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Performance assessment of the anticipatory approach to optimal experimental design for model discrimination

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ABSTRACT

The problem of model discrimination arises when several models are proposed to describe one and the same process, a situation encountered in many research fields. To identify the best model from the set of rival models, it may be necessary to collect new information about the process, and thus additional experiments have to be performed. Several approaches have been described in literature to design optimal discriminatory experiments. The anticipatory approach is one of them and is very appealing from a conceptual point of view because the expected information content of the newly designed experiment is considered, even before the experiment is performed (anticipatory design). In this paper, the performance of this approach is evaluated by comparing it with the performance of other, established approaches to optimal experimental design for model discrimination. To conduct this comparison four performance measures were defined: (1) whether the most appropriate model could be identified, (2) the number of additional experiments that have to be designed and performed to achieve model discrimination, (3) the quality of the parameter estimates of the model that is eventually identified as the most appropriate one, and (4) the rate at which the inadequate models are identified. The results clearly indicate that the anticipatory approach has its benefits and may be the preferred approach in many applications in (bio)chemical engineering and *in-silico* biology.

1. Introduction

Mathematical models are frequently used for the design, optimization and control of sometimes complex (bio)chemical processes. They also have the potential to be(come) very valuable tools to organize data and to consider interactions in complex systems in a rational way. In fact, they are increasingly used for this purpose in many research areas, especially in the emerging fields of systems biology [3,13,19] and synthetic biology [1,21]. In his influential overview paper [23], Kitano stresses that although the advances made in molecular biology to accurately gather quantitative experimental data have been enormous and will certainly continue, insights into the functioning of biological systems will not result from educated guesses alone, because of their intrinsic complexity. Instead, a combination of experimental and computational approaches is expected to resolve this challenging problem and, consequently, experimental design techniques will become increasingly important, as recognized by many researchers in the field [5,18,26,33,36,40].

The methods to design experiments that allow discriminating among rival models in an effective and efficient way, often referred to as optimal experimental design for model discrimination (OED/MD) or optimal experimental design for (model) structure characterization [41], will be the main focus of this paper. Indeed, when insight in a process is insufficient, several hypotheses can be postulated on how the process actually works. Each of these hypotheses can subsequently be translated into a unique model structure, and a set of rival models for the process arises. Obviously, one is especially interested in the model that describes the process under study in the most appropriate way. To identify this model from the set of rival models, it may be necessary to collect new information about the process, and thus additional experiments have to be performed.

The problem of model discrimination has been addressed in a number of ways (see [14] for a review), but common to all design criteria is the fact that the problem is tackled as and translated into an optimization problem. In the pioneering work of Hunter and Reiner (1965) [22], the difference between the model predictions is simply maximized (as explained in more detail further on). Although this approach does not take into account the uncertainties inherently involved in both the modelling phase and the experimentation phase, the basic rationale is still present in (as good as) all design criteria for OED/MD developed so far.

Buzzi-Ferraris and co-workers presented a design criterion that takes into account both the uncertainty on the measurements and the (resulting) uncertainty on the parameter estimates and model

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predictions [8]. The latter was further refined in [15] and [38], where the so-called anticipatory approach to OED/MD was introduced. In this approach, the expected information content of the newly designed experiment is considered, even before the experiment is performed (whence the term anticipatory design). In this way, a better estimate of the uncertainties can be achieved and an experiment with an increased discriminatory potential can be obtained. Because of the similarity of this approach with the conventional, state-of-the-art design criteria for optimal experimental design for parameter estimation (OED/PE), improved parameter estimates can be obtained in addition to model discrimination [15,38].

The objective of this paper is to determine whether different approaches to OED/MD differ in their ability to bring forth a series of (informative) discriminatory experiments. In the evaluation of their performance, four aspects are considered after applying them to a case study with nine rival models that was used in previous work on the subject [15–17]. The first aspect has to do with the outcome of the model discrimination procedure, that is, how the procedure ends (most appropriate model identified or all rival models rejected). The second aspect is related to the number of additional experiments that have to be (designed and) performed before the most appropriate model can be identified. It is clear that this is very important, as one obviously wants to minimize the number of additional experiments. The third aspect is related to the quality of the parameter estimates of the model that is eventually identified as the best one (if any). The fourth and last aspect of the performance evaluation is related to the rate at which the inadequate models are identified.

This paper is organised as follows. In Section 2, the basic rationale of optimal experimental design for model discrimination is explained and formalized in a mathematical manner. The section also presents the approaches to design optimal discriminatory experiments that were considered in this paper, as well as the four performance measures that were used in their evaluation. To conclude, this section explains how a case study was designed to investigate the performance of the OED/MD methods. The results obtained after applying these methods to the case study are presented and discussed in Section 3 and the conclusions are presented in Section 4.

2. Methods

2.1. Mathematical model representation

In what follows, general deterministic models in the form of a set of (possibly mixed) differential and algebraic equations are considered, using the following notations:

$$\dot{x}(t) = f(x(t), u(t), \theta, t); \quad x(t_0) = x_0 \tag{1}$$

$$\hat{y}(t) = g(x(t)) \tag{2}$$

where $x(t)$ is an n_s-dimensional vector of time-dependent state variables, $u(t)$ is an n_u-dimensional vector of time-varying inputs to the process, θ is an n_p-dimensional vector of model parameters taken from a continuous, realizable set Θ, and $\hat{y}(t)$ is an n_m-dimensional vector of measured response variables that are function of the state variables, $x(t)$. An experiment will be denoted as ξ, and is determined by the experimental degrees of freedom such as measurement times, initial conditions and time-varying or constant process inputs.

2.2. Parameter estimation

The values of the model parameters, which by definition do not change during the course of the simulation, have to be determined from experimental data. This process is called parameter estimation, and typically consists of minimizing the weighted sum of squared errors (WSSE) functional through an optimal choice of the parameters θ. The WSSE is calculated as follows

$$\mathrm{WSSE}\left(\hat{\theta}\right) = \sum_{k=1}^{n_e} \sum_{l=1}^{n_{sp_k}} \Delta\hat{y}\left(\xi_k, \hat{\theta}, t_l\right)' \cdot Q \cdot \Delta\hat{y}\left(\xi_k, \hat{\theta}, t_l\right), \tag{3}$$

where

$$\Delta\hat{y}\left(\xi_k, \hat{\theta}, t_l\right) = y(\xi_k, t_l) - \hat{y}\left(\xi_k, \hat{\theta}, t_l\right) \tag{4}$$

represents the difference between the vector of the n_m measured response variables and the model predictions at time t_l ($l = 1, \ldots, n_{sp_k}$) of experiment ξ_k ($k = 1, \ldots, n_e$). Further, n_e represents the number of experiments from which data is used for estimating the parameters, n_{sp_k} represents the number of sampling points in experiment ξ_k, and Q is an n_m-dimensional matrix of user-supplied weighing coefficients. Typically, Q is chosen as the inverse of the measurement error covariance matrix $\sum$ [28,35,42]. In this way, the measurement uncertainty is incorporated in the WSSE.

2.3. Model adequacy testing

To test a model's adequacy, a lack-of-fit test, as outlined for instance in [9–11], can be used. This test is based on the property of the WSSE-functional being a sample from a χ^2 distribution with $n - n_p$ degrees of freedom. However, this property only holds under two assumptions [11]: (i) the measurements are disturbed with random zero mean normally distributed noise with known (or a priori estimated) variance, and are not subject to systematic errors; and (ii) no model errors are present.

In this work, the data to which the models are fitted (see below) is generated by adding noise to the simulation results of which the characteristics are known, so the first assumption is always valid. Consequently, when the WSSE is significantly larger than the expected value of the appropriate $\chi^2_{n-n_p}$ distribution, one can conclude that the model is not able to describe the experimental data in a reasonable manner and the model can thus be rejected.

2.4. Optimal experimental design for model discrimination

In general, optimal experimental design is an optimization problem, where the optimum of a well-defined objective function is sought by varying the experimental degrees of freedom. This can be formalized as follows

$$\xi^{\star} = \arg\max_{\xi \in \Xi} T(\xi). \tag{5}$$

The experimental degrees of freedom, ξ, are restricted by a number of constraints that define a set of possible experiments, denoted as Ξ. These constraints are determined by the experimental setup and are specified before the start of the experimental design exercise. Note that in this context, the objective functions are also called design criteria, and these terms will be used as synonyms in the following.

2.4.1. Design criterion of Hunter and Reiner (1965)

Suppose, for simplicity, that one has to design an experiment to discriminate between two rival models ($m = 2$). It is clear that the data expected from the designed experiment should be predicted differently by the two models to allow for model discrimination. Hunter and Reiner translated this heuristic into an objective function [22] given by

$$T_{ij}(\xi) = \sum_{l=1}^{n_{sp}} \Delta\hat{y}_{ij}\left(\xi, \hat{\theta}_i, \hat{\theta}_j, t_l\right)' \cdot \Delta\hat{y}_{ij}\left(\xi, \hat{\theta}_i, \hat{\theta}_j, t_l\right), \tag{6}$$