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Optimal experimental design for discriminating between microbial growth models as function of suboptimal temperature

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ABSTRACT

In the field of predictive microbiology, mathematical models play an important role for describing microbial growth, survival and inactivation. Often different models are available for describing the microbial dynamics in a similar way. However, the model that describes the system in the *best* way is desired. Optimal experimental design for model discrimination (OED-MD) is an efficient tool for discriminating among rival models.

In this work the T_{12}-criterion proposed by Atkinson and Fedorov (1975) [1] and applied efficiently by Ucinski and Bogacka (2005) [2] and the Schwaab-approach proposed by Schwaab et al. (2008) [3] and Donckels et al. (2009) [4] will be applied for discriminating among rival models for the microbial growth rate as a function of temperature. The two methods will be tested *in silico* and their performances will be compared.

Results from a simulation study indicate that it is possible to validate the case that one of the proposed models is more accurate for describing the temperature effect on the microbial growth rate. Both methods are able to design inputs with a sufficient discrimination potential. However, it has been observed that the Schwaab-approach provides inputs with a higher discrimination potential in combination with more accurate parameter estimates.

1. Introduction

The need to find the best model arises when different models are proposed for the same process. For describing the influence of temperature on the microbial growth rate μ_{max} there exist several models in predictive microbiology. Two of these models are the Cardinal Temperature Model with Inflection (CTMI) [5] and the adapted CTMI (aCTMI) [6,7]. Whereas the CTMI assumes a one-phase linear relation between $\sqrt{\mu_{max}}$ and the temperature in the suboptimal temperature range, the aCTMI is build from the observation of two phases in this temperature region. As this suboptimal temperature range typically covers the temperature span in which food products are stored, an accurate model description of the growth rate is of highest importance. Upto now, it is assumed that the CTMI is generally valid for all strains. Divergence from this model only has been observed for *Listeria* [6,7] and *Escherichia coli* K12 [8].

The main objective of this simulation study is to discriminate CTMI and aCTMI, by performing *in silico* experiments. For performing these *in silico* experiments two specific experimental design procedures for model discrimination will be tested and their performances will be compared. The first one is *T*-procedure applied efficiently by Ucinski and Bogacka [2], based on the T_{12}-criterion proposed by Atkinson and Fedorov [1], that leads to non sequential T_{12}-optimal designs. The second one is the Schwaab-procedure based on the approach proposed by Schwaab et al. [3] and Donckels et al. [4], that leads to sequential designs. At the T_{12}-criterion the minimum of the sum of squares for the lack of fit of the model is maximized. The Schwaab-approach includes the posterior covariance matrix of the estimated model parameters.

In this simulation study, for the two approaches – the *T*-procedure and the Schwaab procedure – typical constraints that arise when modeling microbial dynamics are taken into account. These constraints involve, e.g., (i) an a priori specification of the number of (time-consuming) experiments and (ii) the uncertainty of the actual parameter values as typically only estimates from literature or a preliminary experiment are present. In contrast to a typical experiment design of an arbitrarily chosen set of constant temperature levels, the dynamic experiments designed within this work will be used to efficiently discriminate between these two models.

The paper is structured as follows. In the first part, optimal experimental design for model discrimination is presented covering the two approaches. Afterwards the complementary tasks for

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the optimal experimental design are sketched out. In the third part, the case study with the two proposed models is outlined followed by the implementation. Finally, in the last part the results from both methods for the discrimination between the two models are presented followed by the conclusions.

2. Optimal experimental design for model discrimination

The procedure for discriminating between two models $\mathcal{M}_1$ and $\mathcal{M}_2$ will be described in this section. The objective function J for model discrimination is typically a discrimination criterion that maximizes a function of the difference between the model predictions. As performing experiments in predictive microbiology is typically time and labor intensive, a practical constraint is to have the same experimental burden, i.e., performing the same number of experiments in both approaches.

2.1. Mathematical model formulation

In a general statistical framework it can be assumed that observations can be repeated for different settings of experimental conditions $T_i(\cdot,\beta_i) \in \mathcal{T} \times B^s,\ i = 1,\ldots,N_s$ where $\mathcal{T}$ is the set of all measurable functions satisfying $T_{low} \leqslant T(t) \leqslant T_{high}$ for all time $t \in [t_0, t_f], B$ is a set of discrete experimental conditions $\beta_i = (\beta_1,\ldots,\beta_s)'$ and N_s is the number of design support points (i.e., number of designed experimental conditions $T_i(\cdot,\beta_i)$).

The following statistical model is considered at each t_k time instant [9]:

$$y_{ij}(t_k) = \eta(t_k,\theta;T_i(\cdot,\beta_i)) + \varepsilon_{ij}(t_k), \quad i = 1,\ldots,N_s;\ j = 1,\ldots,r_i. \tag{1}$$

where $\eta()$ is the true model of the process, sampled at given time instants $t_0 < t_1 < \cdots < t_k < \cdots < t_f$. It is assumed that all the errors $\varepsilon_{ij}(t_k)$ are normal and independent with each other $\forall i,j,k$. Moreover $\forall i,j,k, E(\varepsilon_{ij}(t_k)) = 0$ and $V(\varepsilon_{ij}(t_k)) = \sigma^2$.

$\sum_{i=1}^{N_s} r_i = N,\ r_i$ is the number of repetitions of an experiment located on a support point i, for an experimental condition $(T_i(\cdot),\beta_i)$.

The two competing monoresponse models $\mathcal{M}_1$ and $\mathcal{M}_2$ are expressed by $\eta_1(t,\theta_1;T(\cdot))$ and $\eta_2(t,\theta_2;T(\cdot))$ where $\theta_1 \in \Theta_1 \in \Re^{p_1}$ and $\theta_2 \in \Theta_2 \in \Re^{p_2}$ are vectors of unknown parameters and Θ_1 and Θ_2 are known compact sets. In the current discrimination procedures the initial conditions parameters β_i are excluded, further there will be no repetitions of the experiments, i.e., $r_i = 1\ \forall i$.

2.2. T_{12}-criterion

The first approach (T_{12}-criterion [2,1]) will be described here. The efficiency of this method is based on the fact that the minimum of the sum of squares for the lack of fit of the model is maximized. Thus, it takes into account the flexibility of the model to fit suitably the responses of the other model. Among others, this criterion has been proven to lead to an increase of the power of the discrimination statistical tests.

In this method the first model $\mathcal{M}_1$ is considered as the true model. Therefore parameter θ_1 is known and can be omitted giving $\eta(\cdot;\cdot) \equiv \eta_1(\cdot,\theta_1;\cdot)$.

The problem of discriminating between the two models is defined by the function [9]

$$T_{12}(\xi_N) = \min_{\theta_2 \in \Theta_2} \sum_{i=1}^{N_s} w_i \sum_{t_k=t_0}^{t_f} \|\eta(t_k;T_i(\cdot)) - \eta_2(t_k,\theta_2;T_i(\cdot))\|^2 \tag{2}$$

where the design ξ_N is defined by:

$$\xi_N = \begin{Bmatrix} (T_1(\cdot)), & \ldots, & (T_{N_s}(\cdot)) \\ w_1, & \ldots, & w_{N_s} \end{Bmatrix} \in \Xi. \tag{3}$$

The experimental conditions $T_i(\cdot)$ represent the design support points, w_i are weights at these support points with $\sum_{i=1}^{n} w_i = 1$ and Ξ is a feasible solution set.

2.3. Schwaab-approach

The second criterion (Schwaab-approach [3,4]) that has been used is typically based on a *sequential* approach and will be described below. The primary objective is the increase of the discrimination power but a decrease of the a decrease of the parameter estimate variances is obtained as well, with the use of the posterior covariance matrix of parameter estimates [3]. Differently from the previous method neither of the two models is considered as true. In this approach for sake of clarity ω is used as a reference for an experiment instead of ξ.

For discriminating between model $\mathcal{M}_1$ and $\mathcal{M}_2$, for experiment ω_{Ne+1} defined by $T_{N_e+1}(\cdot)$ and t_k (with N_e the number of available experiments either preliminary or discrimination experiments since it is a sequential approach) the discrimination function, that has to be maximized, is defined at every t_k by:

$$\mathbf{D}_{1,2}(\boldsymbol{\omega}_{N_e+1}) = d_{1,2}^T(\boldsymbol{\omega}_{N_e+1})\mathbf{V}_{1,2}^{-1}(\boldsymbol{\omega}_{N_e+1})d_{1,2}(\boldsymbol{\omega}_{N_e+1}) \tag{4}$$

with:

$$d_{1,2}(\boldsymbol{\omega}_{N_e+1}) = \hat{\eta_1}(\boldsymbol{\omega}_{N_e+1},\hat{\theta}_1) - \hat{\eta_2}(\boldsymbol{\omega}_{N_e+1},\hat{\theta}_2)$$

$$\mathbf{V}_{1,2}(\boldsymbol{\omega}_{N_e+1}) = 2\mathbf{V} + \mathbf{V}_1(\boldsymbol{\omega}_{N_e+1}) + \mathbf{V}_2(\boldsymbol{\omega}_{N_e+1})$$

$$\mathbf{V}_1(\boldsymbol{\omega}_{N_e+1}) = \mathbf{B}_1(\boldsymbol{\omega}_{N_e+1})\mathbf{V}_{\theta_1}(\boldsymbol{\omega}_{N_e+1})\mathbf{B}_1^T(\boldsymbol{\omega}_{N_e+1})$$

$$\mathbf{V}_{\theta_1}(\boldsymbol{\omega}_{N_e+1}) = \left[\mathbf{B}_1^T(\boldsymbol{\omega}_{N_e+1})\mathbf{V}^{-1}\mathbf{B}_1(\boldsymbol{\omega}_{N_e+1}) + \mathbf{V}_{\theta,1}^{-1}(\boldsymbol{\omega}_{N_e})\right]^{-1}$$

In the following formulas t_k is omitted for sake of simplicity. Here, $\hat{\eta_1}(\boldsymbol{\omega}_{N_e+1},\hat{\theta}_1)$ is the *prediction for model* $\mathcal{M}_1$ (similarly for model $\mathcal{M}_2$), $\mathbf{V}_{1,2}(\boldsymbol{\omega}_{N_e+1}) \in \Re^{K\times K}$ is the *posterior covariance matrix* of the differences between model predictions, K is the number of discrete time points t_k, $\mathbf{V} \in \Re^{K\times K}$ is the *covariance matrix of the experimental deviations* and $\mathbf{V}_1(\boldsymbol{\omega}_{N_e+1}) \in \Re^{K\times K}$ is the *covariance matrix of model prediction variations* calculated for model $\mathcal{M}_1$ (and similar for model $\mathcal{M}_2$). The model uncertainty includes the uncertainty on the model predictions and on the measurements [3,4].

$\mathbf{B}_1(\boldsymbol{\omega}_{N_e+1}) \in \Re^{K\times p_1}$ is the sensitivity matrix that contains the first derivatives of model m responses with respect to its parameters:

$$\left(\frac{\partial\eta_1(\boldsymbol{\omega}_{N_e+1},\theta_1)}{\partial\theta_1}\right)$$

$\mathbf{V}_{\theta_1}(\boldsymbol{\omega}_{N_e+1}) \in \Re^{p_1\times p_1}$ is the *posterior covariance matrix of model parameter estimates*. It can be seen that $\mathbf{V}_{\theta_1}$ consists two parts, i.e., the covariance matrix of the new designed experiment with experiment condition $T_{N_e+1}(\cdot)$ and the current covariance matrix of the parameter estimates. The covariance matrix of the estimated parameters is approximated by the inverse of the Fisher information matrix (FIM), since the errors are assumed independent [10].

3. Complementary tasks for model discrimination

Apart from the main optimization task there are some complementary tasks for the discrimination. Before the discrimination a preliminary experiment has to be designed for obtaining an initial estimate of the parameters. When an experiment is performed (either preliminary or discriminatory) it provides measurements that can be used in a parameter estimation task. Finally after the design of inputs for the discrimination a model adequacy test