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A new methodology to robustify an experimental design: Application to the Baranyi model

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ABSTRACT

A robust experimental design is a desired object for practitioners when there is uncertainty about any of the assumptions necessary to compute the optimal design. For instance, when they use non-linear models, which requires having nominal values of the parameters. Several alternatives have been developed in the literature to obtain robust experimental designs such as adaptive or Bayesian designs, among others. Here a new methodology is proposed to robustify the optimal experimental design. Based on the maximin idea, the method adds support points to the optimal design, to obtain designs that are robust. It is applied to the Baranyi model, one of the most used mathematical models in predictive microbiology to describe the behaviour of microorganisms in food products, an essential issue for human health. Previously, D-optimal designs are provided for the model, considering 4 and 6 parameters to be estimated. A sensitivity analysis is carried out regarding the deviations in the nominal values of the parameters, which shows a greater loss of efficiency for two of them. Given these results, the new methodology is applied to the D-optimal design, checking the robustness of the augmented designs through the efficiency achieved. Finally, c-, A- and I-optimal designs are calculated to provide accurate estimation of the model parameters and the predictions.

1. Introduction

It is a common problem that practitioners have a theoretical model that explains a phenomenon and they want to obtain an optimal design that allows them to estimate the model parameters efficiently. When the theoretical mathematical model is non-linear, obtaining the optimal design requires prior knowledge of the values of the parameters, which leads in fact to the calculation of locally optimal designs. This is when the problem arises if there is uncertainty in the values of such parameters. Practitioners want to be covered against this uncertainty and they want the design to be applied to allow them to have precise estimates of the parameters, regardless of the initial values they have or can obtain. That is, they want a robust design.

The perspectives that have traditionally been proposed to minimise this dependence involve the approaches of adaptive designs, Bayesian designs or maximin or minimax criteria. The articles by Dragalin et al. [1] and Wang and Yang [2] can serve as a reference for adaptive designs. They propose carrying out an optimal pilot design to have a first estimate of the parameters that are used to obtain new support points based on them, and so on. This approach involves readjusting the nominal values obtained and combining the information as experiments are carried out. Chaloner and Verdinelli [3] gave a review paper on Bayesian experimental design and the paper by Dette [4] is one of the first to use the Bayesian approach to deal with the uncertainty of nominal values. Other authors who have used Bayesian designs are Tommasi et al. [5] and Amo-Salas et al. [6], the latter shows the application of both strategies, adaptive and Bayesian. Bayesian approach starts from assuming an a priori distribution of the parameters, which implies a different perspective of the uncertainty in the parameters but the definition of this distribution could be complicated for a practitioner without a moderate statistical knowledge. Conversely, the maximin or minimax approach only requires to define an appropriate range of values for the parameters, which is more natural for the practitioners. However, maximin criterion is not differentiable and to obtain optimal designs, analytical or numerical, is complicated, have a high computational burden and only ad hoc algorithms have been proposed [7]. After the pioneering work of [8], different authors have dealt this problem, for instance we can cite the works of King and Wong [9], who use minimax criteria and that of Chen et al. [10] that use the maximin criterion. Both criteria are similar, but while the first is based on the value of the criterion function, the second is based on the value of the efficiency. In this work, a methodology based on the idea of maximin criteria is proposed but with a prior step intended to save the computational cost of maximin designs.

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On the other hand, the increasing importance that food safety has acquired over the decades has been matched by the development of predictive microbiology, and thus the latter has become an essential tool in food science [11]. Food safety is linked with the human health and nowadays represents an important part of the health regulations. Predictive microbiology focuses on developing mathematical models which describe the growth or inactivation of microorganisms in food as a function of time (primary models) and of other environmental conditions, such as temperature, pH or water activity (secondary models).

Experiments therefore play a crucial role in this field in developing mathematical models appropriately and accurately estimating their parameters. This can be seen by the large amount of literature that exists related to experimental design and analysis of parameter estimation in predictive microbiology. One of the pioneering studies in this line is that of Versyck et al. [12], which applies the techniques of Optimal Experimental Design in an Arrhenius-type secondary model, for the maximum inactivation rate as a function of temperature. The work of Grijspeerdt and Vanrolleghem [13] calculates exact optimal designs for the Baranyi model, and carries out an analysis of the estimation of its parameters. Bernaerts et al. [14,15], taking the primary Baranyi model as a starting point, use Optimal Experimental Design to estimate the parameters of the square-root model, as a secondary model. Grijspeerdt and De Reu [16] apply Optimal Experimental Design to two practical examples, using the Baranyi model combined with the Ratkowsky square-root model. Considering the modified Gompertz model, Gil et al. [17] sets out optimal designs for microbial inactivation processes under isothermal and non-isothermal conditions. More recently, the works of Longhi et al. [18,19] apply accurate estimation of parameters for different microorganisms in non-isothermal conditions; the work of Akkermans et al. [20] compares the classical and optimal experimental design in static environmental conditions, and Peñalver-Soto et al. [21] describe a guide, and develop an R package to calculate optimal design in isothermal inactivation experiments. However, alternative approaches have been developed to deal with the problem of parameter estimation. Thus, [22] consider the application of a wavelet neural network to describe the inactivation pattern of *Listeria monocytogenes*.

Thus, this paper has the goal of providing a new methodology for obtaining designs which are robust with respect to uncertainty in the nominal values of the parameters. This allows to provide efficient designs for estimating the parameters within a range of possible nominal values. In this paper a general methodology, valid for any FIM-based criterion, is applied to the D-optimal design obtained for the Baranyi model, in order to get precise estimates of the parameters of the model, as this is one of the main concerns seen in the literature.

The structure of the paper is as follows: Section 2 gives an introduction to the theory of Optimal Experimental Design. Section 3 develops a methodology for calculating designs that are robust with respect to the nominal values of the parameters of the model. Section 4 presents the Baranyi model and provides D-optimal designs for this model considering 4 and 6 parameters for the case study presented in [13]. Section 5 includes a sensitivity analysis for the parameters of the model and applies the methodology introduced in Section 3 providing augmented robust designs. c-, A- and I-optimal designs for accurate estimation of the parameters of the model and the prediction are shown in Section 6 with their corresponding efficiencies. Finally, Section 7 presents the discussion of the study.

2. Optimal experimental design

A non-linear regression model, such as that considered throughout this paper, can be expressed as

$$y(x) = \eta(x, \boldsymbol{\theta}) + \varepsilon, \qquad \varepsilon \sim N(0, \sigma^2), \qquad x \in \mathcal{X}$$

where y is the response variable, x is the designable or controllable variable, taking values on the compact set $\mathcal{X}$, called the design space, and $\boldsymbol{\theta} = (\theta_1, \dots, \theta_k)^T$ is the vector of unknown parameters. It is assumed that the error, ε, follows a normal distribution with mean zero and constant variance σ^2. In practice, for non-linear models, the aim is to work with a linear expression, obtained via Taylor series:

$$\eta(x, \boldsymbol{\theta}) \approx \eta(x, \theta^{(0)}) + \sum_{i=1}^{k} \left(\left. \frac{\partial \eta(x, \boldsymbol{\theta})}{\partial \theta_i} \right|_{\theta^{(0)}} \right) (\theta_i - \theta_i^{(0)}),$$

where $\theta^{(0)} = (\theta_1^{(0)}, \dots, \theta_k^{(0)})^T$ are initial values of the parameters, known as nominal values. Therefore, if

$$f_i(x) = \left. \frac{\partial \eta(x, \boldsymbol{\theta})}{\partial \theta_i} \right|_{\theta^{(0)}}$$

it is possible to work with the simplified version of the model function

$$\eta(x, \boldsymbol{\theta}) - \eta(x, \theta^{(0)}) = \sum_{i=1}^{k} f_i(x)(\theta_i - \theta_i^{(0)}).$$

Assuming beforehand that the number of observations that can be made is N, let define an exact design as a collection of N experimental observation points of $\mathcal{X}$: $x_1, \dots, x_N$ (also known as support points of the design), where eventually some of them could coincide. Denote by N_x the number of observations made at point x. Thus, the discrete measure $\xi(x) = N_x/N$ can be associated with this design. The approximate design of n distinct support points is defined as

$$\xi = \begin{Bmatrix} x_1 & x_2 & \dots & x_n \\ w_1 & w_2 & \dots & w_n \end{Bmatrix} \in \Xi, \qquad \sum_{i=1}^{n} w_i = 1,$$

where $\xi(x_i) = w_i$ are the weights or proportions of observations at each point x_i and Ξ is the set of all the approximate designs in $\mathcal{X}$. In this paper, approximate designs are calculated and also compared with exact designs from the literature, approximating the latter. The goal of Optimal Experimental Design is to obtain designs for the accurate estimation of the parameters of the model in question. In order to do this, one of the main tools in this field is the Fisher Information Matrix (FIM) [23]. By definition, the inverse of the FIM is asymptotically proportional to the matrix of variances and covariances of the estimators of the model parameters. Thus, optimising the estimation of the parameters of a model is equivalent to optimising the inverse of the FIM. Assuming normality in the observations, the FIM can be defined as

$$M(\xi) = \sum_{x \in \mathcal{X}} f(x) f(x)^T \xi(x),$$

where $f(x) = (f_1(x), \dots, f_k(x))^T$ and k is the number of parameters of the model. The entire development of the derivation of the FIM for the exponential family of distributions can be consulted at [24].

Given that there are different ways of optimising this matrix, different optimality criteria arise. Each of these criteria is defined by a convex and lower bounded criterion function, Φ, defined on $\mathcal{M}$, the set of all the information matrices. The design ξ which minimises $\Phi[M(\xi)]$ is called Φ-optimal. This work uses the D-, c-, A- and I-optimality criteria.

The D-optimality criterion is the most popular in the theory of Optimal Experimental Design, and is equivalent to minimising the volume of the confidence ellipsoid of the model parameters. Its criterion function is defined by $\Phi_D[M(\xi)] = |M^{-1}(\xi)|^{1/k}$ when $|M(\xi)| \neq 0$ and is 0 otherwise. In practice, this criterion is equivalent to maximising the determinant of the FIM, given the property that the determinant of the inverse of a matrix is the inverse of the determinant.

The c-optimality criterion allows a linear combination of the parameters $\boldsymbol{c}^T\boldsymbol{\theta}$ with minimum variance to be estimated, where $\boldsymbol{c}$ is a known vector of constants. Its criterion function is given by $\Phi_c[M(\xi)] = \boldsymbol{c}^T M^{-1}(\xi)\boldsymbol{c}$.

In A-optimality, the total variance of the parameter estimates, is minimised, equivalent to minimising the average variance. Its criterion function is given by $\Phi_A[M(\xi)] = trM^{-1}(\xi)$ when $|M(\xi)| \neq 0$ and is ∞ otherwise.

I-optimality, will optimise the mean value of the variances of the predictions according to a probability measure, μ, on a particular set S of interest for predictions. Its criterion function is given by $\Phi_I[M(\xi)] = \int_S f^T(x)M^{-1}(\xi)f(x)\mu(dx)$ when $|M(\xi)| \neq 0$ and is ∞ otherwise.

The General Equivalence Theorem (GET) [25,26], via the sensitivity function, allows the Φ-optimality of a design to be checked, for those criteria that are based on the FIM. The sensitivity function for the D-optimality criterion is defined as $\psi(x,\xi) = k - d(x,\xi)$ where $d(x,\xi) = f^T(x)M^{-1}(\xi)f(x)$ is the generalised variance function and k is the number of parameters of the model. For the c-optimality criterion it is defined as $\psi(x,\xi) = \boldsymbol{c}^T M^{-1}(\xi)\boldsymbol{c} - (f^T(x)M^{-1}(\xi)\boldsymbol{c})^2$ [27]. For A-optimality the sensitivity function is $\psi(x,\xi) = trM^{-1}(\xi) - f^T(x)M^{-2}(\xi)f(x)$, and for I-optimality it is $\psi(x,\xi) = tr[BM^{-1}(\xi)] - f^T(x)M^{-1}(\xi)BM^{-1}(\xi)f(x)$ where $B = \int_S f^T(x)M^{-1}(\xi)f(x)\mu(dx)$.

The Φ-efficiency of a design $\xi \in \Xi$ is a measure of the goodness of the design ξ with respect to the Φ-optimal design, $\xi^\star$. It takes values between 0 and 1 and is defined as

$$\Phi\text{-eff}(\xi) = \frac{\Phi[M(\xi^\star)]}{\Phi[M(\xi)]}. \quad (1)$$

The efficiency of a design is commonly calculated with respect to the optimal design, but relative efficiencies of a design can also be calculated with respect to another design. In this study, the Wynn–Fedorov algorithm was programmed in Python to obtain optimal designs [28, 29].

3. Methodology for obtaining robust designs

A new methodology is presented for obtaining designs, by increasing the number of support points of the optimal design, with the aim of minimising the loss in efficiency with respect to the uncertainty in the nominal values of the parameters; that is, the designs obtained should be robust.

The proposed algorithm augments the Φ-optimal design (where Φ is a FIM-based optimality criterion) by adding an even number of points, based on the assumption that taking a nominal value, the overestimation of it makes the tentative support points to add move in a direction of $\mathcal{X}$, while its underestimation makes them move in the opposite direction.

Thus, let $\boldsymbol{\beta} = (\beta^1,\dots,\beta^p) \subseteq \boldsymbol{\theta}$ be a subset of the model parameters, for which it is assumed uncertainty in their nominal values, with $\beta^i_j \in [\beta^i_{min}, \beta^i_{max}]$, $i = 1,\dots,p$ and $j = 1,\dots,r_i$ varying in a discretised interval for each parameter in $\boldsymbol{\beta}$. The discretisation of the grid is left to the choice of the researcher as it will depend on the characteristics of the parameter and the exhaustiveness with which the researcher intends to search for candidate points to augment the design. For simplicity, let $\boldsymbol{\beta}_z \in \Omega = [\beta^1_{min}, \beta^1_{max}] \times [\beta^2_{min}, \beta^2_{max}] \times \cdots \times [\beta^p_{min}, \beta^p_{max}]$, $z = 1,\dots,R = \prod r_i$, be the vector of the nominal values of β. The nominal values of the other $k - p$ parameters are fixed in accordance with $\theta^{(0)}$. Therefore $\xi^\star_0$ and $\xi^\star_{\beta_z}$ are the Φ-optimal designs when the values of the parameters of $\boldsymbol{\beta}$ are $\boldsymbol{\theta}^{(0)}$ and $\boldsymbol{\beta}_z$, respectively.

The general procedure is summarised in Algorithm 1 where x is a set of support points and $\xi^1_{(x)} = \alpha\xi_x + (1-\alpha)\xi^\star_0$ is an augmented design, where ξ_x is the design supported in x.

This algorithm can be summarised in two main steps:

- **First step:** the set of support points $x^\star_1$ is chosen from Δ which gives the maximum difference between the Φ-efficiency of the augmented design $\xi^1_{(x^{\beta_z})}$ and the Φ-efficiency of $\xi^\star_0$ in the grid.
- **Second step:** a second set of support points $x^\star_2$ is added, again from among the points in Δ, which will be the one that maximises the minimum Φ-efficiency in the entire grid.

The efficiencies in the algorithm are computed using Eq. (1). This algorithm may be used in different ways, depending on how the value α is set. One strategy consists of fixing α from the start, so that the augmented part and the optimal design always have a constant weight within the augmented design. This case is described in Algorithm 1. Another strategy would be varying the value of α at each step, so that the augmented design is equally weighted.

Algorithm 1

1: Define a discretised grid for Ω.
2: Fix α, for each $\boldsymbol{\beta}_z \in \Omega$ define $\xi^1_{(x^{\beta_z})} = \alpha\xi_{x^{\beta_z}} + (1-\alpha)\xi^\star_0$ where:

$$x^{\beta_z} = \arg\max(\Phi\text{-eff}_{\beta_z}(\xi^1_{(x)}))$$

Define the set $\Delta = \{x^{\beta_1}, x^{\beta_2}, \dots x^{\beta_R}\}$.
3: Compute $x^\star_1$ as:

$$x^\star_1 = \arg\max_{\Delta}(\Phi\text{-eff}_{\beta_z}(\xi^1_{(x^{\beta_z})}) - \Phi\text{-eff}_{\beta_z}(\xi^\star_0))$$

4: For each $\boldsymbol{\beta}_z$ define $\xi_{(x^{\beta_z}_2, x^\star_1)} = \frac{\alpha}{2}\xi_{x^{\beta_z}_2} + \frac{\alpha}{2}\xi_{x^\star_1} + (1-\alpha)\xi^\star_0$.
5: Compute $x^\star_2$ as:

$$x^\star_2 = \arg\max \min_{\Delta} \Phi\text{-eff}_{\beta_z}(\xi_{(x^{\beta_z}_2, x^\star_1)}), \qquad \boldsymbol{\beta}_z \in \Omega$$

6: The augmented design is $\xi_{augm} = \frac{\alpha}{2}\xi_{x^\star_2} + \frac{\alpha}{2}\xi_{x^\star_1} + (1-\alpha)\xi^\star_0$.

Appendix presents the formulae developed to simplify the computation of the candidate points to augment a design for the D-optimality criterion, used in Section 5.

4. D-optimal designs

The Baranyi model is one of the most widely used in the predictive microbiology literature, due to its specificity and the physical meaning of its parameters. The explicit expression of the model [30] is as follows:

$$y(t) = y_0 + \mu_{max}A(t) - \frac{1}{m}ln\left(1 + \frac{e^{m\mu_{max}A(t)} - 1}{e^{m(y_{max} - y_0)}}\right) + \varepsilon, \quad \varepsilon \sim N(0,\sigma^2), \quad (2)$$

where $y(t) = ln(x(t))$ and $x(t)$ is the cell concentration (colony-forming units/mL) at time t; $y_0 = ln(x_0)$ and $y_{max} = ln(x_{max})$ where x_0 and x_{max} are the initial and asymptotic cell concentration, respectively; μ_{max} is the specific maximum growth ratio; m and ν are curvature parameters that characterise the transition from and to the exponential phase, respectively, and h_0 is a non-dimensional parameter quantifying the initial physiological state of the cells. The function $A(t) = t + \frac{1}{\mu_{max}}ln(e^{-\mu_{max}t} + e^{-h_0} - e^{-\nu t - h_0})$ plays the role of a gradual delay in time. The error, ε, is assumed to follow a normal distribution with zero mean and constant variance σ^2.

As mentioned above, the Baranyi model includes six parameters, two of which are curvature parameters (ν and m) and are typically assumed to be known [31]. Therefore two scenarios are presented, firstly one in which the remaining four parameters are to be estimated, and subsequently in which optimal designs are sought to estimate the six parameters. The case studied by [13] is addressed, where data is gathered on the growth of *Salmonella enteritidis* in egg yolk at 30 °C. The nominal values are thus considered $\theta^{(0)} = (y_0,\ y_{max},\ \mu_{max},\ h_0,\ \nu,\ m) = (2.364,\ 21.097,\ 1.089,\ 2.657,\ 1.089, 1)$ and the design space for the controllable variable, time, is defined by the interval $[0,28]$ (in hours). The D-optimal design for the Baranyi model, when four parameters are taken to be unknown, assuming ν and m are known, is

$$\xi^\star_4 = \left\{\begin{array}{cccc} 0 & 4.8 & 17.31 & 28 \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{array}\right\}.$$

This design is compared with the exact D-optimal designs obtained in the case study considered. In order to make these comparisons the exact designs are approximated, denoted by $\tilde{\xi}_n$ where n is the number of observations that use the exact design (see Table 1).

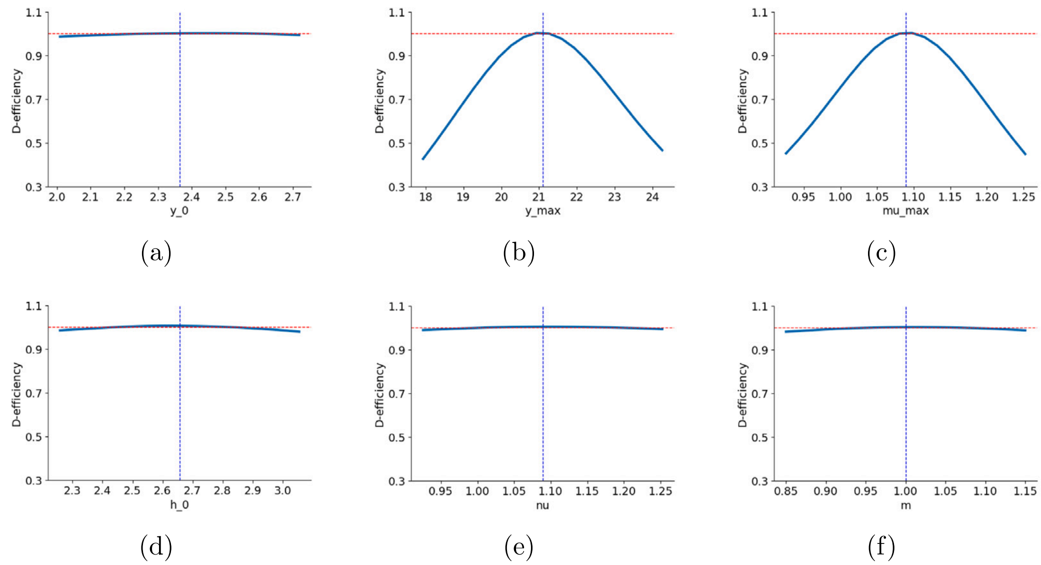

Fig. 1. Sensitivity analysis of the D-optimal design $\xi_6^\star$ with respect to the nominal values of the parameters y_0 (a), y_{max} (b), μ_{max} (c), h_0 (d), v (e) and m (f).

Table 1
D-efficiencies obtained by comparing the designs of [13], $\tilde{\xi}_n$, with the D-optimal design $\xi_4^\star$.

Design	$\tilde{\xi}_7$	$\tilde{\xi}_{10}$	$\tilde{\xi}_{12}$	$\tilde{\xi}_{14}$	$\tilde{\xi}_{18}$
D-efficiency	0.961	0.911	0.927	0.945	0.924

It may be seen that these exact designs are not in fact optimal. Thus, the exact optimal designs provided by [13] for 4 and 12 observations are $\xi_4 = \{0, 4.8, 17.31, 28\}$ and $\xi_{12} = \{0, 0, 4.65, 4.79, 4.83, 17.3, 17.3, 17.3, 17.3, 17.3, 28, 28\}$. The design ξ_{12} is noteworthy, as its exact optimal design should be the 3-fold replica of the design which consists in observing once at each point of the optimal design, ξ_4. However, the authors introduce new support points and the distribution of the replicas among the support points is unbalanced, and so greater loss of efficiency is observed in $\tilde{\xi}_{12}$ (Table 1).

The assumption that the parameters v and m are known simplifies to some extent the complexity of the model, but it can also be seen as a strong assumption, since it assumes the equality of the curvature v and the maximum growth ratio μ_{max}, assuming the joint variation of the two. Therefore, despite the complexity of the full model, it can be convenient to take these parameters as unknown, starting with the nominal values suggested for them.

The D-optimal design obtained for the Baranyi model that takes six unknown parameters, $\xi_6^\star$, has a D-efficiency of 0.829 with respect to $\xi_4^\star$ and is given by

$$\xi_6^\star = \left\{ \begin{array}{cccccc} 0 & 2.02 & 5.49 & 15.97 & 19.71 & 28 \\ \frac{1}{6} & \frac{1}{6} & \frac{1}{6} & \frac{1}{6} & \frac{1}{6} & \frac{1}{6} \end{array} \right\}.$$

Henceforward the scenario with six parameters is considered, since it addresses a more general situation of the problem, but in turn starts from initial estimates of the curvature parameters that are equal to the values taken if they are held to be known.

5. Robust designs for the Baranyi model

5.1. Sensitivity analysis

Fitting the model with the data obtained means uncertainty in the estimates of the parameters. The D-optimal design guarantees accurate estimates of the parameter set, but it is dependent on the nominal values taken. It is therefore interesting to study the influence of the nominal values on the D-optimal design, which parameters influence the design most, and whether overestimating or underestimating any of the nominal values of these parameters has the same effect.

To undertake the sensitivity analysis, each of the six parameters is studied separately. The nominal value of the chosen parameter is made to vary up to $\pm 15\%$ of the nominal value taken in the case study, then the D-optimal design is obtained for each variation, and the D-efficiency of the D-optimal design $\xi_6^\star$ is calculated with respect to the optimum of the nominal value varied. The results are shown in Fig. 1. The design $\xi_6^\star$ shows greater sensitivity with respect to the variations of the nominal values of parameters y_{max} and μ_{max}, while it behaves robustly with respect to variation of the nominal values of the other parameters. This means acceptable variations in the nominal values of y_0, h_0, v and m do not imply a significant loss of efficiency in the D-optimal design. However, for y_{max} and μ_{max}, efficiency losses of up to 60% are observed. Furthermore, these efficiency losses are practically symmetric, and so overestimating or underestimating the nominal value of the parameter leads to a similar efficiency loss. Fig. 2 (in blue) shows the D-efficiency of the D-optimal design $\xi_6^\star$ on co-varying the nominal values of y_{max} and μ_{max} by $\pm 15\%$ of the original nominal value.

The sensitivity analysis was also undertaken for the D-optimal design $\xi_4^\star$, in which the four corresponding parameters are studied (assuming those of curvature are known), with very similar results. The design is sensitive to variations of the nominal values of the parameters y_{max} and μ_{max}, whereas it behaves robustly with respect to variation of the other two parameters. In this case, however, the sensitivity is notably asymmetric presenting a greater loss of efficiency when the nominal value of the parameter μ_{max} is underestimated, or the nominal value of the parameter y_{max} is overestimated.

5.2. Application of the methodology

Faced with the loss of efficiency observed in the D-optimal design with respect to the nominal values, the methodology to obtain robust designs set out in Section 3 is applied, adding the support points necessary to improve the robustness of the design (and so minimise the loss of efficiency). There are proposed four different scenarios with respect to the number of points to be added and the value α:

- Two points and α fixed with value $\alpha = 0.25$.
- Two points and equally weighted designs.
- Four points and α fixed with value $\alpha = 0.25$.
- Four points and equally weighted designs.

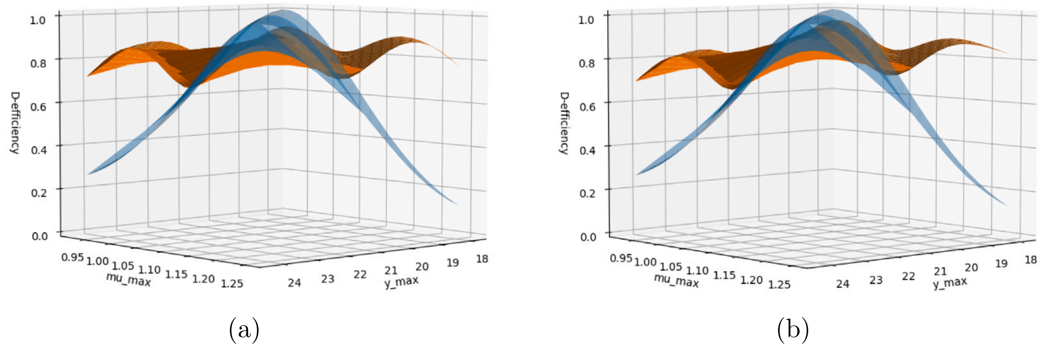

Fig. 2. D-efficiencies of the designs $\xi_6^\star$ (blue), $\xi^\alpha_{augm_2}$ (a) and $\xi^\alpha_{augm_4}$ (b), in orange. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

These scenarios with respect to α are motivated by the assumption that the D-optimal design should keep an important weight in the final design, so a value less than 30% for α is advisable. In the case of equally weighted designs, which means that the value of α varies as a function of the points to be added at each step, this assumption is only valid for a small number of points. Our purpose is to compare both strategies and, in a sense, to check the assumption. With respect to the number of points, the initial assumption is to add two points for each parameter to robustify, one to fix the overestimation and the other the underestimation of each parameter. However, in some situations it is possible that fewer points are necessary for obtaining robust designs.

For the two first scenarios, the augmented designs match in the case of the equally weighted augmented design ($\xi^{ew}_{augm_2}$) and when the value of $\alpha = 0.25$ ($\xi^\alpha_{augm_2}$) is fixed, adding to the D-optimal design the support points 12.5 and 24.2. These provide considerable improvement in the minimum D-efficiency compared to the design $\xi_6^\star$, whose minimum D-efficiency is 0.1325.

In the last two scenarios, different augmented designs are obtained depending on the strategy chosen for α. For the equally weighted design, $\xi^{ew}_{augm_4}$, the points added to the support are 2, 11.7, 14.6 and 24.2. The design built with fixed weight ($\alpha = 0.25$), $\xi^\alpha_{augm_4}$, which adds the support points 0, 11.7, 14.6 and 24.3, gives greater robustness with respect to variations in the nominal values. This is because the D-optimal design has a significant weight (75%) within the augmented design, unlike the equally weighted case (60%), where, as points are added, the more weight it loses. It therefore seems more advisable to fix the value of α. A summary of D-efficiencies of the augmented designs are given in Table 2 and are shown in Fig. 2 in orange.

The D-efficiency of $\xi^\alpha_{augm_2}$ is very similar to the obtained for $\xi^\alpha_{augm_4}$, the maximum and mean increase and the minimum decreases slightly, so it is not advisable to continue augmenting the design with 3 points at each step, given the complexity of the calculations. Moreover, it can be seen that in $\xi^\alpha_{augm_4}$, one of the support points that is added, 0, corresponds to a support point of the D-optimal design, and so the algorithm is reassigning part of the weight of the augmented part to the D-optimal design. This latter could be considered as a stop criterion of the methodology with respect to the number of points to add.

Finally, the last two columns of Table 2 show the D-efficiencies obtained for the augmented designs with respect to $\xi_4^\star$ and $\xi_6^\star$. It may be noted that the maximum D-efficiencies obtained in the augmented designs are higher than these, as the maxima are obtained for values of the grid which are different from the nominal values taken in $\xi_4^\star$ and $\xi_6^\star$.

6. c-, A And I-optimal designs and efficiencies

As mentioned in the Introduction, one of the main concerns seen in the literature of predictive microbiology is accurate parameter estimation. When the goal of the experiment is to obtain a precise estimate

Table 2
Summary of D-efficiencies obtained for each augmented design at the different points of the grid, and with respect to $\xi_4^\star$ and $\xi_6^\star$.

	Max	Mean	Min	$\xi_4^\star$	$\xi_6^\star$
$\xi^\alpha_{augm_2}$	0.915	0.8348	0.7073	0.7916	0.9121
$\xi^{ew}_{augm_4}$	0.8878	0.8082	0.6733	0.7497	0.8831
$\xi^\alpha_{augm_4}$	0.9456	0.8433	0.6954	0.753	0.8811

of one of the parameters, or of a linear combination of them, it is of interest to find the c-optimal design. Table 3 shows the c-optimal designs obtained for each of the parameters of the Baranyi model (6 first rows). The resemblance should be noted between the support points of all of them and also those of the D-optimal design $\xi_6^\star$, while there is a greater difference in the distribution of weights. In the case of the c-optimal design obtained for the parameter h_0, it can be seen that 0 is not included in the support, whereas this is true of the others, and it also has 7 points instead of 6 like the others. However, support point 28, the maximum of the design space, is included in all the c-optimal designs, except to c-optimal design for y_0 which is an one-point design with 0 as support point due to this parameter represents the initial concentration. In the case of the c-optimal design for the curvature parameter v it may be seen that the weights of the last 2 support points are negligible, taking more than 90% of the weight between points 0 and 5.81, which is due to the physical interpretation of this parameter, characterising the transition from the lag phase to the exponential phase of logarithmic growth of the colony-forming units, which happens in the earliest moments. The opposite occurs for the c-optimal design for the curvature parameter m, where the majority of the weight is concentrated between points 15.76 and 28.

With respect to an accurate parameter estimation, the A-optimality criterion can be seen as an intermediate criterion between D- and c-optimality, due to it minimises the sum of variances of the estimates of the parameters of the model. Therefore, it considers all the parameters, as D-optimality, but it focuses only on the variances and does not take into account the covariances. In this case, the A-optimal design (7th row of Table 3) has the same support points as the D-optimal design but more than 50% of the weight of the design is concentrated in two points, 15.35 and 19.62. Finally I-optimality offers a different perspective focusing on the prediction variance. This design (8th row of Table 3), except to 0, shows a more balanced distribution of the weights with again the same support points than the D-optimal design. c- A- and I-optimal designs have been computed with the *optedr* package in R (https://CRAN.R-project.org/package=optedr).

Table 4 shows the efficiencies of $\xi_6^\star$ and the augmented designs $\xi^\alpha_{augm_2}$, $\xi^{ew}_{augm_4}$ and $\xi^\alpha_{augm_4}$ with respect to the previous optimal designs. As previously mentioned, the main difference between these designs and the D-optimal design is in the distribution of the weights among the support points. This is why the design $\xi_6^\star$ loses less efficiency than

Table 3
c-optimal designs for each of the Baranyi model parameters (6 first rows), A- and I-optimal designs (2 last rows).

Criteria	Design							
c_{y_0}	x_i :	0						
	w_i :	1						
$c_{y_{max}}$	x_i :	0	1.91	5.8	15.77	19.86	28	
	w_i :	0.0046	0.0103	0.0903	0.2918	0.4604	0.1426	
$c_{\mu_{max}}$	x_i :	0	1.91	5.79	15.68	19.85	28	
	w_i :	0.0223	0.0495	0.433	0.4315	0.0444	0.019	
c_{h_0}	x_i :	0.4386	1.59	2.75	4.99	15.587	19.831	28
	w_i :	0.338	0.000724	0.0001772	0.48512	0.156	0.014697	0.006238
c_v	x_i :	0	1.93	5.81	15.76	19.87	28	
	w_i :	0.2831	0.435	0.209	0.062	0.00681	0.00293	
c_m	x_i :	0	1.91	5.81	15.76	19.86	28	
	w_i :	0.00414	0.00918	0.0815	0.2634	0.414	0.2278	
A	x_i :	0	1.82	5.25	15.35	19.62	28	
	w_i :	0.115	0.08	0.18	0.214	0.31	0.101	
I	x_i :	0	2	5.62	15.69	19.59	27.99	
	w_i :	0.07	0.13	0.21	0.22	0.15	0.22	

Table 4
c-efficiencies of the design $\xi_6^\star$ and augmented designs with respect to the c-optimal designs for each of the parameters of the Baranyi model (6 first columns) and A- and I-efficiencies of the design $\xi_6^\star$ and augmented designs (2 last columns).

	$\xi^*_{y_0}$	$\xi^*_{y_{max}}$	$\xi^*_{\mu_{max}}$	$\xi^*_{h_0}$	ξ^*_v	ξ^*_m	ξ^*_A	ξ^*_I
$\xi_6^\star$	0.1667	0.4957	0.4579	0.4533	0.5173	0.5466	0.7928	0.8993
$\xi^\alpha_{augm_2}$	0.125	0.4197	0.3587	0.3409	0.3909	0.479	0.6579	0.8994
$\xi^{ew}_{augm_4}$	0.1	0.3671	0.334	0.29	0.4561	0.4167	0.5736	0.8468
$\xi^\alpha_{augm_4}$	0.1875	0.4289	0.3864	0.3746	0.4263	0.4815	0.6833	0.8694

the augmented designs, where different points are added to the support. The low c-efficiencies are justified by the large number of parameters in the Baranyi model, so the design that is optimal at estimating them all accurately, $\xi_6^\star$, is not as efficient at estimating each of them due to the different distribution of the weights. Thus, the I-efficiencies are higher due to the weights of ξ_I^* are distributed more equally. Moreover, among the augmented designs $\xi^\alpha_{augm_4}$ shows the best c- and A-efficiencies.

7. Discussion and conclusions

One of the criticisms levelled at Optimal Experimental Design is the need to assume the initial values of the parameters in non-linear models, which leads in fact to the calculation of locally optimal designs. These designs can be sensible to misspecification in the nominal values, which can imply an important loss of efficiency. These problem is faced up in this paper providing a new methodology based on maximin criteria and applied to a food safety model.

Food safety plays a key role in human health and its importance has been increasing along the last decades. In this context, the Baranyi model is one of the most widely-used primary models in predictive microbiology, and so is often considered in work on experimental design applied to this field. This paper provides D-optimal designs, both taking 4 parameters to be estimated, assuming the curvature parameters are known, following the suggestion of [31], and also taking the 6 parameters of the complete model, $\xi_4^\star$ and $\xi_6^\star$, respectively (Section 4). Firstly, $\xi_4^\star$ allows a relative loss of efficiency in the exact designs in the work of [13] to be shown. In cases where it is not possible to apply the approximate design directly, because of the overall number of experiments to be carried out, a number of efficient rounding techniques can be applied to the approximate design, as for example that proposed by [32] implemented in the *optedr* package in R. Thus, for example, the exact design obtained using this package, for 10 support points, starting from the approximate $\xi_4^\star$ has an efficiency of 98% as opposed to 91% for that described in the work of [13] (see Table 1).

On the other hand, the parameters v and m were considered as unknown in order to perform a less restrictive study despite the complexity this entails. In addition, the sensitivity analysis with respect to the nominal values of the parameters given in this work (Section 5) shows that the uncertainty in the nominal values does not behave in the same way for the two parameters, where the efficiency loss of the D-optimal design is not similar with respect to v and μ_{max}. Furthermore, the c-optimal design shows differences for accurate estimation of these parameters, both at the support points and in the distribution of their weights.

The sensitivity analysis also shows that the design is fairly robust with respect to 4 of the parameters. This implies that deviations in the real values of the parameters with respect to the nominal values taken do not lead to a significant loss of efficiency in the D-optimal design. However, it can be seen that this is not true of the parameters y_{max} and μ_{max} where the deviations common to both parameters can cause efficiency losses greater than 80%. For this reason, the new methodology developed is applied to add support points to the D-optimal design, to make the resulting augmented design more robust with respect to uncertainty in the nominal values. The methodology devised is based on the maximin criterion, with a prior step that allows a preselection of the candidate points for inclusion in the design, and resulting in major computational saving. Instead of assuming a probability distribution for the parameters, as Bayesian approach does, maximin idea presents the advantage of choosing a range of values for them, which is more natural from a practitioner point of view. However, the high computational cost of the maximin criteria has been pointed out in papers as [33], where authors remark that this procedure is numerically intractable in many cases and different algorithms have been implemented to reduce it, as [34] based on a theorem 2 of [35], [36] where is proposed nature-inspired optimality algorithm or [37] applied to binary response mixture model and computing exact designs instead of continuous designs as are computed in this paper. It is important to take into account that to compute a maximin optimal design requires to optimise support points and weights and it supposes at least 11 parameters (6 support points and 5 weights) in a non-singular design for the model considered in this paper, which is a complex non-linear model. Therefore, to obtain the maximin D-optimal design could be an intractable problem, even numerically. However, the methodology presented in this paper consist to add a limited number of points from a bounded set of "optimal" candidates, which reduces the computational burden significantly.

Moreover, it is a flexible method, since it is applicable to any type of experiment and criterion, allowing the practitioner to fit the number of points to be added as considered appropriate. Therefore, this methodology, as well as improving the robustness of the design under consideration, when adding points to the design, solves one of the main criticisms of optimal design: it is supported at as many points as there are parameters, and generally at the extremes of the design space. This can be sometimes a problem, mainly in models with only 2 or 3 parameters.

Different methodologies have been proposed in the literature for augmenting designs, with different goals, such as performing a lack of fit test, or accurately estimating specific environments of the chosen model [38–40]. Among these, attention may be drawn to the methodology recently proposed by [41] where regions of the design space are defined in which to augment a D-optimal design, keeping a lower bound on efficiency. The possibility of adapting the methodology proposed in this paper, using regions that guarantee a lower bound to efficiency, is a future line of research which could simplify calculations and save computational time.

The methodology described here has two aspects, the value of α and the number of points to be added, which are chosen by the practitioner. With respect to the value of α, it seems reasonable to assign a significant weight to the initial D-optimal design, in order to avoid a large drop in efficiency in the neighbouring environment of the nominal values taken. Therefore, assigning a fixed value of α from 20% and 30%, independently of the number of points to be added, could be a good strategy. With respect to the points to be added, a first approximation would be twice as many points as parameters taken, with the aim of controlling the efficiency loss, due to both underestimating and overestimating the true value of the parameter. Nonetheless, fewer points would be needed if, as in the case studied here, the efficiency loss is compensated in one parameter with respect to the other, or if the efficiency loss only occurs in one direction, being, for example, sensitive to underestimation, but robust to overestimation.

One of the conclusions shown by the calculation of the c- and A-optimal designs is the efficiency loss of the D-optimal design, and so also of the augmented designs. This may be due to the considerable number of parameters to be estimated, and mainly to the varied weight distribution among the c- and A-optimal designs, as the support points are similar to those of the D-optimal design. Thus, for instance, while the c-optimal design, for some parameters, puts a greater weight on the initial points, others do so on the intermediate or final points. This further means that it is almost impossible to make practical use of these c-optimal designs because of the almost zero weight at some of the points, but they may be considered as a reference for measuring the goodness of the design to be used in practice. It is important to highlight that in augmented designs, when adding points with the purpose of making the D-optimal design more robust with respect to uncertainty in any of the nominal values, the c-efficiency loss increases, since the points added are different from those of the c-optimal designs. One possible solution to this problem could be to use compound criteria, although the methodology presented here could be adapted to add points to the c-optimal design, with the idea of improving efficiency in the precision of a given parameter.

CRediT authorship contribution statement

Alba Muñoz del Río: Writing – original draft, Writing – review & editing, Methodology, Software. **Víctor Casero-Alonso:** Writing – original draft, Writing – review & editing, Methodology. **Mariano Amo-Salas:** Writing – original draft, Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data used are from other research referenced in the paper.

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Appendix

Let the D-optimal design augmented with one point, with a weight α fixed beforehand, be defined by $\xi^1_{(x)} = \alpha\xi_x + (1-\alpha)\xi^\star_0$, where $\xi^1_{(x)}$ is the single-point design in x. The determinant of the information matrix of $\xi^1_{(x)}$ can be expressed as (see for instance [23]):

$$|M(\xi^1_{(x)})| = |M(\xi^\star_0)|(1-\alpha)^k\left(1+\frac{\alpha d(x,\xi^\star_0)}{1-\alpha}\right),$$

where $d(x,\xi^\star_0)$ is the generalised variance function given in Section 2. Then, the D-efficiency of this design is:

$$\begin{aligned} D\text{-eff}_{\beta_z}(\xi^1_{(x)}) &= \left(\frac{\left|M_{\beta_z}(\xi^1_{(x)})\right|}{\left|M_{\beta_z}(\xi^\star_{\beta_z})\right|}\right)^{\frac{1}{k}} \\ &= \left(\frac{\left|M_{\beta_z}(\xi^\star_0)\right|(1-\alpha)^k\left(1+\frac{\alpha d_{\beta_z}(x,\xi^\star_0)}{1-\alpha}\right)}{\left|M_{\beta_z}(\xi^\star_{\beta_z})\right|}\right)^{\frac{1}{k}} \\ &= D\text{-eff}_{\beta_z}(\xi^\star_0)(1-\alpha)\left(1+\frac{\alpha d_{\beta_z}(x,\xi^\star_0)}{1-\alpha}\right)^{\frac{1}{k}}, \end{aligned} \tag{A.1}$$

whose maximum can be expressed as

$$\max(D\text{-eff}_{\beta_z}(\xi^1_{(x)})) = \max_{x\in\chi} d_{\beta_z}(x,\xi^\star_0) = \max_{x\in\chi} f^T(x)M^{-1}_{\beta_z}(\xi^\star_0)f(x).$$

Therefore, in Algorithm 1, step 2 can be simplified:

$$x^{\beta_z} = \arg\max(D\text{-eff}_{\beta_z}(\xi^1_{(x)})) = \arg\max_{x\in\chi} f^T(x)M^{-1}_{\beta_z}(\xi^\star_0)f(x).$$

If it is wished to add more points to the optimal design, the D-efficiency expression would be calculated, in a similar way to (A.1), corresponding to the augmented design sought. The following is the case of adding 4 points. Let now the D-optimal design augmented with two points, with a weight α fixed beforehand, be defined by $\xi_{(x_1,x_2)} = \alpha_1\xi_{x_1} + \alpha_2\xi_{x_2} + (1-\alpha)\xi^\star_0$, where:

- $\alpha_1 + \alpha_2 = \alpha$
- $\alpha^*_1 = \frac{\alpha_1}{1-\alpha_2}$,
- $\hat{\xi}_1 = \alpha^*_1\xi_{x_1} + (1-\alpha^*_1)\xi^\star_0$ and
- $\xi_{(x_1,x_2)} = \alpha_2\xi_{x_2} + (1-\alpha_2)\hat{\xi}_1$.

The D-efficiency of this design is:

$$\begin{aligned} &D\text{-eff}_{\beta_z}(\xi_{(x_1,x_2)}) \\ &= \left(\frac{\left|M_{\beta_z}(\xi_{(x_1,x_2)})\right|}{\left|M_{\beta_z}(\xi^\star_{\beta_z})\right|}\right)^{\frac{1}{k}} \\ &= \left(\frac{\left|M_{\beta_z}(\xi^\star_0)\right|(1-\alpha^*_1)^k\left(1+\frac{\alpha^*_1 d_{\beta_z}(x_1,\xi^\star_0)}{1-\alpha^*_1}\right)(1-\alpha_2)^k\left(1+\frac{\alpha_2 d_{\beta_z}(x_2,\hat{\xi}_1)}{1-\alpha_2}\right)}{\left|M_{\beta_z}(\xi^\star_{\beta_z})\right|}\right)^{1/k} \\ &= D\text{-eff}_{\beta_z}(\xi^\star_0)(1-\alpha^*_1)(1-\alpha_2)\left[\left(1+\frac{\alpha^*_1 d_{\beta_z}(x_1,\xi^\star_0)}{1-\alpha^*_1}\right)\left(1+\frac{\alpha_2 d_{\beta_z}(x_2,\hat{\xi}_1)}{1-\alpha_2}\right)\right]^{1/k}. \end{aligned}$$

The generalised variance $d_{\beta_z}(x_2,\hat{\xi}_1)$ can be expressed as (see for instance [42]):

$$d_{\beta_z}(x_2,\hat{\xi}_1)=\frac{1}{1-\alpha_1^*}\left(d_{\beta_z}(x_2,\xi_0^\star)-\frac{\alpha_1^*\left(f^T(x_2)M^{-1}(\xi_0^\star)f(x_2)\right)^2}{1-\alpha_1^*+\alpha_1^* d_{\beta_z}(x_1,\xi_0^\star)}\right).$$

Then the maximum of the D-efficiency is:

$$\max D\text{-eff}_{\beta_z}(\xi_{(x_1,x_2)})=\max_{x_1,x_2\in\chi}\left(1+\frac{\alpha_1^* d_{\beta_z}(x_1,\xi_0^\star)}{1-\alpha_1^*}\right)\cdot\left(1+\frac{\alpha_2\left(d_{\beta_z}(x_2,\xi_0^\star)-\frac{\alpha_1^*\left(f^T(x_2)M^{-1}(\xi_0^\star)f(x_2)\right)^2}{1-\alpha_1^*+\alpha_1^* d_{\beta_z}(x_1,\xi_0^\star)}\right)}{(1-\alpha_1^*)(1-\alpha_2)}\right).$$

And after performing some algebraic operations, it leads to the expression of the efficiency to be maximised:

$$4+\alpha\Big[2(d_{\beta_z}(x_1,\xi_0^\star)+d_{\beta_z}(x_2,\xi_0^\star)-4)+\alpha(d_{\beta_z}(x_1,\xi_0^\star)-2)\times(d_{\beta_z}(x_2,\xi_0^\star)-2)-\alpha(f^T(x_2)M_{\beta_z}^{-1}(\xi_0^\star)f(x_1))^2\Big].$$

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