (\sigma^2 F(t_1, ..., t_n, \theta_0))^{-1}), \tag{5}$$

where $F(t_1, ..., t_n, \theta) \in \mathbb{R}^{4\times 4}$ is the Fisher information matrix whose ij-th entries are defined by

$$F_{ij}(t_1, ..., t_n, \theta) = \sum_{k=1}^{n} \frac{\partial u}{\partial \theta_i}(t_k, \theta) \frac{\partial u}{\partial \theta_j}(t_k, \theta). \tag{6}$$

The partial derivatives $\dfrac{\partial u}{\partial \theta_j}(t_k, \theta)$ are the (traditional) sensitivity functions that, assuming smoothness on u, quantify the variations in u with respect to changes in the j-th component of θ. A precise discussion on the hypothesis and the approximations involved in the above statements is given in Banks et al. (2014). For the model we consider, the sensitivities of u with respect to θ_j, $j = 1, ..., p$, that we plot in Figure 1, can be easily computed from the equation (2).

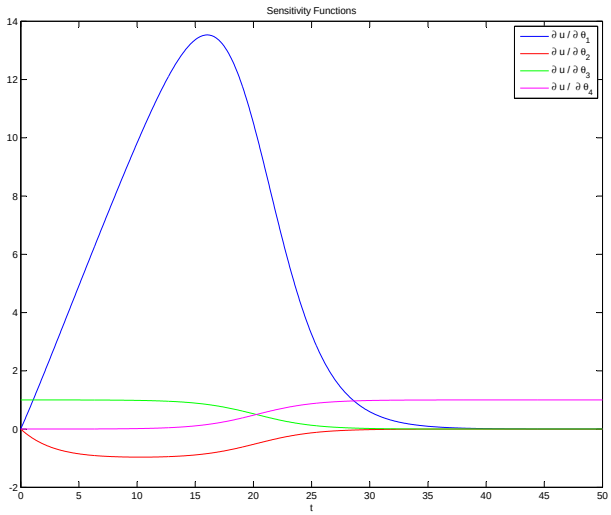

Figure 1: Sensitivity functions $\frac{\partial u}{\partial \theta_j}(t_k, \theta_0)$ for the Baranyi model.

Different choices of the instants $t_1, \ldots, t_n \in \Lambda$ might lead to different estimates. In consequence it is important to look for a set of observation points that will lead to accurate parameter

estimations. This is the purpose of the *optimal design* methods. In this work we choose the set $\Lambda = \{t_1, \ldots, t_n\}$ based on four different criteria: uniformly distributed in $[0, T]$, the D-optimal and SE-optimal designs and a new criterion based to the incremental generalized sensitivity functions (defined below).

2.2.1 Generalized and Incremental Generalized Sensitivity Functions

The GSF were introduced in Thomaseth and Cobelli (1999) to analyze the information content in a data set with respect to model parameters. It was meant to understand how the estimation of model parameters is related to observed system output. In that work, the authors introduce the GSF along with the incremental generalized sensitivity Functions (IGSF). Their definitions are related and both were introduced for a dynamical system as discrete functions defined on a finite set of observations at some time instants.

Definition 2.1 *(Thomaseth and Cobelli, 1999) Consider a nonlinear parametric dynamical system*

$$\dot{y}(t, \theta) \quad = \quad f(t, y, \theta) \tag{7}$$

where $\theta \in \mathbb{R}^p$, $y, f, \in \mathbb{R}^N$, together with a set of observations $u_1(\theta), .., u_n(\theta)$ of the form

$$u_j(\theta) = y(t_j, \theta) + e_j, \qquad j = 1, ..., n \tag{8}$$

where the $e_j, \in \mathbb{R}$ are realizations of i.i.d. random variables with fixed variance σ^2. The GSF at t_k, $k = 1, ..., n$, is the vector $gs(t_k) = (gs_1(t_k), .., gs_\ell(t_k), ..., gs_p(t_k)) \in \mathbb{R}^p$ given by

$$gs(t_k) = \quad \frac{1}{\sigma^2} \sum_{j=1}^{k} [F^{-1} \nabla_\theta u(t_j, \theta_0)] \odot \nabla_\theta u(t_j, \theta_0), \qquad k = 1, ..., n. \tag{9}$$

The vector of incremental generalized sensitivity functions (IGSF) at t_k, $k = 1, ..., n$, is defined by

$$igs(t_k) = \quad \frac{1}{\sigma^2} [F^{-1} \nabla_\theta u(t_k, \theta_0)] \odot \nabla_\theta u(t_k, \theta_0). \tag{10}$$

In these expressions F is the corresponding $p \times p$ Fisher information matrix, $F = F(t_1, ..., t_n, \theta)$, and the symbol "$\odot$" represents element-by-element vector multiplication.

We point out that ℓ-th component of $igs(t_k)$, is given by

$$igs_\ell(t_k) = \quad \frac{1}{\sigma^2} [F^{-1} \nabla_\theta u(t_k, \theta_0)]_\ell \, \frac{\partial u}{\partial \theta_\ell}(t_k, \theta_0) \tag{11}$$

and, for the sake of simplicity, we have omitted the dependence of the vector functions gs and igs on $t_1, ..., t_n$ and θ_0.

Note that the gs and igs are defined only at a set of discrete time points $t_1, ..., t_n$ at which measurements are taken. In the case of the GSF, the value for each t_k, $k = 1, ..., n$, involves all the contributions of those measurements up to and including t_k. On the other hand, the IGSF at t_k for a given parameter ℓ, i.e. $igs_\ell(t_k)$, measures the contribution provided by the information at the t_k-th observation over $t_1, \cdots, t_n$.

2.3 Optimal Design Techniques

In practical experiments it is important to avoid running the experiment many times to reduce costs and invasive procedures. Thus, it is useful to have some criteria to determine when or where the measurements should be taken. This is the goal of the optimal design techniques: to look for a set of observation points yielding to accurate estimates.

Different criteria give rise to different sets of observation instants. In general, optimal design methods choose a sampling distribution by minimizing a specific cost function.

In view of the asymptotic distribution given in (5)-(6) it is natural to select t_i that minimize a function of the Fisher matrix $F(t_1,..,t_n,\theta_0)$ (see Banks et al. (2007, 2010)). In this work we consider four sets of n points $\{t_1,\dots,t_n\}$ following different criteria:

- **Uniform**: Uniformly distributed points in $[0,T]$, i.e.

$$\Lambda_U := \{t_i^{unif} = (i-1)\frac{T}{n-1}, \quad i=1,\cdots,n\}.$$

- **D-optimal design**: The n points that minimize $\det\ F(t_1,...t_n,\theta)^{-1}$,

$$\Lambda_D := \{t_1^D,...t_n^D\} = \arg\max_{t_1,\cdots,t_n} \det\ F(t_1,\cdots,t_n,\theta)^{-1}.$$

  Geometrically, it corresponds to minimize the volume of the confidence ellipsoid for the covariance matrix $Cov = \sigma^2 F^{-1}$.

- **SE-optimal design**: The n points that minimize the standard errors

$$\Lambda_{SE} := \{t_1^{SE},...t_n^{SE}\} = \arg\max_{t_1,\cdots,t_n} = \sum_i (F(t_1,...t_n,\theta)^{-1})_{ii}.$$

- **IGS-Design**: We propose a design based on the highest values of each IGSF given in equation (11) and the sensitivity functions $\dfrac{\partial u}{\partial \theta_j}(t_k,\theta)$.

  For this problem, we select the n points as follows. First, we define a fine grid on $[0,T]$ as a domain for each IGSF. Then we take the $m=[n/4]$ highest values of each igs_ℓ, $\ell = 2,3,4$,

$$\{t_1^{IGS_2},\cdots,t_m^{IGS_2}\} = \arg\max_{t_1,\cdots,t_m} igs_2(t_1,\cdots,t_m),$$

$$\{t_1^{IGS_3},\cdots,t_m^{IGS_3}\} = \arg\max_{t_1,\cdots,t_m} igs_3(t_1,\cdots,t_m),$$

$$\{t_1^{IGS_4},\cdots,t_m^{IGS_4}\} = \arg\max_{t_1,\cdots,t_m} igs_4(t_1,\cdots,t_m).$$

  Finally, we choose the remaining $nm = n-3m$ based on igs_1,

$$\{t_1^{IGS_1},\cdots,t_{nm}^{IGS_1}\} = \arg\max_{t_1,\cdots,t_{nm}} igs_1(t_1,\cdots,t_{nm}).$$

  Therefore, the set becomes

$$\Lambda_{IGS} = \{t_1^{IGS_1},\cdots,t_{nm}^{IGS_1},t_1^{IGS_2},\cdots,t_m^{IGS_2},t_1^{IGS_3},\cdots,t_m^{IGS_3},t_1^{IGS_4},\cdots,t_m^{IGS_4}\}.$$

Note that $nm > m$, thus we take more data based igs_1, the IGSF for the first parameter, μ_{max}. This is due to the fact that the highest sensitivity corresponds to $\theta(1) = \mu_{max}$, as it can be seen in Figure 1.

For the sake of simplicity, from here on we refer to this set as

$$\Lambda_{IGS} = \{t_1^{IGS}, \cdots, t_n^{IGS}\}.$$

These sampling criteria lead to different sets Λ_U, Λ_D, Λ_{SE} and Λ_{IGS}, and, possibly, different estimates of θ_0, denoted by $\hat{\theta}_D$, $\hat{\theta}_{SE}$, $\hat{\theta}_U$ and $\hat{\theta}_{IGS}$, respectively.

Notice that, since θ_0 is unkown, we must use an initial guess θ_g to calculate the FIM, and hence, to calculate the sets of observation points as explained above. The same initial guess used for the calculation of FIM is be used to perform the LS minimization.

3 NUMERICAL EXPERIMENTS

The numerical results that we present in this section correspond to $\theta_0 = (0.4, 0.1, 2, 10)$ and $\theta_g = (0.5, 0.08, 1.5, 8)$.

In order to be able to compare the different estimations, we numerically simulate noisy data $u_j(\theta_0)$, $j = 1, \ldots, n$, in $[0, 50]$ and randomly generate the perturbations $e_j \in N(0, \sigma^2)$ where $\sigma \in \{0.5, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35\}$. Figure 2 show the simulated Baranyi curve as a function of time for $e_j \in N(0, 0.3^2)$.

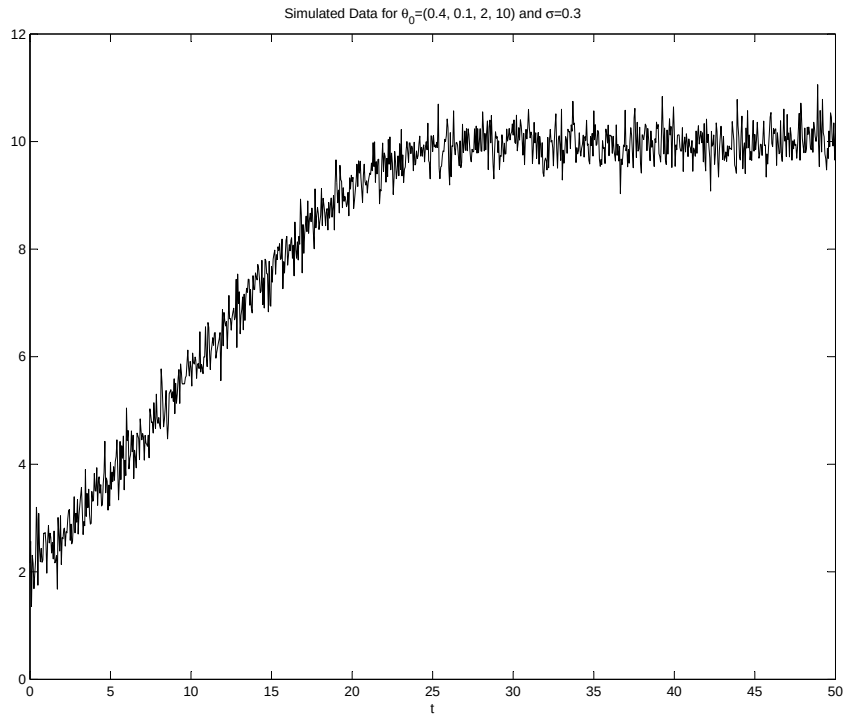

Figure 2: Simulated Baranyi Data for $\theta_0 = (0.4, 0.1, 2, 10)$ and $\sigma = 0.3$.

We calculate four data sets Λ_U, Λ_D, Λ_{SE} and Λ_{IGS} as described in the previous section, for $n = 5, \cdots, 12$. Then, for each data set, we estimate the vector parameter $\theta = (\mu_{max}, h_0, y_0, y_{max})$

for the Baranyi model given by the equation (2). The estimations are obtained by minimizing the sum of the square errors,

$$J_\Lambda(\theta) = \sum_{j=1}^{n} |y(t_j, \theta) - u_j(\theta_0)|^2,$$

where initially $\theta = \theta_g$. A vector parameter estimation is obtained for each data set $y(t_j, \theta)$, $j = 1, \ldots, n$.

We repeat these procedures K times by generating a new set of perturbations $\epsilon_1, \ldots, \epsilon_n$ each time. Then we average the results to obtain estimates $\hat{\theta}_{unif}$, $\hat{\theta}_D$, $\hat{\theta}_{SE}$, $\hat{\theta}_{IGS}$.

For instance, for $n = 5$, $\sigma = 0.35$ and $K = 10$ we obtain

$$\begin{aligned}
\hat{\theta}_{unif} &= (0.4775,\ 2.9923,\ 2.0830,\ 10.0773)\\
\hat{\theta}_D &= (0.4175,\ 0.1817,\ 1.8440,\ 10.0888)\\
\hat{\theta}_{SE} &= (0.3770,\ 0.1232,\ 1.8311,\ 10.0782)\\
\hat{\theta}_{IGS} &= (0.3845,\ 0.0284,\ 1.8363,\ 10.1094)
\end{aligned}$$

as estimates for $\theta_0 = (0.4, 0.1, 2, 10)$. Figure 3 show the bacterial growth populations simulated by using these results. The same color code is used in all figures presented here: blue for uniform, red for D-optimal, green for IGS and magenta for SE-optimal.

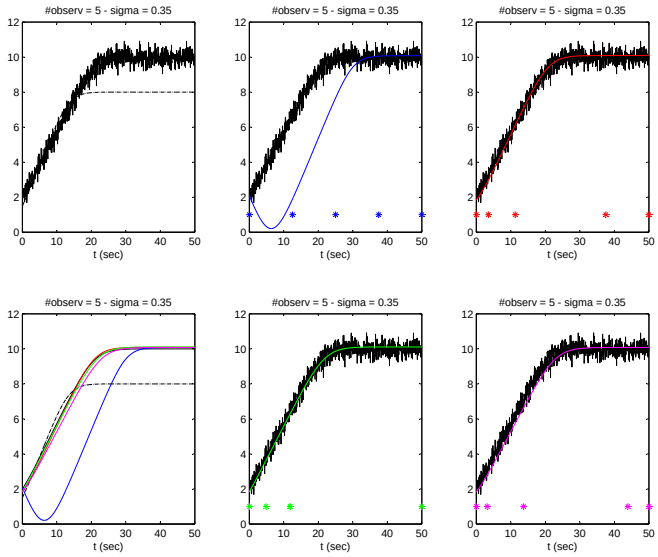

Figure 3: Simulated curves with the different parameter values. Solid black: $\theta = \theta_0$ and $\sigma = 0.35$. Dashed black: $\theta = \theta_g$, Blue: $\theta = \hat{\theta}_{unif}$, Red: $\theta = \hat{\theta}_D$, Green: $\theta = \hat{\theta}_{IGS}$, Magenta: $\theta = \hat{\theta}_{SE}$. The colored stars show the corresponding time instant in Λ_U, Λ_D, Λ_{IGS} and Λ_{SE}.

We compute the relative errors e^j_{unif}, e^j_D, e^j_{SE}, e^j_{IGS}, $j = 1, .., K$ for the modeling parameters μ_{max}, h_0, y_0, y_{max}:

$$e^j_{design}(\mu_{max}) := \frac{\|\hat{\theta}^j_{design}(1) - \theta_0(1)\|}{\|\theta_0(1)\|}, \qquad e^j_{design}(h_0) := \frac{\|\hat{\theta}^j_{design}(2) - \theta_0(2)\|}{\|\theta_0(2)\|},$$

$$e^j_{design}(y_0) := \frac{\|\hat{\theta}^j_{design}(3) - \theta_0(3)\|}{\|\theta_0(3)\|}, \qquad e^j_{design}(y_{max}) := \frac{\|\hat{\theta}^j_{design}(4) - \theta_0(4)\|}{\|\theta_0(4)\|},$$

and we average them

$$\bar{e}_{design}(\theta(\ell)) = \frac{1}{K}\sum_{j=1}^{K} e^j_{design}(\theta(\ell)), \quad \ell = 1, \cdots, 4. \tag{12}$$

Figures 4, 5, 6, 7 show the mean relative errors when $K = 10$ for $n = 5, \ldots, 12$ and $\sigma = 0.1, 0.15, 0.2, 0.25, 0.3, 0.35$ for the different sampling designs.

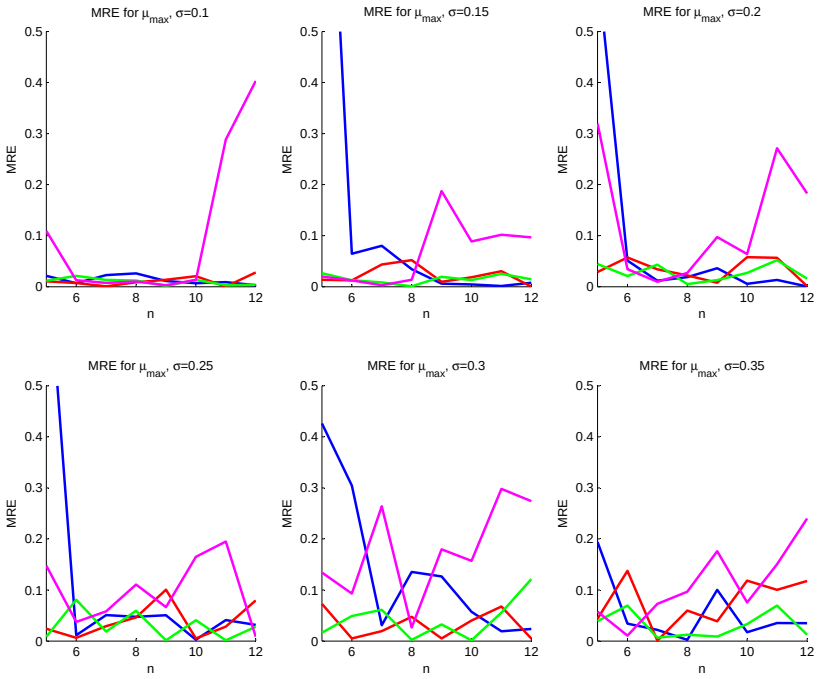

Figure 4: Mean relative errors for $\theta(1) = \mu_{max}$ vs. n for $\sigma = 0.1, 0.15, 0.2, 0.25, 0.3, 0.35$.

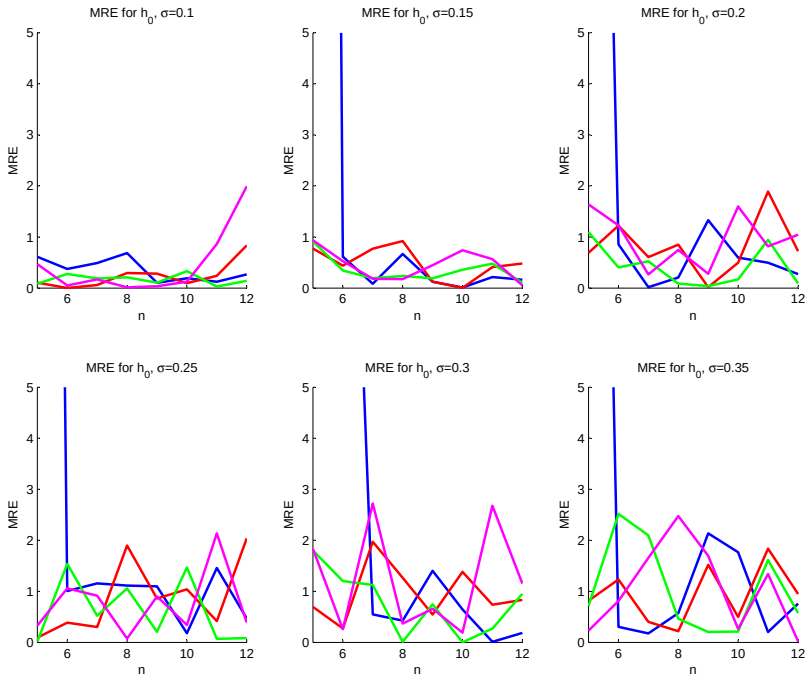

Figure 5: Mean relative errors for $\theta(2) = h_0$ vs. n for $\sigma = 0.1, 0.15, 0.2, 0.25, 0.3, 0.35$.

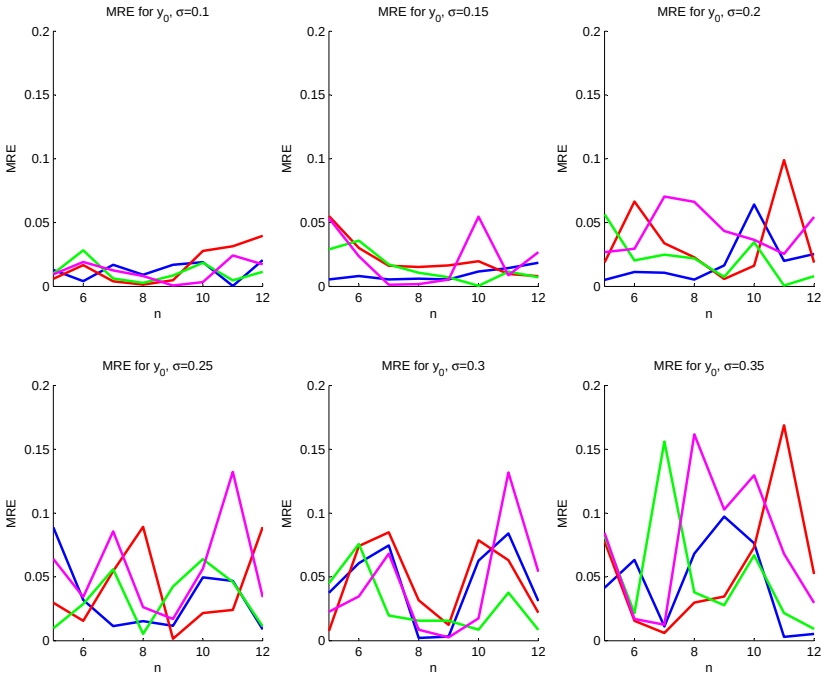

Figure 6: Mean relative errors for $\theta(3) = y_0$ vs. n for $\sigma = 0.1, 0.15, 0.2, 0.25, 0.3, 0.35$.

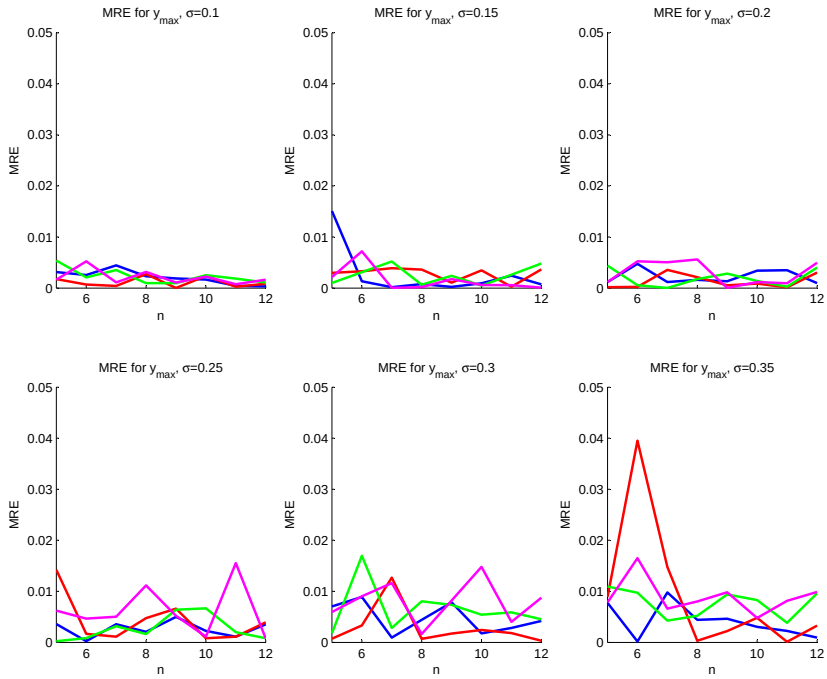

Figure 7: Mean relative errors for $\theta(4) = y_{max}$ vs. n for $\sigma = 0.1, 0.15, 0.2, 0.25, 0.3, 0.35$.

3.1 Statistical Analysis of the Estimations

To compare the statistical relevance of $\hat{\theta}_{unif}$, $\hat{\theta}_D$, $\hat{\theta}_{SE}$ and $\hat{\theta}_{IGS}$, we compute the confidence intervals (CI). We first generate four sets of simulated observations $\{u_{i,unif}\}_{1\le i\le n}$, $\{u_{i,D}\}_{1\le i\le n}$, $\{u_{i,SE}\}_{1\le i\le n}$, $\{u_{i,IGS}\}_{1\le i\le n}$ using the sets of observation points Λ_{unif}, Λ_D, Λ_{SE}, Λ_{IGS} respectively. The estimated variances $\hat{\sigma}^2_{unif}$, $\hat{\sigma}^2_D$, $\hat{\sigma}^2_{SE}$, $\hat{\sigma}^2_{IGS}$ are computed as

$$\hat{\sigma}^2_{design} = \frac{1}{n-4}\sum_{i=1}^{n}\left(u_{i,design} - u(t_i^{design}, \hat{\theta}_{design})\right)^2.$$

The standard errors $SE(\hat{\theta}_{unif})$, $SE(\hat{\theta}_D)$, $SE(\hat{\theta}_{SE})$, $SE(\hat{\theta}_{IGS}) \in \mathbb{R}^4$ are then defined as

$$SE^2_\ell(\hat{\theta}_{design}) = \hat{\sigma}^2_{design}\left(F\left(t_1^{design}, \ldots, t_n^{design}; \hat{\theta}_{design}\right)^{-1}\right)_{\ell\ell},$$

where $\ell = 1, \ldots, 4$.

The approximated CI at the $100(1-\alpha)\%$ level for the ℓ-th component of θ_0 corresponding to $\hat{\theta}_{unif}$, $\hat{\theta}_D$, $\hat{\theta}_{SE}$ and $\hat{\theta}_{IGS}$ are then

$$\left[\hat{\theta}_{design,\ell} - t_{1-\alpha/2}\, SE_\ell(\hat{\theta}_{design})\,,\, \hat{\theta}_{design,\ell} + t_{1-\alpha/2}\, SE_\ell(\hat{\theta}_{design})\right] \tag{13}$$

where $t_{1-\alpha/2}$ is the t-score that has cumulative probability of $\alpha/2$ for the Student's t distribution with $n-1$ degrees of freedom.

Figure 8 show the CI at the 90% level when $\sigma = 0.3$. The horizontal solid black and dashed cyan lines correspond to the true and the initial guess values of the parameter, respectively. The

blue, red, magenta and green vertical segments correspond to the CI for the uniform, D, SE and IGS estimators, respectively, for $n = 6, \cdots, 12$.

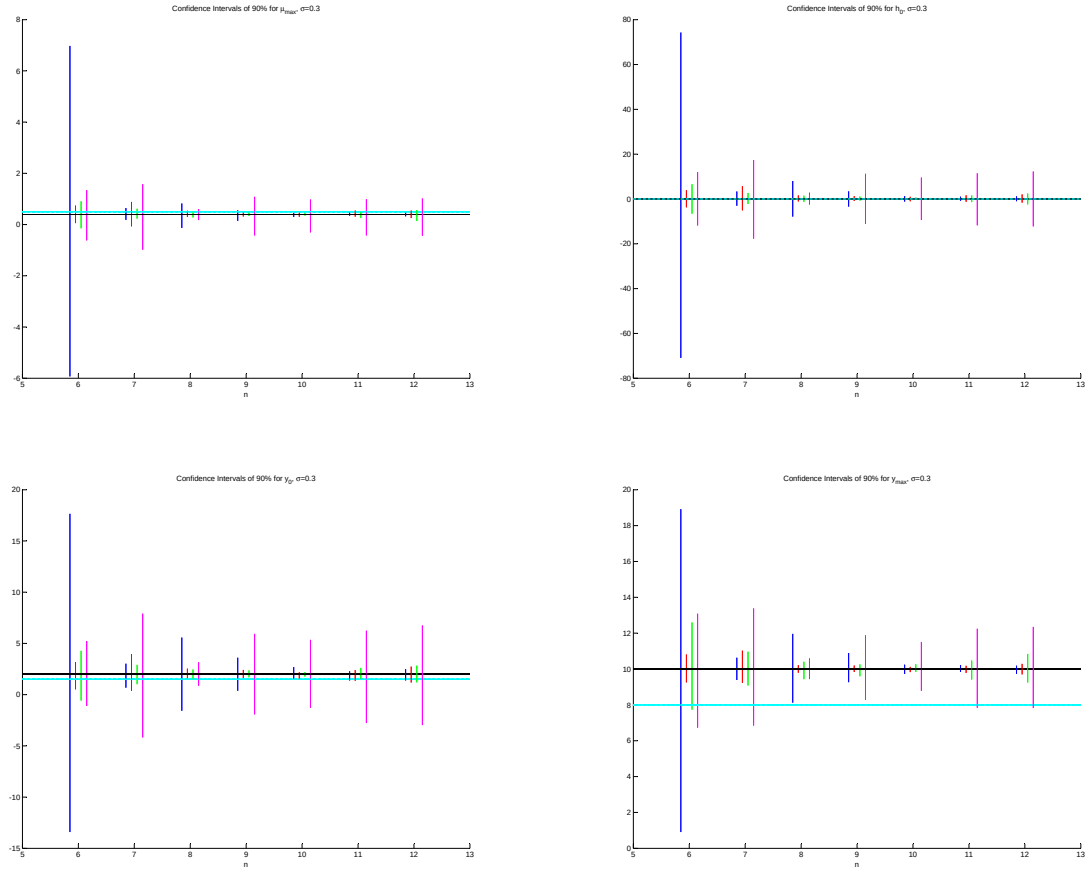

Figure 8: Confidence interval for each parameter vs. n for $\sigma = 0.3$. Solid black: True value, dashed cyan: guess value red, magenta and green: CI for uniform, D, SE and IGS methods, respectively.

4 CONCLUSIONS

In this work, we consider a model introduced by Baranyi to describe the growth of a bacteria population with the purpose of analyzing the performance of different optimal desing techniques for parameter estimation.

We numerically simulate noisy data in the time interval $[0, 50]$. We choose n observation instants before performing the estimation following four different criteria: uniformly distributed instants in $[0, 50]$, D-optimal and the SE-optimal design techniques, and a new criterion, introduced here, based on the incremental generalized sensitivity functions. In order to measure the accuracy of the estimations we compute the relative errors and the confidence intervals of the estimators. From the numerical experiments we conclude that, in all cases the length of the confidence intervals as well as the mean relative error do not decrease significantly for $n > 8$. The D-optimal design technique and the IGS provide a set observations points, that in general, lead to a more accurate estimation. The relative errors as well as the length of the confidence interval are smaller when we select the observation instants following these two criteria and we remark that the calculations that are neccesary to implement the IGS are easier than the ones

associated to the D-optimal. In the case of IGS the optimization is performed over a finite set of points while the D-optimal design requires the optimization over the interval of interest and an initial set of points.

The results obtained encourage us to explore more deeply this new IGS design and its application to other problems of modeling parameter estimations.

REFERENCES

Banks H., Dediu S., and Ernstberger S. Sensitivity functions and their uses in inverse problems. *J. Inverse and Ill-posed Problems*, 15:683–708, 2007.

Banks H., Dediu S., Ernstberger S., and Kappel F. A new optimal approach to optimal design problem. *J. Inverse and Ill-posed Problems*, 18:25–83, 2010.

Banks H., Holm K., and Kappel F. Comparison of optimal design methods in inverse problems. *Inverse Problems*, 27:075002, 2011.

Banks H., Hu S., and Thompson W. *Modeling and Inverse Problems in the Presence of Uncertainty*. CRC Press, Boca Raton, 2014.

Banks H. and Rehm K. Experimental design for distributed parameter vector systems. *Applied Mathematics Letters*, 26:10–14, 2013a.

Banks H. and Rehm K. Experimental design for vector output systems. *Inverse Problems in Sci. and Engr.*, 1:10–14, 2013b.

Banks H., Rubio D., Saintier N., and Troparevsky M. Optimal design techniques for distributed parameter systems. *Proceedings 2013 SIAM Conference on Control Theory*, pages 83–90, 2013a.

Banks H., Rubio D., Saintier N., and Troparevsky M. Optimal electrode positions for the inverse problem of eeg in a simplified model in 3d. *Revista MACI 4*, pages 521–524, 2013b.

Baranyi J. and Roberts T. A dynamic approach to predicting microbial growth in food. *Int. J. of Food Microbiology*, 23:277–294, 1994.

Baranyi J. and Roberts T. Mathematics of predictive food microbiology. *Int. J. of Food Microbiology*, 26:199–218, 1995.

Baranyi J., Roberts T., and McClure P. A non-autonomous differential equation to model bacterial growth. *Food Microbiology*, 10:43–59, 1993.

Baranyi J., Robinson T., and Mackey B. Predicting growth of brochotrix thermosphacta at changing temperature. *Int. J. of Food Microbiology*, 27:61–75, 1995.

Buchanan R. Predictive food microbiology. *Trends Food Sci. Technol*, 4:6–11, 1995.

George S., Richardson L., and Peck M. Predictive models of the effect of temperature, ph and acetic and lactic acids on the growth of listeria moncytogenes. *Int. J. of Food Microbiology*, 32:73–90, 1996.

Gibson A., Bratchell N., and Roberts T. The effect of sodium chloride and temperature on the rate and extent of growth of clostridium botulinum type a in pasteurized pork slurry. *J. Appl. Bacteriol*, 62:479–490, 1987.

Grijspeerdt K. and Vanrolleghem P. Estimating the parameters of the baranyi-model for bacterial growth. *Food Microbiol.*, 16:593–605, 1999.

Hutchinson G. Circular casual systems in ecology. *Ann. N.Y. Acad. Sci*, 50:211–246, 1948.

McClure P., Beaumont A., Sutherland J., and Roberts T. Predictive modelling of growth of listeria moncytogenes. the effects on growth of nacl, ph, storage temperature and nano2. *Int. J. of Food Microbiology*, 34:221–232, 1997.

McMeekin T., Brown J., Krist K., Miles D., Neumeyer K., Nichols D., Olley J., Presser K., Ratkowsky D., Ross T., Salter M., and Soontranon S. Quantitative microbiology: a basis for

food safety. *Emerging Infectious Diseases*, 3:541–549, 1997.

McMeekin T., Olley J., Ross T., and Ratkowsky D. *Predictive microbiology: theory and application*. Research Studies Press LTD.,Taunton, UK, 1993.

Peleg M. Modelling microbial populations with the original and modified versions of the continuous and discrete logistic equations. *Crit. Rev. Food Sci. Nutrition*, 37:471–490, 1997.

Seber G. and Wild C. *Nonlinear regression*. NJ: Wiley Intersciences, 2003.

Skinner G. and Larkin J. Mathematical modeling of microbial growth: a review. *Journal of Food Safety*, 14:175–217, 1994.

Thomaseth K. and Cobelli C. Generalized sensitivity functions in physiological system identification, annals of biomedical engineering. *Annals of Biomedical Engineering*, 27:607–616, 1999.

Vadasz A., Vadasz P., Abashar M., and Gupthar A. Recovery of an oscillatory mode of batch yeast growth in water for a pure culture. *Int. J. of Food Microbiology*, 71:219–234, 2001.

Verhulst P. Notice sur la loi que la population suit dans son accroissement. *Corr. Math. et Phys. Publ.*, pages 113–121, 1838.

Virene E. Reliability growth and its upper limit. *IEEE 68 C33-R*, 71:265–270, 1968.

Zwietering M., Jongenburge R.I., Rombouts F., and van't Riet K. Recovery of an oscillatory mode of batch yeast growth in water for a pure culture. *Appl. Environ. Microbiol.*, 56, 1990.