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Model-based design of experiments for parameter precision: State of the art

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Abstract

Due to the wide use and key importance of mathematical models in process engineering, experiment design is becoming an essential tool for the rapid building and validation of these mechanistic models. Several experiment design techniques have been developed in the past and applied successfully to a wide range of systems. This paper is focused on the so-called model-based design of experiments (DOE) and aims at presenting an up-to-date state of the art in this important field. In order to provide an adequate and thorough background to this technique, a detailed description of the key elements of a model identification procedure (the model itself, the experiment, the statistical tools, etc.) and the major steps of a model-building strategy are introduced before focusing on the experiment design for parameter precision, which is the topic of this survey. An overview and critical analysis of the state of the art in this sector are proposed. The main contributions to model-based experiment design procedures in terms of novel criteria, mathematical formulations and numerical implementations are highlighted. A list of the most recent applications of these techniques in various fields (from chemical kinetics to biological modelling) is then presented highlighting the key role of model-based DOE in the process engineering area.

Keywords: Mathematical modelling; Model-based experiment design; Model validation; Non-linear dynamics; Optimisation; Parameter identification; Process engineering

1. Introduction

The use of dynamic mathematical models is common in process engineering since the detailed study of a scientific phenomenon very often leads to the formulation of a corresponding mathematical representation (a model) able to simulate its behaviour. In particular, high-fidelity models based on description of the underlying physics can allow a better understanding of the different phenomena which occur within the system under investigation, of the system overall behaviour and extrapolation to conditions beyond those encountered during laboratory experimentation. Therefore, building high-quality and validated models of process systems is key to many applications such as model-based product and process design, control and optimisation.

The capability of a model to represent a physical system must ultimately be assessed by comparing model predictions with actual measured behaviour. This is equivalent to say that all mathematical models must be validated: spectacularly erroneous conclusions can be drawn from simulation results obtained with inadequate models. When building mechanistic models, one uses a priori knowledge such as physical, chemical or biological laws to propose one or more possible alternatives. These laws largely dictate the model structure and such models invariably contain adjustable parameters that may have physical meaning. Typically, one desires to establish if it is at all possible to determine the parameter values and their maximum precision and to validate their estimates and the model statistically. However, collecting the data which are required to build and validate a model can be resource intensive. Furthermore, poorly planned experiments can cause a waste of time and resources and yield little useful information. Therefore, there is a need to develop such models in a systematic way in order to maximise the information obtained from each experiment and to minimise the number of analyses, the cost of materials and the time required. The technique of *design of experiments* (DOE) is an important link between the experimental and the modelling world. It aims at obtaining the maximum

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Fig. 1. Model validation procedure based on model-based experiment design techniques.

information from an experimental apparatus being modelled by devising experiments that will yield the most informative data, in a statistical sense, for use in parameter estimation and model validation. Before collecting the data, an experiment is therefore designed, i.e. it is decided how the system will be perturbed (initial conditions, which input variables are modified, when and how, etc.) and where, how and when the experimenter will observe the phenomena under investigation (which variables are measured, type and location of sensors, sampling schedules, etc.) (Walter and Pronzato, 1990).

Several experiment design techniques for model validation have been developed in the past and applied successfully to a wide range of systems. Fig. 1 illustrates the three main steps in a model validation procedure which employs model-based experiment design techniques. After one or more mathematical models have been proposed as candidates to describe the system under study, some preliminary tests may be carried out to investigate whether it is at all possible in principle to obtain information about the model from the prospective experimental data (if not, alternative models or experiments must be selected) (see Section 3.1). Some experiments may then be designed and performed in order to discriminate between the rival models which passed the preliminary tests (see Section 3.2). After the inadequate models have been rejected, a surviving model may undergo another experiment design study in order to improve the precision of its parameters (see Section 4). In each of these stages, if poor results are obtained, the various steps are repeated until a validated model is achieved. In principle, parameter estimation and model discrimination may also be alternated.

This paper is focused on the last step of this validation procedure, the so-called model-based DOE for parameter precision, and aims at presenting an up-to-date review of the state of the art in this field. The paper is structured as follows: first, the main experiment design techniques are introduced, together with the key elements of a model identification procedure. For completeness, the major steps of the model-building strategy illustrated in Fig. 1 (preliminary checks and model discrimination) are also but only briefly described. Then a detailed review and critical analysis of model-based experiment design for parameter precision are presented. The main contributions to model-based experiment design procedures in terms of novel objective functions, formulations and numerical implementations are highlighted. Finally, a list of the most recent applications of these techniques in various fields (from chemical kinetics to biological modelling) and an overview of possible future developments for model-based experiment design conclude this work.

1.1. Black-box, model-based and incremental approaches

Experiments followed by analysis of the collected data are frequently performed to measure the effects of one or more important factors on a response. For this purpose, a good experiment design is essential: when experiments are badly designed, even the more sophisticated data analysis techniques can fail to extract useful information from the data collected. The importance of designing a priori an experiment that can provide good information with minimum effort was understood very early in the scientific community. The first ideas of DOE were introduced by Fisher (1935), who described the basic problem of experiment design as deciding what pattern of factors combination (the design points) will best reveal the properties of the response and how this response is influenced by the factors. This type of DOE views an experiment as simply connecting inputs (factors) and outputs (responses) and is therefore called “black-box experiment design”. Its aim is to select the combinations of factor values to be employed that will provide the most information on the input–output relationship in the presence of variation (for a recent application see Chen and Wang, 2004). Many classical design methods were presented in numerous publications and reference is made to the books of Box et al. (1978), Box and Draper (1987) and Atkinson and Donev (1992) as authoritative texts on the subject.

The main class of statistical design techniques of this type is the so-called factorial methods. Such designs are straightforward to implement and their results can be very easily interpreted; these methods are created to measure the additive effects on a response for each of the input factors. In addition, the effects of interactions between factors can also be investigated. In case of a large number of factors, the experimental cost required is very high since all possible combinations of factor values must be taken into consideration. Usually in this case, fractional factorial designs can be used to reduce the size of the design matrix (Box et al., 1978). These factorial methods are not suited to the situation where there are some constraints on the outputs (or internal states of the experiment such as temperatures, pressures, etc.). They are also not well suited to handle dynamic experiments, where both “factors” and “responses” may not be single values (say, a constant temperature, a conversion) but complex time profiles of the same variables. However, in view of their simplicity these methods are still widely used in the DOE, particularly in the biological area (see, for example, the recent publications of Swinnen et al., 2005; Valdramidis et al., 2006), but will not be discussed any further here.

As opposed to these "black-box" statistical experiment design methods, another form of optimal design has been developed which takes explicit advantage of some (usually incomplete) knowledge of the structure of the underlying system, as represented by a mathematical model. This type of design is the focus of this paper and, in order to distinguish it from the "black-box" case just described, the denomination of "model-based experiment design" will be used in the remaining of this work. In particular, models in the form of a rather general class of Differential and Algebraic Equation (DAE) systems will be considered. These model-based experiment design techniques can be applied to any system including linear, non-linear, steady state or dynamic processes. Their goal is typically to assist in the rapid development, refinement and statistical validation of deterministic process models.

What characterises the model-based experiment design approach is:

1. the explicit use of the model equations (including any constraint) and current parameters to predict the "information content" of the next experiment (through the evaluation of some suitable objective function), and
2. the application of an optimisation framework to the solution of the resulting numerical problem.

Early developments in experiment design considered mainly steady-state models (both linear and non-linear model forms) and the applications reported in the literature are very broad: from engineering and science to social disciplines. Pioneering works in the application of this technique to chemical models (in particular reaction kinetics) are the studies of Box and Lucas (1959), Box and Hunter (1965a, b), Draper and Hunter (1966, 1967a, b), Box (1968), Hill et al. (1968) and Hunter et al. (1969). The extension of experiment design concepts to dynamic experiments/models has been a slow process (Shirt et al., 1994) although already in 1977 the potential benefits of these techniques for dynamic studies were amply recognised (Goodwin and Payne, 1977). The review of Mehra (1974b) is the first detailed survey of the field of optimal input design for dynamic systems and covers the most significant works on the subject over the previous two decades while presenting some new original results for linear discrete time models. Shirt et al. (1994) noted that the issue of optimal input signal selection to identify dynamic models was treated for the first time in the case of differential equation models by Espie and Macchietto (1989). These authors formulated the design of transient experiments as an optimal control problem and proposed a robust and efficient algorithm valid both for model discrimination and improvement of parameter precision. They were the first to attempt an extension of the Hunter and Reiner (1965) criterion for model discrimination and of the concept of marginal posterior density covariance (Box and Lucas, 1959) for parameter precision to the case of dynamic systems described by DAEs.

Around the same time, Munack (1988) and Munack and Posten (1989) dealt with the problem of identifying the parameters of a Monod model and showed that, while with batch experiments they are practically non-identifiable, a fed-batch experiment with an optimally designed feed-rate can easily solve the problem. To our knowledge, these works represent the first application of model-based experiment design techniques to the biological field, which, as highlighted later, is now one of the areas (together with chemical kinetics) where these methods are becoming essential (see Sections 4 and 5).

More recently, several studies have tried to improve the experiment design method by developing new objective functions and/or novel and more efficient algorithms for the numerical solution of the underlying optimisation problem (see Section 4).

For completeness, a different approach to (kinetic) model identification is noted here, which was recently proposed by Marquardt and co-workers (see Bardow and Marquardt, 2004a, b; Bardow et al., 2005; Brendel et al., 2006; Marquardt, 2005) and applied to different systems such as Raman-spectroscopy experiments for determination of concentration-dependent diffusion coefficients (Bardow et al., 2005) or an industrially relevant chemical process: the acetoacetylation of pyrrole with diketene (Brendel et al., 2006). The authors oppose their method (*incremental identification* approach) to the traditional model-based procedure, which they call *simultaneous model identification*. Based on physical insight, the authors propose the decomposition of the identification problem into a set of nested sub-problems, namely the calculation of reaction fluxes, reaction stochiometry, reaction rates (without assuming any kinetic structure) and finally kinetic laws. The main advantage of this procedure is the significant reduction in the computational time (with respect to the traditional model-based discrimination approach) for multiple reaction systems with a large number of kinetic model candidates, thanks to the simplicity of the individual sub-problems. The approach, however, requires a significant amount of reliable data to overcome the bias introduced by the flux estimation procedure and, in some cases, only a partial identification of the system can be obtained. In this situation, however, the approach can be easily and effectively coupled with a simultaneous model-based identification method for each sub-problem. As noted, the proposed sub-problem decomposition only applies to the specific physical situations considered.

2. Fundamentals

2.1. Model-building strategy

Based on earlier work of Espie and Macchietto (1989), Zullo (1991) and Asprey and Macchietto (2000), a systematic procedure for the development and statistical verification of dynamic process models is outlined in Fig. 2. This procedure involves up to three stages:

- a preliminary analysis based on the concepts of identifiability and distinguishability to enable a first selection between rival models, or analysis of a single model, before collecting any data (Fig. 2a);
- the optimal DOE to discriminate between rival models that passed step 1 (Fig. 2b);

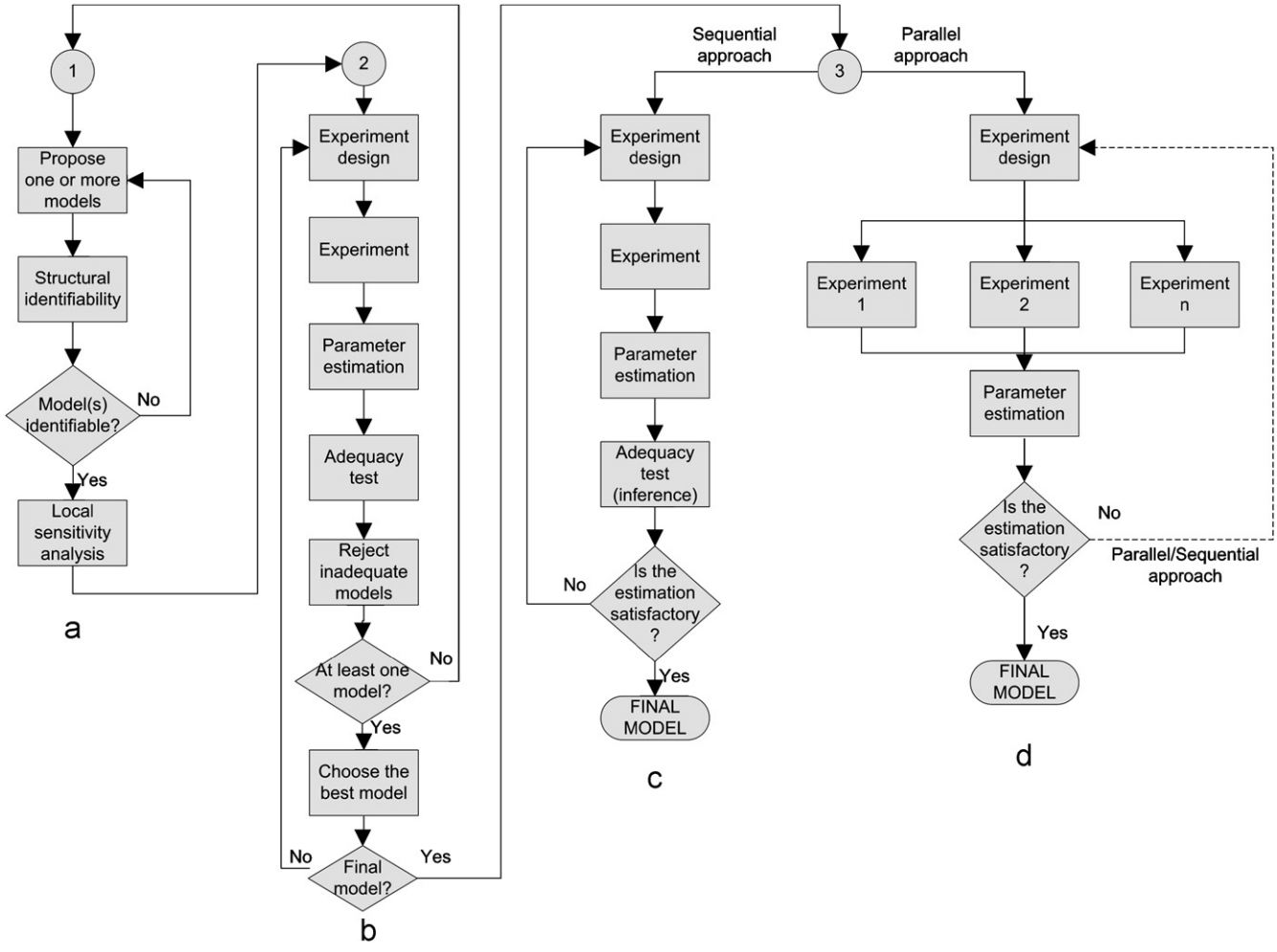

Fig. 2. The overall model-building strategy (based on the schemes reported in Asprey and Macchietto, 2000 and Galvanin et al., 2007) with reference to sequential, parallel and parallel–sequential approaches to model-based design of experiments for parameter precision.

- the optimal DOE to improve the precision of the parameter estimates for a model selected in step 2.

Of course, it may well be appropriate to skip some steps, for example, the first two, and just carry out a DOE for precise parameter estimation for a single candidate model. Since the information available at each step is often scarce, incomplete or imprecise, the approach required to validate a model statistically is necessarily iterative, with several loops back within and between the main steps above.

There are three main approaches to an iterative DOE. Sequential is the most used strategy (Fig. 2c); see, for example, Bernaerts et al. (2002), DiStefano (1981), Ford et al. (1985, 1989), Hosten and Emig (1975), Kalogerakis and Luus (1983, 1984), Pinto et al. (1990), Walter and Pronzato (1997) and Wu (1985). As proposed by Galvanin et al. (2007) and discussed later in the paper, multiple experiments may be performed sequentially or in parallel depending on the available experimental equipment, leading to a parallel (Fig. 2d) and mixed parallel/sequential iterative strategies.

In a strictly sequential approach, the basic idea consists in improving the initial choice of the parameter values by alternating experiment design and identification of the parameters. Each new experiment is designed using the estimates obtained from the previous estimation step as nominal values for the parameters (Fig. 2c), until the estimation can be considered statistically satisfactory. In a parallel approach (Fig. 2d), several experiments are designed simultaneously (all adopting the same nominal values for the parameters) and then performed in the laboratory. Using the data collected from all the parallel optimal experiments, the parameters are estimated and their adequacy assessed. If the information obtained from the n_{exp}^{P} experiments designed in parallel is shown to be insufficient after the parameter estimation, the procedure can be repeated (parallel/sequential approach).

2.2. The model

The mathematical model considered is in the form of a very general system of implicit DAEs represented by:

- a p-dimensional set of parameters $\boldsymbol{\theta}$ usually to be determined. The vector $\hat{\boldsymbol{\theta}}$ contains the best currently available estimate of their values; these values are characterised by a certain

precision, which is defined by suitable statistical information, in particular the parameter variance–covariance matrix, $\boldsymbol{\Sigma}_\theta$ (see Section 4.2);

- an n_u-dimensional set of time-varying controls or inputs to the process, $\mathbf{u}(t)$, which usually can be manipulated during the experiment (see Section 4.1);
- an $n_{\bar{w}}$-dimensional set of constant controls, $\bar{\mathbf{w}}$, which again can be manipulated during the experiment;
- an n_s-dimensional set of time-dependent variables, $\mathbf{x}(t)$, defining the state of the system;
- an n_{resp}-dimensional set of measured response variables, $\widehat{\mathbf{y}}(t)$, that are functions of the state variables, $\mathbf{x}(t)$;
- an n_{eq}-dimensional set of DAEs $\mathbf{f}$ and an n_{resp}-dimensional set of relations $\mathbf{h}$ between the measured response variables $\widehat{\mathbf{y}}(t)$ and the state variables $\mathbf{x}(t)$:

$$\begin{cases} \mathbf{f}(\dot{\mathbf{x}}(t), \mathbf{x}(t), \mathbf{u}(t), \bar{\mathbf{w}}, \boldsymbol{\theta}, t) = 0, \\ \widehat{\mathbf{y}}(t) = \mathbf{h}(\mathbf{x}(t)), \end{cases} \tag{1}$$

where $\mathbf{f}$ is assumed to have continuous first partial derivatives with respect to its arguments, $\dot{\mathbf{x}}(t)$ is an n_{diff}-dimensional vector of differential variables and t is the time, with t between 0 and τ, the duration of the experiment. In most cases, $\mathbf{h}(\mathbf{x}(t))$ is simply a "selector" function, selecting those state variables that are in fact measured;

- an n_{diff}-dimensional set of equations $\mathbf{y^0}$ defining the initial conditions (for $t = t_0 = 0$):

$$\mathbf{y^0} = \begin{cases} \mathbf{f}(\dot{\mathbf{x}}(t_0), \mathbf{x}(t_0), \mathbf{u}(t_0), \bar{\mathbf{w}}, \boldsymbol{\theta}, t_0) = 0, \\ \widehat{\mathbf{y}}(t_0) = \mathbf{h}(\mathbf{x}(t_0)), \end{cases} \tag{2}$$

where $\mathbf{y^0}$ is a set of $\mathbf{x}$, $\dot{\mathbf{x}}$ sufficient to establish initial conditions for the system, here assumed of index 1 (for index greater than 1 these conditions are modified slightly, without loss of generality in respect of the experiment design methods discussed). The vector $\mathbf{y^0}$ is not to be confused with the measured response vector $\widehat{\mathbf{y}}$;

- an n_{sp}-dimensional set of sampling times $\mathbf{t}_{\text{sp}}$ when the measured response variables $\widehat{\mathbf{y}}(t)$ are sampled and collected. Here it is assumed for simplicity that all measurements are sampled at the same time. To allow for distinct responses to be sampled at different times, one such $\mathbf{t}_{\text{sp},r}$ vector can be defined for each measured variable r, $(r = 1, \ldots, n_{\text{resp}})$;
- an n_c-dimensional set of equality and/or inequality constraints on the state variables $\mathbf{x}(t)$ identified by particular limitations of the experimental apparatus and/or procedure:

$$\mathbf{x}(t)|^L \leqslant \mathbf{x}(t) \leqslant \mathbf{x}(t)|^U, \tag{3}$$

where the superscripts L and U indicate the lower and upper bounds, respectively.

Once the control variables $\mathbf{u}(t)$ and $\bar{\mathbf{w}}$, the parameters $\boldsymbol{\theta}$ and the duration of the experiment τ are fixed to suitable values, the trajectories $\mathbf{x}(t)$, $\dot{\mathbf{x}}(t)$ and $\widehat{\mathbf{y}}(t)$ remain to be determined and can be calculated by integrating the DAE system (1) subject to constraints (3). The definition of a feasible range for the control vectors $\mathbf{u}(t)$, $\bar{\mathbf{w}}$, $\mathbf{t}_{\text{sp}}$ and τ to match those of the experimental apparatus allows the experiment design space $\boldsymbol{\Phi}$ and the experiment responses to be modelled (see Section 4.1). Finally, the definition of a feasible region for the parameters (typically in the form of upper and lower bounds) defines the allowable parameter space $\boldsymbol{\Theta}$.

2.2.1. Sensitivity of responses to parameters (according to the model)

As we are interested in fitting a model to experimental data and establishing the model best parameter estimates, it is important to evaluate how much a variation of the estimated parameter vector influences the predicted output trajectories of the model. For this purpose the local first-order sensitivity of the measured responses to the parameters is useful, defined as an $n_{\text{resp}} \times p$ matrix $\mathbf{Q}$ (where n_{resp} is the number of responses and p the number of parameters):

$$\mathbf{Q} = \begin{bmatrix} \dfrac{\partial \widehat{y}_1}{\partial \theta_1} & \cdots & \dfrac{\partial \widehat{y}_1}{\partial \theta_p} \\ \cdots & \cdots & \cdots \\ \dfrac{\partial \widehat{y}_{n_{\text{resp}}}}{\partial \theta_1} & \cdots & \dfrac{\partial \widehat{y}_{n_{\text{resp}}}}{\partial \theta_p} \end{bmatrix}. \tag{4}$$

The sensitivity coefficients in Eq. (4) are obtained from partial differentiation of the model equations (1), from which the following expression is obtained (assuming that the measured responses $\widehat{\mathbf{y}}$ are a subset of the state variable $\mathbf{x}$):

$$\frac{\mathrm{d}}{\mathrm{d}t}\frac{\partial \widehat{\mathbf{y}}}{\partial \boldsymbol{\theta}} = \frac{\partial \mathbf{f}}{\partial \widehat{\mathbf{y}}} \cdot \frac{\partial \widehat{\mathbf{y}}}{\partial \boldsymbol{\theta}} + \frac{\partial \mathbf{f}}{\partial \boldsymbol{\theta}} \tag{5}$$

with $\partial \mathbf{f}/\partial \mathbf{y}$ as the Jacobian of the system. In dynamic models, the matrix $\mathbf{Q}$ is time varying and has a value at each instant t. It may be obtained by integration of Eq. (5) (together with the model equations (1) or afterwards) from the initial conditions $\mathbf{Q}(t_0) = 0$. The dynamic sensitivity matrix $\mathbf{Q}_r$ $(n_{\text{sp}} \times p)$ of the rth response variable computed at each of the n_{sp} sampling times is defined as

$$\mathbf{Q}_r = \begin{bmatrix} \left.\dfrac{\partial \widehat{y}_r}{\partial \theta_1}\right|_{t_1} & \cdots & \left.\dfrac{\partial \widehat{y}_r}{\partial \theta_p}\right|_{t_1} \\ \cdots & \cdots & \cdots \\ \left.\dfrac{\partial \widehat{y}_r}{\partial \theta_1}\right|_{t_{n_{\text{sp}}}} & \cdots & \left.\dfrac{\partial \widehat{y}_r}{\partial \theta_p}\right|_{t_{n_{\text{sp}}}} \end{bmatrix}. \tag{6}$$

Both $\mathbf{Q}$ and $\mathbf{Q}_r$ depend on the conditions where they have been evaluated (initial conditions, trajectories, sampling times, etc.) and, clearly, also on the current values of the parameters used in model (1). They are therefore only locally valid.

2.3. The experiment

The experimental conditions which define an experiment $\boldsymbol{\varphi}_E$ (within a feasible experimental space, $\boldsymbol{\Phi}_E$) include:

- quantities that can be controlled such as:
  - time-varying control variables, $\mathbf{u}_E(t)$,
  - constant controls, $\bar{\mathbf{w}}_E$,

- sampling times $\mathbf{t}_{sp}$ and measured responses $\mathbf{y}(\mathbf{t}_{sp})$,
- initial conditions, $\mathbf{y}_E^{\mathbf{0}}$,
- the duration of the experiment τ_E;

- quantities that cannot be controlled such as:
  - the systematic errors of the experiment, $\boldsymbol{\eta}_s$ (not measurable),
  - the random errors of the experiment, $\boldsymbol{\eta}$ (not directly measurable).

The variables $\boldsymbol{\eta}_s$ and $\boldsymbol{\eta}$ disturb our observation of the system and the experimenter should minimise them. While the systematic errors can be eliminated once the cause of the problem has been identified (such as, for example, interferences between measurement systems, imprecise calibrations, etc.), the random errors (such as, for example, measurement errors) will always be present. They are responsible for the fluctuations in the response values, which can be observed when exactly the same experiment is repeated. After an experiment has been performed, its outcome is the n_{resp}-dimensional vector of the measured responses $\mathbf{y}(t)$:

$$\mathbf{y}(t) = f'(\mathbf{y}_E^{\mathbf{0}}, \mathbf{u}_E(t), \bar{\mathbf{w}}_E, \boldsymbol{\eta}_s, \boldsymbol{\eta}, \tau_E) \quad \forall t \in \mathbf{t}_{sp}, \tag{7}$$

which depend on the specific realisation of the experimental space mentioned above.

The n_{resp}-dimensional vector of the responses predicted by the model $\widehat{\mathbf{y}}(t)$ is a function of the p-dimensional set of parameters $\boldsymbol{\theta}$, the state and differential variables $\mathbf{x}(t)$ and $\dot{\mathbf{x}}(t)$, the initial conditions $\mathbf{y}^{\mathbf{0}}$, the process duration τ and the control variables $\mathbf{u}(t)$ and $\bar{\mathbf{w}}$:

$$\widehat{\mathbf{y}}(t) = f(\dot{\mathbf{x}}(t), \mathbf{x}(t), \mathbf{u}(t), \bar{\mathbf{w}}, \boldsymbol{\theta}, \tau). \tag{8}$$

If $\boldsymbol{\Phi}=\boldsymbol{\Phi}_E$, $\mathbf{u}=\mathbf{u}_E$, $\bar{\mathbf{w}}=\bar{\mathbf{w}}_E$, $\tau=\tau_E$ and $\mathbf{y}^{\mathbf{0}}=\mathbf{y}_E^{\mathbf{0}}$ (the experimental space, input and constraints for the model and the experiment are set to be the same), and assuming the model structure and the parameter values are correct (both assumptions to be verified), then the predicted responses (8) differ from the experimentally measured ones (7) only because of the error terms $\boldsymbol{\eta}_s$ and $\boldsymbol{\eta}$. If all the causes of systematic errors are eliminated before performing the experiments, it is possible to write

$$\mathbf{y}(t) = \widehat{\mathbf{y}}(t) + \boldsymbol{\eta}(t) \quad \forall t \in \mathbf{t}_{sp}. \tag{9}$$

2.3.1. Response and measurement errors

The choice of which variables to measure during an experiment depends on several considerations, mainly the availability of sampling devices and analytical methods, the characteristics of the equipment and resource limitations (in time and/or cost). This choice may significantly affect the outcome of an experiment design calculation: completely different experiments can be designed if only one or two or more responses can be measured, or a response can be measured more precisely.

According to the assumptions of the previous section, the measured responses of the jth experiment can be expressed in vector form as

$$\mathbf{y}_j(t) = \widehat{\mathbf{y}}_j(t) + \boldsymbol{\eta}_j(t), \quad j = 1, \ldots, n_{exp}, \tag{10}$$

where $\boldsymbol{\eta}_j$ is the n_{resp}-dimensional vector of the experimental measurement errors in experiment j. This stochastic component is assumed to be multivariate normally distributed with

$$E[\boldsymbol{\eta}_n] = 0 \quad \text{and} \quad E[\boldsymbol{\eta}_n \boldsymbol{\eta}_r] = \begin{cases} \boldsymbol{\Sigma}_y & n = r, \\ 0 & n \neq r, \end{cases} \tag{11}$$

where $\boldsymbol{\Sigma}_y$ is the $(n_{resp} \times n_{resp})$ variance–covariance matrix of the experimental errors:

$$\boldsymbol{\Sigma}_y = \begin{bmatrix} \sigma^2_{y_1} & \sigma^2_{y_1 y_2} & \cdots & \sigma^2_{y_1 y_{n_{resp}}} \\ \sigma^2_{y_2 y_1} & \sigma^2_{y_2} & \cdots & \vdots \\ \vdots & \vdots & \ddots & \vdots \\ \sigma^2_{y_{n_{resp}} y_1} & \cdots & \cdots & \sigma^2_{y_{n_{resp}}} \end{bmatrix}. \tag{12}$$

Eq. (11) implies that measurements from different experimental settings are independent but measurements of multiple responses taken under the same experimental conditions are possibly correlated (the non-diagonal elements of matrix $\boldsymbol{\Sigma}_y$ quantify these correlations). The diagonal elements in Eq. (12) represent the variances of the various responses, which can often be modelled in the following analytical form:

$$\sigma^2_{y_i}|_{Exp.j} = \sigma^2_{ij} = \omega_i^2 (\widehat{y}^2_{ij})^{\gamma_i/2}, \tag{13}$$

where $\widehat{y}_{ij}$ represents the ith response of experiment j as predicted by the model, ω_i the standard deviation of the ith response and γ_i its so-called heteroscedastic factor. It is worth noting that, if the measurement variance model is incorrect, the estimation of the measurement error is also erroneous. A different notation (with an additional index for the experiment) has been used in Eq. (13) and will be adopted hereafter (for the sake of clarity) to express the model predicted responses of a certain experiment. The parameters ω_i and γ_i define the specific variance model considered (Table 1) and are generally grouped together into a single vector, $\boldsymbol{\beta}$.

In matrix notation, we may define $\hat{\mathbf{Z}}$ as the residual matrix ($\hat{\mathbf{Z}}=\mathbf{Y}-\widehat{\mathbf{Y}}$) where $\mathbf{Y}$ and $\widehat{\mathbf{Y}}$ are the matrices of the experimental measurements and of the responses predicted by the model for each experiment.

2.4. Parameter estimation and model adequacy

The estimation of model parameters $\boldsymbol{\theta}$, given a new set of data, can be done using standard methods, usually based on maximum likelihood estimators and software. If required, such estimation will also provide values for parameters $\boldsymbol{\beta}$ in the measurement variance models (Table 1). After an estimation is performed, it is of primary importance to statistically assess the reliability and adequacy of the model and of the new parameter estimates. This can be done using standard checks (i.e. on residuals distributions) and statistical tests. In order to check whether or not the model explains the observed data in a satisfactory way, a lack-of-fit test is usually adopted (Hines et al., 2003). The sum of squares of residuals (the deviations between experimental data and simulated profiles), $S_r(\boldsymbol{\theta})$, consists for

Table 1
Variance models and values assumed by the parameters of vector $\boldsymbol{\beta}$

Model	Mathematical description	ω	γ
Constant variance	$\sigma^2 = \omega^2$	Any	0
Constant relative variance	$\sigma^2 = \omega^2(\widehat{y}^2)$	Any	1
Heteroscedastic variance	$\sigma^2 = \omega^2(\widehat{y}^2)^\gamma$	Any	Any within the range [0–1]
Linear variance	$\sigma = \bar{\alpha} \cdot \widehat{y} + \bar{\beta}$ with any possible value for $\bar{\alpha}$ and $\bar{\beta}$		

any parameter estimation of a contribution due to measurement noise and a contribution due to lack-of-fit of the model:

$$S_r(\boldsymbol{\theta}) = \sigma_p^2 + \text{LOF}. \tag{14}$$

If the pure error variance, σ^2, is known, the LOF can be estimated using a χ^2-value:

$$\chi^2 = \frac{S_r(\hat{\boldsymbol{\theta}})}{\sigma^2} = \frac{\text{tr}(\hat{\mathbf{Z}}\boldsymbol{\Sigma}_y^{-1}\hat{\mathbf{Z}}^{\text{T}})}{\sigma^2} \tag{15}$$

with $\hat{\mathbf{Z}}$ as the residual matrix. This χ^2-value can be tested by reference to a χ^2-distribution with $(n - p)$ degrees of freedom (n is the total number of available data). Smaller χ^2-values than those in the distribution indicate an adequate fit of the model to the observed data since this implies that the deviations between experimental data and simulated profiles can be entirely attributed to random errors (measurement errors). In this case, the model can be considered adequate to represent the physical system under investigation. When the pure error of the experimental data, σ^2, is not known, repeat measurements are required to estimate the variance:

$$s^2 = \frac{\sum_{k=1}^{r}(y_k - \bar{y})^2}{r - 1}, \tag{16}$$

where y_k and $\bar{y}$ are, respectively, the kth measurement and the average of the r repeated measurements of response y. Using the estimated variance s^2, the LOF can be calculated using an F-value:

$$F = \frac{(S_r(\hat{\boldsymbol{\theta}}) - r \cdot s^2)/(n - p - r)}{s^2}, \tag{17}$$

where n is the total number of observations available and p is the number of parameters. This F-value can be tested by reference to an F-distribution with $(n-p-r)$ and $(r-1)$ degrees of freedom. Values of F lower than those in the distribution suggest a satisfactory fit of the model to the data.

In order to establish the statistical significance of the parameter estimates, a Student t-value for each parameter is usually defined (Asprey and Naka, 1999):

$$t_i = \frac{\hat{\theta}_i}{\sqrt{V_{ii}}}, \tag{18}$$

where V_{ii} is the variance of the ith parameter (i.e. the ith diagonal element of the parameter variance–covariance matrix). The t-value may be tested by reference to a t-distribution with $(n-p)$ degrees of freedom; higher t-values than those in the distribution tend to indicate reliable estimates. Very low t-values suggest that confidence intervals or regions involving that parameter may include zero and such a situation means that the parameter could be statistically dropped from the model. It should be noted that sometimes in multi-parameter models, a t-value might be low because of high correlation between parameters.

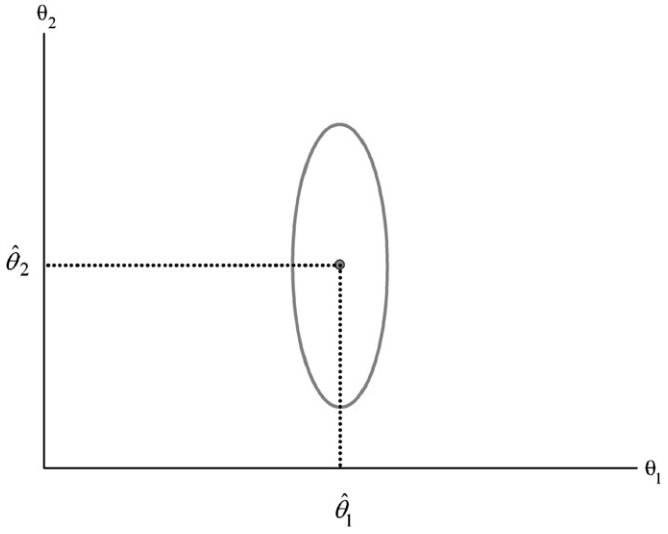

Fig. 3. Example of a joint confidence region for a pair of parameters. $\hat{\theta}_1$ and $\hat{\theta}_2$ are the estimated values of the true parameters θ_1 and θ_2.

Besides the t-test, joint confidence regions are another very suitable tool to assess the reliability of parameter estimates; for example, from Fig. 3 it is immediately evident that parameter θ_2 is estimated with a larger uncertainty than parameter θ_1. Linear approximation inference regions can be obtained from a first-order Taylor series approximation to the expectation function (Asprey and Naka, 1999). In this case, the linear approximation variance–covariance matrix is expressed as

$$\mathbf{V} = (\mathbf{Q}^{\text{T}}\mathbf{Q})^{-1}s^2 = (\mathbf{Q}^{\text{T}}\mathbf{Q})^{-1}S_r(\hat{\boldsymbol{\theta}})/(n - p), \tag{19}$$

where s^2 is the variance estimate, $S_r(\boldsymbol{\theta})$ the residual sum of squares and n and p the number of observation and parameters, respectively. $\mathbf{Q}$ is the derivative matrix evaluated at $\hat{\boldsymbol{\theta}}$ whose npth element is

$$q_{np} = \left.\frac{\partial \widehat{y}_n}{\partial \theta_p}\right|_{\hat{\boldsymbol{\theta}}}, \quad i = 1, 2, \ldots, p, \tag{20}$$

where $\widehat{y}_n$ represents the nth model response. A linear approximation $(1-\alpha)$ joint confidence region for the parameters can therefore be calculated as

$$(\boldsymbol{\theta}-\hat{\boldsymbol{\theta}})^{\mathrm{T}}\mathbf{Q}^{\mathrm{T}}\mathbf{Q}(\boldsymbol{\theta}-\hat{\boldsymbol{\theta}}) \leqslant p \cdot s^2 \cdot F_{(p,n-p,\alpha)}, \tag{21}$$

where α is the probability level (usually 90–95%), F the Fisher statistical distribution and $\hat{\boldsymbol{\theta}}$ the parameter estimate. As pointed out by several authors (Bates and Watts, 1988; Watts, 1994; Witkowsky and Allen, 1993), these linearisation techniques apply only approximately to non-linear models and in case of high non-linearity can be quite unreliable.

3. Model-building strategy

Although the main focus of this paper is experiment design for parameter precision, the first two steps of the overall model-building strategy illustrated in Fig. 2 are also briefly reviewed for completeness.

3.1. Preliminary analysis of the models

Given a candidate set of models and a proposed set of variables to be measured, the aim of a preliminary analysis is to identify a priori whether or not it is possible:

- to design an experiment such that the model parameters can be *uniquely* identified (identifiability),
- to distinguish between the different model structures (distinguishability).

Past approaches for testing identifiability in non-linear dynamic models used differential geometry and approximated the model locally by its input–output mapping adopting functional expansions (Walter, 1987). Coefficients of these expansions can then be evaluated at two different parameter sets, $\boldsymbol{\theta}$ and $\boldsymbol{\theta}^*$, and used to form systems of non-linear algebraic equations whose unique solution $\boldsymbol{\theta}=\boldsymbol{\theta}^*$ ensures identifiability (Asprey and Macchietto, 2000). The main disadvantage of this symbolic procedure is that it can be applied only to very small models with a number of equations and parameters in the order of 10. In order to overcome this drawback, Asprey and Macchietto (2000) proposed an optimisation-based approach, which requires the calculation of global maxima and minima of quadratic expressions. According to this procedure, a model is *globally identifiable* if the largest distance (global maximum) between two parameter vectors that still give (essentially) the same response trajectories is small. A model is *distinguishable* from a second model if the largest value of the minimum distance (global minimum) between the responses of the two models over the time horizon of interest is sufficiently large. This approach is not limited to any particular model form or size; however, semi-infinite or max–min dynamic optimisation problems must be solved (a complex challenge since a global solution is required). This optimisation-based identifiability method was successfully applied by Asprey and Mantalaris (2001) to an unstructured hybridoma cell model; the authors were able to conclude, prior to any experimentation, that the parameters could not be uniquely identified. For a more detailed discussion on these topics and the mathematical formulations, reference is made to Asprey and Macchietto (2000).

3.1.1. Parameter estimability

Given a model in the form of Eq. (1), the goal here is to verify whether or not it is possible to estimate its parameters. This test is called "parameter estimability" or "quantitative identifiability" (Vajda et al., 1989) and checks for ill-conditioning of the estimation problem. Using the concepts of sensitivity analysis introduced in Section 2.2.1, the parameter estimability matrix $\mathbf{P}_E$ can be formed (Shaw, 1999) and its rank evaluated:

$$\mathbf{P}_E = \begin{bmatrix} \left.\frac{\partial \widehat{y}_1}{\partial \theta_1}\right|_{t_1} & \cdots & \left.\frac{\partial \widehat{y}_1}{\partial \theta_p}\right|_{t_1} \\ \cdots & \cdots & \cdots \\ \left.\frac{\partial \widehat{y}_{n_{\mathrm{resp}}}}{\partial \theta_1}\right|_{t_1} & \cdots & \left.\frac{\partial \widehat{y}_{n_{\mathrm{resp}}}}{\partial \theta_p}\right|_{t_1} \\ \left.\frac{\partial \widehat{y}_1}{\partial \theta_1}\right|_{t_2} & \cdots & \left.\frac{\partial \widehat{y}_1}{\partial \theta_p}\right|_{t_2} \\ \cdots & \cdots & \cdots \\ \left.\frac{\partial \widehat{y}_{n_{\mathrm{resp}}}}{\partial \theta_1}\right|_{t_{n_{\mathrm{sp}}}} & \cdots & \left.\frac{\partial \widehat{y}_{n_{\mathrm{resp}}}}{\partial \theta_p}\right|_{t_{n_{\mathrm{sp}}}} \end{bmatrix}. \tag{22}$$

If $\mathrm{rank}(\mathbf{P}_E) < p$, the sensitivity coefficients are not linearly independent (Asprey and Naka, 1999; Beck and Arnold, 1977; Shaw, 1999) and it is not possible to estimate all the parameters. It is worth noting that the values of $\mathbf{P}_E$ are all local (based on specific trajectories, values of the parameters, etc.), hence the test here presented is a "local" estimability test. It is quite possible that estimability problems that arise for a particular set of conditions (parameter values, trajectories, etc.) may well disappear in different conditions.

Overall, these preliminary tests may be of some help, but there is still ample room for improvement on practical methods to assist in establishing a priori whether a model is structurally or numerically not identifiable, or not identifiable from a specific candidate experiment (measured variables, measurement precision, etc.).

3.2. Experiment design for model discrimination

Only a very brief review of the main issues of model discrimination is presented here. The question of model discrimination occurs when n_m rival models have been proposed to describe a system and it is not certain whether one is "best", or in fact they are all equivalently good (or equivalently bad), in a statistical sense. As mentioned earlier, the residuals obtained after parameter estimation result from two main sources: experimental data noise and model lack-of-fit. Model discrimination experiment design aims at maximising the contribution due to the lack-of-fit so that the divergence between the predictions of alternative models is enhanced, thus facilitating

comparison (Sidoli et al., 2004). This problem was first addressed by Hunter and Reiner (1965) for a case with two rival models and their approach required maximising the average difference in the model predictions.

Box and Hill (1967) noted that this criterion did not take into account the variance of the predicted responses and suggested an improvement. In the same paper, the authors proposed a new approach based on the concept of entropy and Bayesian analysis for a single-response case. This method was extended to the multi-response case by Draper and Hunter (1966).

An alternative approach was taken by Buzzi-Ferraris and co-workers (Buzzi-Ferraris and Forzatti, 1983; Buzzi-Ferraris et al., 1984), who proposed as a criterion for the design the ratio of the average squared difference between predictions to the average variance in the predictions:

$$T = \frac{s_N^2}{s_D^2} = \frac{\sum_{i=1}^{n_m}\sum_{j=i+1}^{n_m}(\widehat{y}_i(x) - \widehat{y}_j(x))^2}{(n_m - 1)(n_m\widehat{\sigma}^2 + \sum_{i=1}^{n_m}\widehat{\sigma}_i^2(x))}, \tag{23}$$

where $\widehat{\sigma}^2$ and $\widehat{\sigma}_i^2$ are, respectively, an independent estimate of the variance and the estimated prediction variances. $\widehat{y}_i$ and $\widehat{y}_j$ in Eq. (23) are the responses predicted by the two models.

Espie and Macchietto (1989) extended the criterion of Buzzi-Ferraris and Forzatti for multi-response systems to the case of dynamic models by using the dynamic sensitivity matrix (6).

Burke et al. (1997) compared three different methods for model discrimination by applying them to a copolymerisation model and concluded that the Buzzi-Ferraris and Forzatti approach was the most effective.

More recently, Chen and Asprey (2003), Chen et al. (2004) and Kremling et al. (2004) applied experiment design techniques for model discrimination, respectively, to a fermentation, a crystallisation process and a biochemical network with excellent results in terms of reduction in the number of experiments required. Ternbach et al. (2005) adopted a simplified version of Box's criterion (1967) and applied it to a model describing a fermentative fed-batch L-valine production process. The authors were able to reject three of the five proposed kinetic models with a single optimally designed experiment, which was proved much more effective in discriminating between rival models than the unplanned experiments.

It is worth noting that many of the ideas and methods discussed in the following sections with reference to DOE for parameter precision are equally applicable to the case of design for model discrimination. Different objective functions are used for the two techniques, but the same solution machinery can be adopted and the same statistical tests applied for model adequacy and parameter significance.

4. Model-based experiment design for parameter precision

The final step of a model validation procedure, and the main subject of this review, is the design of optimal experiments to improve the precision and therefore the reliability of the model parameters. This section describes the statistical theory and the mathematical formulation required to achieve this aim.

The model-based experiment design procedure considered requires the following elements:

- a model in the form of Eq. (1) with a set of parameters $\boldsymbol{\theta}$ to be estimated;
- an initial estimate of the parameters, and (optionally) a set of preliminary statistical information ($\boldsymbol{\Sigma}_\theta$) on the parameter uncertainties;
- a definition of the design space (see Section 4.1);
- a metric to measure the information content of the new set of experiments (Section 4.2);
- a definition of the set of variables to be measured and their corresponding error models;
- a criterion for the discretisation of the control variables $\mathbf{u}(t)$ (such as, for example, the control vector parameterisation (CVP) technique, see below).

4.1. Design vector and dynamic optimisation framework

When an optimal experiment is designed, the values of the control variables characterising the experiment are determined so as to optimise the predicted information content of the experiment or analogous requirements. These are in an analytical form by means of a suitable objective function, Of (see Section 4.2). All the control variables which can be manipulated by the experimenter and optimised during the design are collected in the so-called design vector $\boldsymbol{\varphi}$:

$$\boldsymbol{\varphi} = \boldsymbol{\varphi}(\mathbf{u}(t), \mathbf{y}^{\mathbf{0}}, \tau, \bar{\mathbf{w}}, \mathbf{t}_{\mathrm{sp}}). \tag{24}$$

$\mathbf{u}(t)$ is the vector of time-varying input controls, $\bar{\mathbf{w}}$ is the vector of time-invariant input controls, τ is the experiment duration, $\mathbf{t}_{\mathrm{sp}}$ is the vector of sampling times (see Fig. 4a) and $\mathbf{y}^{\mathbf{0}}$ is the vector of the initial conditions which can be optimised during the design. Of course, $\boldsymbol{\varphi}$ must be constrained to lie within the experiment design space $\boldsymbol{\Phi}$.

The DOE for dynamic systems requires the optimisation of the control variables, some of which are time dependent. For this purpose, the continuous time-varying inputs, $\mathbf{u}(t)$, must be approximated so as to pass from an infinite-dimensional problem to a discretised form of the controls that can be mathematically manipulated. Various optimisation methods can be used to achieve this goal, such as orthogonal collocation (Cuthrell and Biegler, 1989; Logsdon and Biegler, 1989) or CVP (Fikar et al., 2000; Teo et al., 1991; Vassiliadis et al., 1994). The first technique belongs to the class of simultaneous optimisation methods: all equations are fully transformed into algebraic equations, with the dynamic state variables approximated by orthogonal polynomials, resulting in large non-linear programming (NLP) optimisation problems. In principle, this is straightforward to use, in particular when inequality constraints on the state variables are considered. Logsdon and Biegler (1989) proposed to discretise the differential equations using orthogonal collocation on finite elements. Lagrange polynomials are suggested as the most suitable means to construct the approximation to the continuous model, resulting in a set of algebraic equations

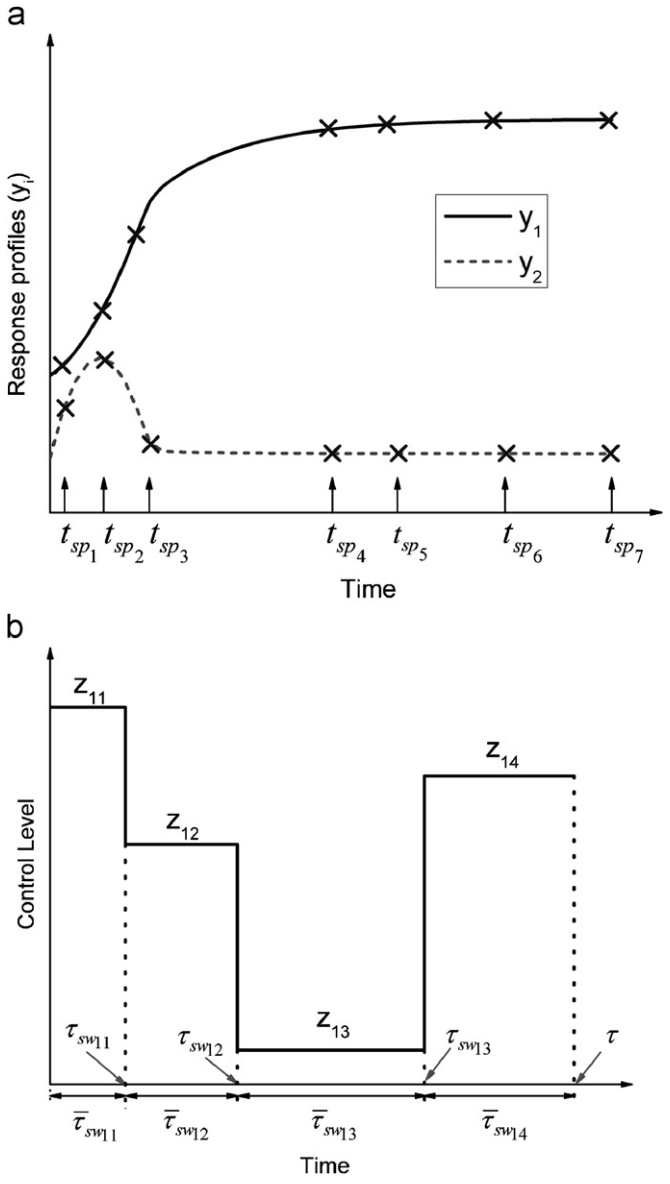

Fig. 4. (a) Sampling times for two generic responses y_1 and y_2 ($n_{\mathrm{sp}} = 7$), which are assumed to be measured at the same time. (b) An illustration of the control vector parameterisation technique for the piecewise constant case over four intervals ($n_{\mathrm{sw}} = 3$).

solved as part of the non-linear optimisation problem. A disadvantage of this approach is that a feasible solution to the simulation problem is only obtained if and when the optimum is reached. The second technique belongs to the class of sequential optimisation methods and is suitable if the problem comprises a large number of state variables. It involves the repeated integration of the DAE system in an inner loop of the optimisation, thus (in principle) augmenting the computational time and requiring efficient solvers. In the CVP technique, the controls $\mathbf{u}(t)$ are mathematically approximated over a pre-defined number of intervals using simple basis functions e.g. piecewise constant, piecewise linear or piecewise quadratic functions. By employing this approach, the time-varying input trajectories can be represented with a small, finite number of optimisation variables and thus the problem can be efficiently solved in the two-level way outlined. For example, in the piecewise constant case (Fig. 4b), the controls are modelled as follows:

$$u_i(t) = z_{ij} \quad \forall t \in \bar{\tau}_{\mathrm{sw}_{i,j}}, \ \ i = 1, \ldots, \ n_u, \quad j = 1, \ldots, n_{\mathrm{sw}} + 1, \tag{25}$$

where

$$\tau_{\mathrm{sw}_{i,j-1}} \leqslant \bar{\tau}_{\mathrm{sw}_{i,j}} < \tau_{\mathrm{sw}_{i,j}},$$

$$\tau_{\mathrm{sw}_{i,0}} = t_0,$$

$$\tau_{\mathrm{sw}_{i,n_{\mathrm{sw}}+1}} = \tau. \tag{26}$$

The notation used in Eqs. (25) and (26) has the following meaning:

- n_u is the number of time-varying controls,
- n_{sw} is the number of switching times,
- $\boldsymbol{\tau}_{\mathrm{sw}_i}$ is the row vector of the switching times defining the intervals $\bar{\tau}_{\mathrm{sw}_i}$ in which the control variable u_i remains constant at values $\mathbf{z}_i$,
- t_0 is the initial time (usually $t_0 = 0$) and τ the experiment duration.

This results in two quantities to be optimised for each interval (the control value z_i and the switching time, τ_{sw_i}). By using piecewise constant approximations for the time-varying controls, the design vector $\boldsymbol{\varphi}$ of Eq. (24) can be rewritten as

$$\boldsymbol{\varphi} = [t_{\mathrm{sp}_1}, \ldots, t_{\mathrm{sp}_{n_{\mathrm{sp}}}}, t_{\mathrm{sw}_{1,1}}, \ldots, t_{\mathrm{sw}_{n_u,n_{\mathrm{sw}}}}, z_{1,1}, \ldots, z_{n_u,n_{\mathrm{sw}}+1}, \mathbf{y}^{\mathbf{0}}, \bar{w}_1, \ldots, \bar{w}_{n_{\bar{w}}}, \tau]. \tag{27}$$

Independent time intervals for each of the time-varying controls and independent sampling times for each of the response variables may be adopted. The number of measurements for each response variable is assumed to be finite and defined by an a priori fixed number $n_{\mathrm{sp},i}$ of sampling times (Fig. 4a).

The design space $\boldsymbol{\Phi}$ typically includes all the possible values which the vector $\boldsymbol{\varphi}$ can assume in the experimental space, compatibly with all the practical and technical limitations and constraints of the experiment, i.e. $\boldsymbol{\Phi} = \boldsymbol{\Phi}_E$. However, it is possible to restrict the design space $\boldsymbol{\Phi}$ to a subset of $\boldsymbol{\Phi}_E$, say, low temperature only rather than the full temperature range. The design space may be identified, for example, by an upper and a lower bound on all the design variables:

$$y_i^0|^L \leqslant y_i^0 \leqslant y_i^0|^U, \quad i = 1, \ldots, n_{\mathrm{resp}},$$

$$\bar{w}_i^L \leqslant \bar{w}_i \leqslant \bar{w}_i^U, \quad i = 1, \ldots, n_{\bar{w}},$$

$$z_{ij}^L \leqslant z_{ij} \leqslant z_{ij}^U, \quad i = 1, \ldots, n_u, \ \ j = 1, \ldots, n_{\mathrm{sw}} + 1 \tag{28}$$

and/or by suitable path constraints on specific variables:

$$x^{\min} \leqslant x(t) \leqslant x^{\max} \quad \forall t \in [0, \tau]. \tag{29}$$

Additional constraints are also included for the sampling and switching times:

$$t_{\mathrm{sp}_1} \geqslant \Delta t_1, \tag{30}$$

$$\Delta t_{\mathrm{sp}}^{\min} \leqslant t_{\mathrm{sp}_i} - t_{\mathrm{sp}_{i-1}} \leqslant \Delta t_{\mathrm{sp}}^{\max}, \quad i = 1, \ldots, n_{\mathrm{sp}}, \tag{31}$$

$$\Delta t_{\mathrm{sw}_i}^{\min} \leqslant t_{\mathrm{sw}_i} - t_{\mathrm{sw}_{i-1}} \leqslant \Delta t_{\mathrm{sw}_i}^{\max}, \quad i = 1, \ldots, n_{\mathrm{sw}}, \tag{32}$$

$$t_{\mathrm{sw}_{i,n_{\mathrm{sw}}}} \leqslant t_{\mathrm{sp}_{n_{\mathrm{sp}}}}. \tag{33}$$

Eq. (30) defines the earliest time at which a measurement can be taken, while $\Delta t^{\min}$ and $\Delta t^{\max}$ in Eqs. (31) and (32) are the minimum and maximum allowable intervals between consecutive sampling or switching times. These constraints are usually active most of the time as the experiment design criteria tend to place sampling times at the maxima of the sensitivity curves repeatedly. Constraint (32) is required to avoid a mathematical singularity caused by the collapse of one or more control intervals, while Eq. (33) prevents useless changes to be made to the controls after the last measurement has been taken. In this formulation, a flexible time for the end of the experiment is used (τ is defined by the final sampling time).

Once a suitable objective function Of is defined to represent the predicted "goodness" of an experiment (see Section 4.2), its maximisation/minimisation becomes therefore the dynamic optimisation problem

$$\min_{\boldsymbol{\varphi} \in \boldsymbol{\Phi}} \mathrm{Of} \tag{34}$$

s.t.:

- model Eqs. (1),
- possibly some specified initial conditions (Eq. (2)) and
- all constraints on experimental conditions (Eqs. (25)–(33)).

Its solution gives the optimal settings and measurements to collect ($\boldsymbol{\varphi}$) in the next experiment.

4.2. Standard metrics to measure the information content of an experiment

Improving parameter precision is equivalent in mathematical terms to decreasing the size of the inference regions of the model parameters (for any given model), that is, to making the elements of the parameter variance–covariance matrix small. By adopting a Bayesian approach to drawing inferences about parameters in multi-response estimation and in particular the Bayesian formulation of the high posterior density region, the following expression for the marginal posterior covariance can be obtained (Bard, 1974):

$$\mathbf{V}(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}) = \left[\sum_{r}^{n_{\mathrm{resp}}} \sum_{s}^{n_{\mathrm{resp}}} \tilde{\sigma}_{rs} \mathbf{Q}_r^{\mathrm{T}} \mathbf{Q}_s + \boldsymbol{\Sigma}_\theta (\hat{\boldsymbol{\theta}})^{-1} \right]^{-1}, \tag{35}$$

where n_{resp} is the number of responses. The parameter variance–covariance matrix $\mathbf{V}$ ($p \times p$) is symmetric and depends on:

- the dynamic sensitivity coefficients of the rth response, $\mathbf{Q}_r$, defined in Eq. (6);
- the variance–covariance matrix of the experimental measurements Σ_y ($\tilde{\sigma}_{rs}$ is the (r, s) element of the inverse of Σ_y defined in Eq. (12));
- an initial approximation of the variance–covariance matrix of the parameters, Σ_θ, which contains preliminary information on parameter uncertainty.

As suggested by Box and Lucas (1959), the prior information on the parameter uncertainty can often be neglected. In such a case, the following equation (where all quantities are calculated using the current model parameters, for experimental conditions $\boldsymbol{\varphi}$) provides an estimate of the variance–covariance matrix that will be obtained after that experiment. The design of an optimal experiment for improving parameter precision therefore reduces to minimising some metric of

$$\mathbf{V}(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}) = \left[\sum_{r}^{n_{\mathrm{resp}}} \sum_{s}^{n_{\mathrm{resp}}} \tilde{\sigma}_{rs} \mathbf{Q}_r^{\mathrm{T}} \mathbf{Q}_s \right]^{-1} \tag{36}$$

by optimally choosing the set of experiment decision variables (length, time-varying and time-invariant controls, initial conditions, sampling times, etc.) subject to equality and inequality constraints.

In his Ph.D. thesis, Zullo (1991) defined a discrete version of the information matrix $\mathbf{M}$ (the inverse of $\mathbf{V}$) suitable for the optimal design of dynamic experiments in non-linear multi-response systems. This ($p \times p$) matrix depends on the sensitivity matrices defined in Eq. (6) and allows the information content from a number of experiments, n_{exp}, to be evaluated:

$$\mathbf{M}(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}) \equiv \sum_{j=1}^{n_{\mathrm{exp}}} \sum_{r=1}^{n_{\mathrm{resp}}} \sum_{s=1}^{n_{\mathrm{resp}}} \tilde{\sigma}_{rs,j} \mathbf{Q}_{r,j}^{\mathrm{T}} \mathbf{Q}_{s,j} + \mathbf{M}^0, \tag{37}$$

where the term $\mathbf{M}^0$ is optional and represents the preliminary information on parameter uncertainty ($\mathbf{M}^0 = \boldsymbol{\Sigma}_\theta (\hat{\boldsymbol{\theta}})^{-1}$). If a traditional sequential procedure is adopted for the design (one experiment at a time), the information matrix after n_{exp} experiment can be expressed as

$$\mathbf{M} = \sum_{k=1}^{n_{\mathrm{exp}}-1} \mathbf{M}_k + \mathbf{M}_{n_{\mathrm{exp}}} (\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}_{n_{\mathrm{exp}}}) = \mathbf{K} + \mathbf{M}_{n_{\mathrm{exp}}} (\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}_{n_{\mathrm{exp}}}), \tag{38}$$

where $\mathbf{K}$ is a constant matrix defined by the previous $(n_{\mathrm{exp}} - 1)$ experiments (Galvanin et al., 2007). In Eq. (38), only the vector $\boldsymbol{\varphi}_{n_{\mathrm{exp}}}$ of the experimental conditions for the new experiment (n_{exp}) is subject to optimisation.

From the information matrix calculated as in Eqs. (37)–(38), the parameter variance–covariance matrix is easily obtained from its definition:

$$\mathbf{V}(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}) = [\mathbf{M}(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi})]^{-1}. \tag{39}$$

It may be worth noting that, for non-linear models, Eq. (39) holds only asymptotically (Atkinson and Bogacka, 2002) and that both information and variance–covariance matrices depend on the unknown parameters, $\boldsymbol{\theta}$. In order to perform a design, an initial guess for these parameters, $\hat{\boldsymbol{\theta}}$ (i.e. the best currently available parameter values), is adopted and an appropriate function of the information or of the variance–covariance matrix (see below) evaluated at $\boldsymbol{\theta} = \hat{\boldsymbol{\theta}}$ is maximised or minimised.

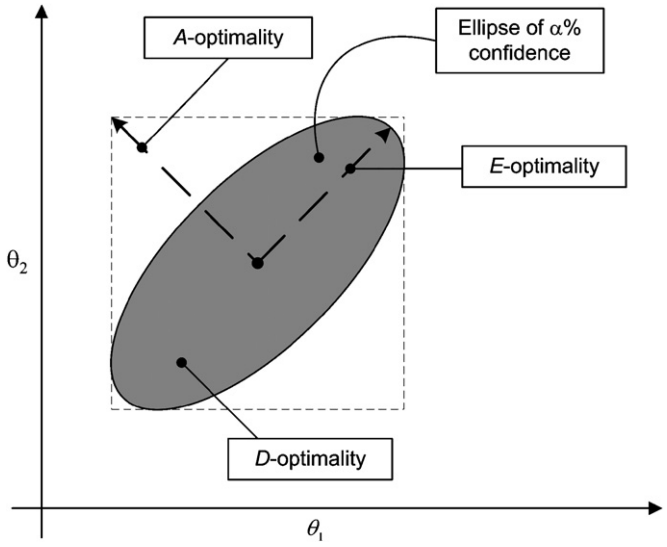

Fig. 5. Geometrical interpretation of the standard criteria for the experiment design. The grey area represents the confidence region of the parameters (typically, 90% or 95%).

Such designs are usually termed locally optimum (Atkinson and Bogacka, 2002) and require an iterative design procedure if the initial parameter guesses are quite unreliable.

As discussed above, the experiment design algorithm can either minimise a suitable metric of **V** or maximise the equivalent metric of **M** by manipulating the element of the design vector **φ**. Various real-valued functions have been suggested as suitable metrics for the "size" of the variance–covariance or information matrix and the most common criteria are three:

1. D-optimality, which maximises the determinant of the information matrix or minimises that of the variance–covariance matrix;
2. E-optimality, which maximises the smallest eigenvalue of the information matrix or minimises the largest eigenvalue of the variance–covariance matrix;
3. A-optimality, which maximises the trace of the information matrix or minimises that of the variance–covariance matrix.

All these criteria have a geometrical interpretation as illustrated for the two-parameter case in Fig. 5. The uncertainty associated with the estimates of the parameters can be represented by joint parameter confidence regions (typically, at $\alpha = 90\%$ or 95% confidence level) and, as it can be seen from Fig. 5, the D-optimal criterion aims at minimising the volume of this joint confidence region, the E-optimal the size of its major axis and the A-optimal the dimensions of the enclosing box around the joint confidence region.

As mentioned by Walter and Pronzato (1990), the D-optimal is the most used of the three standard criteria cited above. This was already evident from the first experiment design studies (Box and Lucas, 1959; Fedorov, 1972; Landaw, 1982; St. John and Draper, 1975) and is due to some appealing properties of the criterion:

- easy geometrical interpretation (Bard, 1974; Box and Lucas, 1959; Galil and Kiefer, 1977; Silvey and Titterington, 1973);
- theoretical invariance with respect to any non-degenerated transformation applied on the model parameters, such as rescaling (Fedorov, 1972; Landaw, 1982; Mehra, 1974a; Rimensberger and Rippin, 1986);
- yielding of optimal experiments which correspond to replications of a small number of different experimental conditions (Atkinson and Hunter, 1968; Box, 1968, 1970, 1972; Landaw, 1982; Pronzato, 1986; Vila, 1988).

The criterion is not, however, free from drawbacks. As pointed out by many authors (e.g. Pinto et al., 1990; Zullo, 1991), the D-optimal design tends to give excessive importance to the parameter to which the model is most sensitive. Thus, although the confidence region volume can be reduced thanks to a decrease in the variance of this model parameter, the uncertainties of all the other parameters may remain very large.

The A-optimal criterion is considered by some authors (Goodwin, 1987; Munack and Posten, 1989; Vanrolleghem et al., 1995; Zullo, 1991, De Pauw, 2005) to be unreliable, in particular in case of high correlations between the parameters. The off-diagonal elements of the information matrix are not included in the objective function and this causes an appreciable loss of information in case of high cross-correlation between parameters. Munack and Posten (1989) clearly recommend that this criterion should not be employed since it may lead to non-informative experiments.

The drawbacks of the standard criteria have led to the search for alternatives, all aimed at the same goal: to reduce the complex information contained in a matrix (either **M** or **V**) to a scalar number. One such criterion often used (see, for example, Versyck et al., 1998a) is the so-called modified E-optimality which minimises the condition number of the information matrix (i.e. the ratio between the maximum and minimum eigenvalue) and thus makes the joint confidence region as spherical as possible. This criterion is often used for the purpose of reducing parameter correlations (Bernaerts et al., 2000) but this is valid only for two-parameter models (Franceschini and Macchietto, 2007b). Sidoli et al. (2004) highlighted how the modified E-optimal design has a significant drawback: its mathematical property (ratio of eigenvalues) means that the criterion is discontinuous and can therefore cause convergence problems when used with a gradient-based optimisation routine. De Pauw (2005) noted another limitation of the modified E-optimal design: since it is a pure shape criterion, circular ellipsoids with very large volumes may be obtained.

For a detailed discussion of other, less used standard criteria (such as G-, L-, C-, D_s-optimality), reference is made to Mehra (1974b), Walter and Pronzato (1990) and Sidoli et al. (2004).

4.3. Alternative formulations based on standard experiment design criteria

As noted, the various design criteria do not easily reduce the complex set of information contained in the **M** or **V** matrices to a single scalar. To obviate, several alternative formulations have been proposed which are based on minor modifications of the

standard design criteria described above. These are reviewed in this section.

Versyck et al. (1998a, b) extended the studies of Munack (1988) to unstructured microbial growth models and stressed how, in the field of microbiology, optimally designed dynamic experiments can be significantly more useful in order to obtain valid models than the more traditional static growth experiments. The authors proposed a new objective function (Of) which combined the modified E-optimal criterion with a penalty function to prevent violations of the model validity:

$$\mathrm{Of} = \Lambda + k\Phi, \tag{40}$$

where Λ is the condition number of the information matrix (modified E-optimal design), k is a weighting factor penalising violations of model validity and Φ is a so-called model validity functional. This new criterion aims at preventing the DOE outside the validity range of the mathematical model and can be very useful for biological systems, where several assumptions are usually made in order to obtain manageable models (i.e. unstructured growth hypothesis). This criterion was applied with satisfactory results to two fermentation processes (one with the Monod and the other with the Haldane kinetics). In the same year, Versyck and Van Impe (1998) proposed another design criterion which combined in a single objective function three of the main scalar measures of the information matrix (the D-, E- and modified E-optimal criteria):

$$\mathrm{Of} = (1-\beta)\log\Lambda - \beta\log|\mathbf{M}|, \tag{41}$$

where β is a weighting factor and Λ and $|\mathbf{M}|$ are, respectively, the condition number and the determinant of the information matrix. By choosing the value of the weighting factor, the trade-off between the different requirements of the three measures can be moved towards one or the other of the criteria (with β equal to 0, 0.5 and 1, the modified E-optimal, the E-optimal and the D-optimal design are obtained, respectively). No recommendations are, however, proposed in this paper to help a user in the choice of a suitable weighting factor.

Bernaerts et al. (2000) reached the same conclusions as Munack (1988) when studying optimal designs to estimate the parameters of the Ratowsky model for the specific growth rate of micro-organisms. The authors concluded that only dynamic temperature changes and therefore optimally designed temperature profiles allow the identification of these parameters. In a subsequent study, Bernaerts and Van Impe (2005) introduced a constrained design in order to define admissible temperature inputs and hence find a trade-off between optimal design and model validity. Most of the experimental results obtained with the previously designed experiments had shown an unexpected intermediate lag-phase (not modelled) with consequent difficulties in the parameter estimation. In this case, a different approach was used with respect to the penalty function method proposed by Versyck et al. (1998a): the criterion was formulated as a standard objective function (modified E-optimal) with the temperature bound by inequality constraints.

Atkinson and Bogacka (2002) addressed the problem of model-based experiment design in the field of chemical kinetics, where the order of the chemical reactions is to be estimated as well as the rate. This important issue of the simultaneous estimation of orders and rates has received very little treatment in the literature. The authors proposed a parameterised compound criterion Ψ:

$$\begin{aligned}\Psi &= (1-\alpha)\log(D_2) + \alpha\log(D_3)\\ &= (1-2\alpha)\log(D_2) + \alpha\log(D_1),\end{aligned} \tag{42}$$

which combines:

- a traditional D-optimal design for determining both rates and orders (D_1),
- a D-optimal design for determining only the rates assuming the orders known (D_2),
- a D-optimal design for determining only the orders assuming the rates known (D_3).

Varying the parameter α in the compound criterion can lead to a design which provides a balance between the three criteria. Since it is unlikely that an experimenter will be able to find a suitable value for the parameter α, the authors proposed to design experiments maximising the compound criterion for a series of values of α and then to identify the desired balance graphically (plotting the relative effectiveness of the designs towards the various requirements). This method has, however, the drawback of significantly increasing the number of design calculations required.

Berkholz et al. (2000) introduced a novel design criterion for a fed-batch fermentation process, which aims at producing a trade-off between optimal process performance (mass of the product) and parameter precision (modified E-optimal):

$$\mathrm{Of} = \omega \cdot J_p/\max(J_p) + (1-\omega)\cdot J_s/\max(J_s), \tag{43}$$

where J_p is the mass of the product at the final time, J_s is the ratio between the smallest and largest eigenvalues of the information matrix (inverse of the modified E-optimal design) and ω is the weight. Maximising the component J_p provides an optimal process performance whereas maximising J_s provides optimal process parameter identification (i.e. confidence ellipsoid as spherical as possible). Starting a sequential design procedure, the first experiment should be designed in a way that the minimisation of the parameter estimation error should be the predominant aim (small ω). Then, an increased weight factor can be used in order to obtain an experiment with more emphasis on maximum product yield and less emphasis on parameter estimation. This criterion allows therefore model parameter identification and productivity optimisation to be combined together in a single sequential experiment design approach. It is noted that, in our experience, this is usually not a recommended approach. It is far better to first perform some experiments to achieve good model identification, and then use the resulting (improved and more reliable) model to optimise production.

4.4. New formulations for model-based experiment design

This section reviews the most significant recent developments which use new design criteria as objective functions, or

altogether new formulations. These formulations recognise that a single scalar criterion is unlikely to represent all that is desired from an optimal experiment. Therefore, in addition to standard information content measures, they take into account additional aspects (such as parameter correlation, curvature, probability, etc.) by introducing them explicitly in the design formulation.

While all other literature has dealt with optimal DOE in sequence (one at a time), Galvanin et al. (2007) were the first to concentrate on designing some experiments in parallel. This may be advantageous if multiple copies of an experimental apparatus are available (say, an array of micro-reactors) and if each experiment is very long. In a parallel design procedure, the number n_{exp} of experiments to be designed at the same time is selected a priori, and the overall information matrix is calculated as

$$\mathbf{M} = \sum_{k=1}^{n_{\text{exp}}} \mathbf{M}_k(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}_k). \tag{44}$$

All the design vectors $\boldsymbol{\varphi}_k$ (one for each experiment) are optimised simultaneously (Galvanin et al., 2007). That is, the conditions of all n_{exp} experiments are optimised so as to maximise their combined information content. Of course, this requires the solution of a much larger optimisation problem. The authors also proposed a new criterion, SV-optimality, which is particularly suited for parallel design. This criterion aims at maximising complementary information by considering multiple different eigenvalues of the information matrix. The underlying idea is that it can be more useful to take into consideration specific directions of the information content than to consider a single overall information measure, such as, for example, the D-optimal design. In a parallel experiment design procedure, this approach allows the various devices available for the experiments to be dedicated to those different and complementary information components, for example, by maximising the information linked to the n_{exp} largest eigenvalues (λ) of the variance–covariance matrix. The overall optimisation problem for a parallel design is therefore split into separate optimisation problems:

$$\min_{\boldsymbol{\varphi}_k \in \boldsymbol{\Phi}} \lambda_k(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}_k), \quad k = 1, \ldots, n_{\text{exp}} \leqslant p \quad \text{and}$$
$$\lambda_1 > \lambda_2 > \cdots > \lambda_{n_{\text{exp}}}, \tag{45}$$

where $\boldsymbol{\varphi}_k$ is the design vector of the kth experiment, $\boldsymbol{\Phi}$ the design space, p the number of parameters and $\hat{\boldsymbol{\theta}}$ the vector of the best currently available parameter estimates. Each optimisation problem has the same size as a traditional D-optimal design and can be solved in a different parallel computer, thus the approach can practically deal with very large models. The method was successfully applied to a bioreactor model with a significant improvement in the results compared with standard D- and E-optimal designs. A potential drawback is that the number of independent experiments which can be designed is limited by the number of model parameters (i.e. $n_{\text{exp}} \leqslant p$).

Imhof et al. (2004) presented a general method for designing an experiment when there are potential experiment failures. The paper demonstrated that the usual optimal designs, which assume all measurements to be available at the end of the experiment, can be quite ineffective if the probability of missing observations is not accounted for at the design stage. The authors recognised that their approach presents some similarities with design problems with heterogeneous error structure (Endrenyi and Chan, 1981; Bezeau and Endrenyi, 1986; Dette and Wong, 1999). The basic assumption of this novel formulation is that at every point x in the design space there is a known probability $p(x)$ that a trial at x will result in a valid observation. The information matrix is therefore constructed in order to include this probability function:

$$\mathbf{M}_{\text{Imhof}} = p(x)\mathbf{M}_{\text{standard}}. \tag{46}$$

An advantage of this approach is that the design avoids taking observations at a location judged to have a high probability of a non-response and selects instead a nearby location with a greater probability of generating a response. Some of the sources of uncertainty related to experimental work are uncontrollable but others can be reasonably modelled. For example, laboratory instrumentation is likely to have a higher chance of malfunction or breakdown at high temperatures or pressures than at normal conditions or in lengthy experiments the operator is likely to miss observations due to fatigue and oversight. The authors successfully applied this design formulation to a Michaelis–Menten model using the D-optimal criterion.

As already noted, for multi-response highly non-linear dynamic models, the asymptotic linear approximation of the model functions usually employed to construct inference regions can be a very poor representation of the true surface and so may generate a poor design. Benabbas et al. (2005) proposed therefore to take directly into account the curvature of the inference regions in the design formulation. The underlying idea is that there is no point in optimising the information content of an experiment if the resulting inference curves (hence parameter variance–covariance information) are unreliable, and it is better to find some compromise between the two requirements. The authors demonstrated the effectiveness of their solution with reference to the same small case study (the bioreactor model) of Asprey and Macchietto (2002). An overall, scalar measure of the parameter inference region curvature was adopted by the authors as the most suitable metric for this requirement and two different design formulations were proposed:

1. to minimise the expected overall curvature c^2 (E is the expected value):

$$\min_{\boldsymbol{\varphi} \in \boldsymbol{\Phi}} E[c^2(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi})], \tag{47}$$

2. to minimise parameter uncertainty (using one of the standard design criteria) subject to an acceptable overall level of curvature, defined in terms of ε, a specified tolerance on the curvature:

$$\min_{\boldsymbol{\varphi} \in \boldsymbol{\Phi}} f(\mathbf{M}(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi})) \quad \text{s.t. } c(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}) < \varepsilon. \tag{48}$$

First, a standard optimal experiment design is carried out. The value of the overall curvature measure (c^2) at this optimal

solution gives an indication of the expected degree of model non-linearity. This can therefore be used to determine whether linear approximations to the joint parameter confidence regions can be trusted and employed. The standard design solution also gives an upper bound on the curvature, hence on the tolerance ε in formulation (48), which can be used to find the best information content achievable when the curvature measure is progressively constrained. The drawback of this approach is that it requires calculations of second-order sensitivities, whose DAE equations must be integrated at each design iteration together with the model and the first-order sensitivity equations, with consequent increase in the computational load.

Stigter et al. (2006) proposed an adaptive, receding-horizon, optimal control problem for the experiment design of fed-batch bioreactor models, which processes the parameter estimates recursively each time an observation becomes available (similar in spirit to model predictive control). Through this approach, their ordinary differential equation (ODE) model is integrated "in tandem" with a recursive parameter update scheme. This exploits the fact that both experiment design and parameter estimation include the output parametric sensitivities to compute, respectively, the information matrix and the gradient pointing to a direction of minimum residuals. This approach essentially solves the design problem "on line": the best current estimate of the set of parameters, that is, $\hat{\boldsymbol{\theta}}(t_k)$, is used to design the optimal experiment. After this, the current estimate is optimally updated to $\hat{\boldsymbol{\theta}}(t_{k+1})$, using a recursive parameter estimation algorithm. It is likely that this approach will be highly sensitive to large errors in individual measurements and missing measurements (possibly even unstable in such situations), but the method is no doubt interesting and extendable to the more general DAE models in the form of Eq. (1).

4.4.1. Experiment design and parameter correlation

One of the traditional application areas of experiment design is the identification of kinetic parameters in a model. As highlighted in a previous publication (Franceschini and Macchietto, 2007a) and by many other authors, this problem is very much complicated by the large number of parameters often involved in kinetic mechanisms and by their significant interactions. Reaction networks or biological pathways constituted of parallel, sequential, competitive or consecutive steps are all examples of models characterised by highly correlated parameters, which often prevent successful experiment design and/or parameter identification. Correlations between model parameters have several detrimental effects on a model validation procedure since they may cause:

- convergence problems in parameter estimation and/or experiment design calculations. High correlations may give rise to objective functions with an elongated valley surface which can create severe complications to some optimisers (Agarwal and Brisk, 1986);
- difficult unique parameter identification (the effect of a change in one parameter can be counterbalanced by a change in the others, as experienced, for example, by Bernaerts et al., 2000);
- inaccurate estimates (Beck and Arnold, 1977);
- a decrease in the reliability of the statistical tests (t-test) by means of which the accuracy of the estimates is assessed. The t-test is more robust against deviations from normality than against departures from the sample independence hypothesis (Lehmann, 1986). Since parameter correlations imply dependent (or partially dependent) samples (Bard, 1974), the results of the test can be inaccurate and unreliable in case of high correlations;
- impossibility of trusting the joint message of individual confidence intervals (Draper and Smith, 1966). Only joint confidence regions which take into account parameter correlations (as the ones described in Section 2.4) can be used (see Franceschini and Macchietto, 2007b, for a more detailed discussion on this issue).

In the last 20 years several studies have highlighted the problems which can affect an estimation procedure when parameters are highly correlated (Cheng and Yuan, 1996; Pritchard and Bacon, 1975, 1978; Rippin, 1988), but only a few have tried to propose and implement a solution based on:

- model reparameterisation and/or variable separation (Agarwal and Brisk, 1985a; Dovi, 1997; Dovi et al., 1994; Espie and Macchietto, 1988),
- "well-designed" experiments (Bernaerts and Van Impe, 2004; Pritchard and Bacon, 1978),
- "independent estimation" of as many parameters as possible (Paterson and Carberry, 1983).

The rest of the authors simply noted the problem and concluded with a generic (but practically useless) exhortation of trying to avoid correlated parameters as much as possible (e.g. Grijspeerdt and Vanrolleghem, 1999).

A few papers in the literature have identified a suitable experiment design procedure as a possible way of overcoming the correlation problem. Box and Hunter (1965b) suggested that for a two-parameter model the volume criterion (D-optimal design) minimises not only the size of the uncertainty region associated with the parameter estimates but also the correlation between them. This characteristic of the design criterion is derived directly from the definition of the determinant of a (2×2) matrix but cannot however be extended to models with three or more parameters. As mentioned in Section 4.1, the same limitation (to only two-parameter models) affects also the modified E-optimal criterion used by Bernaerts et al. (2000).

Pritchard and Bacon (1978) proposed a new criterion alternative to the traditional D-optimal design, which has a measure of the overall correlation among the parameters directly as objective function to be minimised i.e. the root square of the individual correlations between pair of parameters:

$$\mathrm{Of} = \left\{ \sum_{\substack{i,j \\ i\neq j}} \frac{\mathrm{Corr}_{ij}^2}{(p^2-p)} \right\}^{1/2}, \tag{49}$$

where p is the number of parameters to be estimated. This approach was applied to a steady-state adsorption model for the catalytic oxidation of benzene and an overall 6% reduction in the correlation measure was obtained.

As this brief overview has shown, all these experiment design criteria aiming at reducing parameter correlations are limited to two-parameter models or have been applied only to steady-state processes. In addition, as Agarwal and Brisk (1985b) and Issanchou et al. (2003) showed, an experiment design criterion which aims only at reducing parameter correlations is likely to produce large confidence regions for the parameters since the information content of the experiment is not included in the design.

A novel approach to the experiment design of models with highly correlated parameters was therefore strongly needed and was recently developed (Franceschini, 2007). This approach is far more general and can be applied to the very large class of non-linear dynamic models in the form of Eq. (1), with a generic number p of parameters. Having established that information content and parameter correlation are distinct requirements, four novel criteria were proposed, all of which work directly on the parameter correlation matrix in order to eliminate/reduce the interactions between (all or selected) parameters by means of suitable objective functions and/or constraints (Franceschini and Macchietto, 2007b). The PAC design formulation has the only aim of decreasing parameter correlations but the other three criteria (ACE, E-AC and AC-V designs) add correlation reduction to the traditional aim of standard experiment design, that is, the improvement in the information content of the optimal experiments. The E-AC design, for example, maximises the information content of the experiment in the objective function while bounding all the correlation coefficients in constraints (one for each parameter pair), so as to force them to be below a chosen threshold level. Mathematically, the formulation is analogous to Eq. (48), with constraints now on selected or all correlation coefficients:

$$\max_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} f(\mathbf{M}(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi})) \quad \text{s.t. } \mathrm{Corr}_{ij}|_{i\neq j} < \varepsilon_{ij}^{C},$$
$$i = 1, \ldots, p-1, \quad j = 2, \ldots, p, \tag{50}$$

where Corr_{ij} is the correlation coefficient between parameters i and j and ε_{ij}^{C} is the bound on this coefficient. The ACE, E-AC and AC-V criteria aim at finding the best possible trade-off between correlation reduction and information content enhancement so as to eliminate the drawback of Pritchard's method (producing large confidence regions).

These three criteria were also formulated so as to design experiments specifically targeted at increasing the precision of a desired parameter or group of parameters and this has been proved particularly useful in conjunction with both parallel and sequential experiment design strategies (Franceschini and Macchietto, 2007b, c). The AC-V design achieves this experiment targeting by directly minimising the variance of one or more specified parameter/s while reducing specific correlations. The ACE and E-AC criteria exploit some concepts of principal component analysis (Saltelli et al., 2000; Turányi, 1990; Vajda et al., 1985) to reach the goal of targeting the experiment. First, the main association between each parameter and the eigenvalues of the information matrix is established; then, in order to improve the estimation of a certain parameter, its specific eigenvalue is maximised. A method to establish the association between specific parameters and eigenvalues is described in detail in Franceschini and Macchietto (2007b). Practically, this also leads to avoiding the discontinuities in the objective function associated with minimisation of the condition number in the modified E-optimal criterion.

This novel approach was applied to various case studies of increasing complexity: a three-parameter epoxidation example (Franceschini and Macchietto, 2007b), a four-parameter bioreactor model (Franceschini and Macchietto, 2007c) and an isothermal biodiesel process with laboratory execution of the optimal experiments (Franceschini and Macchietto, 2007d). The anti-correlation formulations were demonstrated to be very effective and suitable for any type of experiment design procedure (sequential, parallel and parallel/sequential). The method is highly flexible in the choice of objective functions and constraints so as to enable a designer to specify a desired trade-off between correlation reduction and increase in information content. The new formulations proved to be much more effective than both Pritchard's criterion (Pritchard and Bacon, 1978) and the standard experiment design methods in reducing the uncertainty regions of the parameters and improving the reliability of the estimates (Franceschini and Macchietto, 2007c). Reference is made to Franceschini and Macchietto (2007b) for a detailed description of these criteria formulations.

4.5. Robust vs. locally optimum designs

As all variational methods, an optimal control formulation of model-based experiment design can be sensitive to the initial estimates of the parameters, in particular if solved using standard gradient-based optimisation methods. Since the design procedure is based on a local sensitivity analysis, unreliable initial guesses for the parameters can significantly complicate the problem and result in a high number of design iterations. For this reason, Asprey and Macchietto (2002) stressed the need of design methods that are insensitive ("*robust*") to the parameter starting values and presented two criteria to provide design robustness, namely the expected value and the maximin design (based on previously proposed methods; see Walter, 1987). Both criteria were applied with good results to a small semi-continuous bioreactor model.

The expected value approach requires prior information about the uncertain model parameters to be available in the form of a probability distribution. In this way, this prior information can be quantified using the probability density function and so can be included in the objective function to maximise

$$\max_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} E_{\hat{\boldsymbol{\theta}}\in\boldsymbol{\Theta}} \left\{ \left| \mathbf{M}(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}) \right| \right\}, \tag{51}$$

where E is the expected value, $\boldsymbol{\Theta}$ the parameter space and $|\mathbf{M}|$ the determinant of the information matrix.

The maximin approach aims at designing experiments that optimise the worst possible performance for any value of $\boldsymbol{\theta} \in \boldsymbol{\Theta}$. In this case, no prior information on the parameters is required other than the admissible domain $\boldsymbol{\Theta}$ (probability distributions are not necessary). The design tries to ensure an acceptable performance for all possible values of the parameter vector (however unlikely). The following objective function is used to maximise the amount of information obtainable from the optimal experiment for the worst possible values of the parameters (as in Eq. (51), the D-optimal criterion is used to measure the information content):

$$\max_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} \min_{\boldsymbol{\theta}\in\boldsymbol{\Theta}} \{|\mathbf{M}(\boldsymbol{\theta}, \boldsymbol{\varphi})|\}. \tag{52}$$

This approach has, however, the drawback of being computationally very heavy.

Bruwer and MacGregor (2006) applied robust D-optimal formulations to a problem of multi-variable identification involving a binary distillation case study. The authors pointed out how, for design of multi-variable controllers, model identification should employ a robust design procedure insensitive to the uncertainty in prior estimates and design implementation. Only in this way, a model that optimises control robustness irrespective of the structure or tuning of the multi-variable controller can be obtained. One of the formulations proposed in the paper provides a single tuning parameter to balance the effectiveness of robust identification and the minimisation of the controller sensitivity to uncertainty.

Dette et al. (2005) applied a robust design approach to a classical Monod growth model. The authors had noted that the designs presented in the literature on this type of models were all locally optimal designs. These methods strongly depend on a preliminary guess of the unknown parameters and for this reason are in many cases not robust with respect to their misspecification. In order to obtain robust and efficient designs for parameter estimation, the authors adopted uniform designs (a Bayesian robust approach which assumes uniform prior distributions for the unknown parameters) and maximin D- and E-optimal methods. The paper demonstrates that maximin optimal designs are substantially more effective than uniform designs: a two-fold decrease was observed in the parameter variances of the chosen case study.

The work of Dette et al. (2006) also dealt with the issue of robust design: a standardised maximin approach based on the D-optimal criterion was applied by the authors to several exponential regression models, which are vastly used in chemistry, microbiology and pharmacokinetics. This approach requires only the specification of a certain range for the unknown model parameters and so overcomes the drawback of the Bayesian methodology (i.e. the need of specifying a prior distribution for the parameters). The two methods are of course different as the Bayesian one considers an average over the parameter space while the maximin design addresses the worst-case scenario. Both were, however, proved very effective for the examples considered in Dette's investigation.

4.6. Numerical aspects

An optimisation formulation of a model-based experiment design problem requires its numerical solution. Espie and Macchietto (1989) were the first to formulate this problem as an optimal control problem (dynamic optimisation) for models represented by general constrained DAE systems. Their solution algorithm included the integration of the DAE systems in an inner loop, using variable step size and variable order integration methods based on backwards differentiation formulas, and the optimisation of the small resulting outer problem using a robust sequential quadratic programming method. The control functions are parameterised over an appropriate user-defined number of intervals and replaced by piecewise continuous functions with a finite-dimensional numbers of degrees of freedom. This decomposition approach appears particularly suited to a DOE application, as the number of variables to be optimised for each design (those in the experiment design vector) is usually less than 50–100 and is reasonably small in comparison to the number of state variables in a model, which may well be several thousands. These authors showed that this approach was quite flexible, in respect of choice of objective function and constraints, and in fact was valid both for model discrimination and improvement of parameter precision. Because of this flexibility, this approach was followed by several researchers in this field.

Bauer et al. (2000) discussed numerical aspects connected with the experiment design approach. They also formulated the design as an optimal control problem with objective function which depends implicitly on the first derivatives of the underlying DAE system. The authors also treated these problems with the decoupled approach, with a CVP of the continuous controls. Path constraints (if required by the design to obtain feasible experiments) were discretised over another user-defined grid (which may be different from the control interval discretisation) and replaced by interior point constraints on this grid. Integration of the DAE system is achieved using a BDF method and optimisation used a structured SQP solver. The benefits of the approach were demonstrated with an example represented by a stiff set of equations describing the reaction of urethane.

Leineweber et al. (2003) further investigated the optimisation problem proposing a simultaneous solution strategy based on multiple shooting and reduced SQP. The NLP problems arising from a discretisation of the dynamic model by multiple shooting instead of orthogonal collocation (see Section 4.1) are typically much smaller. In addition, the integrations on multiple shooting intervals are completely decoupled and can therefore be performed in parallel. In order to exploit this feature, the authors adopted a new partially reduced SQP strategy (Leineweber, 1999). The structured NLP problem resulting from the multiple shooting DAE discretisation was projected onto the reduced space of differential variables plus control parameters. The advantage of the proposed approach is that the computationally expensive calculation of the full set of differential state sensitivities can be avoided and replaced by the calculation of a limited set of directional sensitivities (provided

that the projection and the gradient evaluation step are suitably connected).

Banga et al. (2002) still treated the experiment design as an optimal control problem but focused on the implementation of stochastic methods of global optimisation for improving the numerical solution. These techniques were suggested as efficient and robust alternatives for similar difficult optimal control problems (Banga et al., 1997). Two stochastic methods, namely the "integrated control random search", which is an adaptive stochastic technique developed by Banga and Casares (1987), and the "differential evolution", which is a population-based stochastic method presented by Storn and Price (1997), were used by Banga et al. (2002) to solve experiment design problems. The authors judge both techniques to be simple to implement and employ: the user needs to set up the global optimisation stochastic solvers coupled with an initial value solver, the process dynamic model and the first-order sensitivity equations needed for the computation of the information matrix. These stochastic global optimisation methods were demonstrated to be computationally efficient when applied to an unstructured microbial growth model, as an example of a non-linear and highly constrained optimisation problem. The use of these optimisation techniques presents another advantage since parallel versions working on clusters of PCs can be easily created.

Zakovic et al. (2003) developed a parallel algorithm for semi-infinite programming problems, suitable for robust experiment design. The term semi-infinite programming arises from the fact that the formulation of the optimisation problem includes an infinite set of constraints $G(x, y) \leqslant 0$ on the state variable x, which must be satisfied for any $y \in Y$. y represents a set of parameters affected by uncertainty and Y is the space of all possible parameter sets. Maximin experiment designs can be easily formulated as semi-infinite problems with significant improvements in the computational efficiency. The computational intensity of the problem remains still quite large and for this reason the authors proposed to use parallelisation in two stages: one for evaluating the global optimum and one for checking the feasibility of the constraints.

Korkel et al. (2004) presented new efficient methods for robust experiment design, without using a semi-infinite formulation but still taking into account the parameter uncertainty. The authors employed the direct approach described by Bauer et al. (2000) to obtain a finite-dimensional, non-linear optimisation problem, which is then solved with a sequential quadratic programming algorithm. The objective function proposed includes a "non-robust part" (standard design criteria) and the "robustness part", which can be interpreted as a penalty for uncertainty in the parameters. In this way, the authors formulated a worst-case problem without recurring to semi-infinite optimisation programming; the approach was proved highly satisfactory by application to a urethane production model (very stiff set of DAE).

Optimisation methods based on a local optimisation theory (such as SQP) are bound to suffer from the usual, well-known drawbacks: dependency on where one starts the design (initial estimates of the parameters and, at each design, of the experiment design vector), difficulty with very flat optima, getting occasionally stuck in local optima, getting lost when there are close multiple optima, etc. There is of course an opportunity to utilise global optimisation techniques, and no doubt their time will come, but at present these do not appear to have been used, due to very high numerical load.

4.7. The role of sensitivity in model-based experiment design

As explained in Section 4.2, model-based DOE requires the computation of the so-called information matrix which, by definition, depends on the local sensitivity coefficients (see Eq. (37)). Therefore, the entire DOE relies both on their accurate and precise calculation and their correct use within the optimal design algorithms. In an experiment design procedure, the sensitivity coefficients are involved not only in the computation of the objective function and so of the design performance criterion but also in the calculation of the gradients of the objective function which are essential for the optimisation routine.

Local sensitivity coefficients are defined (in dynamic systems) as the time-varying derivatives of model responses with respect to the model parameters (see Eq. (6)). They are therefore affected by scale: variations due to the magnitude of responses or parameters have a significant effect on their values. These scale effects are frequently encountered in practice: for example, with an Arrhenius' equation, the several orders of magnitude difference between pre-exponential factor and activation energy affect the sensitivity calculations. Several formulations of scaled and normalised sensitivities (Saltelli et al., 2000) have been proposed aimed at eliminating these scale effects. Franceschini and Macchietto (2006) investigated how these scale effects and the use of scaled sensitivities can influence the outcomes of the experiment design. The role played by sensitivity analysis in the design of a new experiment was investigated and the use of different types of sensitivity scaling in the calculation of the information matrix was explored with reference to several numerical examples. The study showed that using standard, unscaled sensitivities can often produce a singularity in the information matrix and prevent the design of the new optimal experiments altogether. A suitable scaling of the information matrix is, therefore, necessary to obtain reliable results. For the experiment design of systems affected by scale effects due to the different magnitudes of the parameters, the "*parameter scaled sensitivity*" (the following equation) was judged the most suitable of the various scaling methods that had been proposed in the literature at various times:

$$q_{ij}^{\mathrm{psc}} = \theta_j \cdot \frac{\partial y_i}{\partial \theta_j} \quad \text{in units of response } i, \tag{53}$$

where θ_j is the jth model parameter and y_i the ith response. It is worth noting that, although D-optimal designs are theoretically invariant to this type of scaling, there are still numerical effects.

Even if the approach was not extended to the DOE, the works of Thomaseth and Cobelli (1999) and Gunawan et al. (2005) are also worth being cited in this section. Thomaseth and Cobelli (1999) defined a new sensitivity function called "generalised sensitivity" suitable for applications in physiological system

identification. The traditional sensitivity analysis has a limited application in this field because it ignores correlations between parameters. The aim of this generalised sensitivity function was to qualitatively predict at which time points measurements were most informative for the estimation of specific parameters. The approach takes into consideration the interactions between parameters and the fact that they will be all simultaneously estimated in a real situation. These new functions combined the traditional sensitivities with the sensitivities of parameter estimates to changes in model outputs.

Classical sensitivity analysis does not directly apply to discrete stochastic dynamic systems, which have recently gained popularity because of their relevance in the simulation of biological processes. Gunawan et al. (2005) developed a sensitivity analysis for discrete stochastic processes. Their approach is based on density function (distribution) sensitivity and uses an analogue of the traditional sensitivity and the Fisher information matrix. The proposed analysis was applied to a bi-stable chemical system (the Schlögl model) and to a synthetic genetic toggle-switch model with very satisfactory results.

4.7.1. Global sensitivity

Global sensitivity analysis (GSA) is another very active area of research on sensitivity concepts. The main advantage of this technique from an experiment design point of view is the promise of taking into account the entire possible range for the uncertain parameters. At present, global sensitivity has not yet been used for the purpose of model-based DOE, but in our opinion it is an area with potential. For this reason, this section presents a brief introduction to the field.

Global sensitivity methods were discussed by Cukier et al. (1978), Iman and Helton (1988), Saltelli and Homma (1992), Saltelli et al. (2000) and Sobol (1993), among others. GSA aims at apportioning the output uncertainty to the uncertainty in the input factors, described typically by probability density functions that cover the factor range. A global sensitivity technique has the advantage of incorporating the influence of the whole variation range of the input (parameter range) while providing quantitative results, which indicate the significance of each parameter. The effect on the output of changing one parameter while all the others are varied as well is evaluated by GSA and this can help in discovering the degree of parameter interactions in a model (with a local method, the other parameters are kept fixed at their nominal value while one parameter is perturbed). The GSA can assist in model building by identifying the factors (the model inputs in the form of variables and parameters) which contribute the most to the output variability. The main techniques used for GSA are two: Fourier amplitude sensitivity test (FAST) and Sobol's methods. They are for all intents and purposes equivalent (Kontoravdi et al., 2005). Sobol's is a variance-based Monte Carlo method that allows the computation of the sensitivity indices of individual parameters and of the interactions between the parameters, which can be identified through the ratio of each sensitivity index to the corresponding total sensitivity index (Sobol, 1993). The total variance of the model output is assumed to be made up of terms of increasing dimensionality and the computation of the higher interaction terms is simple and similar to the calculation of the main effects. The FAST method (Cukier et al., 1973, 1975, 1978; Schaibly and Shuler, 1973) offers a sensitivity technique that is independent of any assumptions on the model structure and works for monotonic and non-monotonic models. The method explores the multidimensional space of the input factors with a search curve that scans the entire input space (Saltelli et al., 2000). This procedure provides a way to estimate the expected value and variance of the output variable and the contribution of individual input factors to this variance. An advantage of FAST is that the evaluation of sensitivity estimates can be carried out independently for each factor using just a single set of runs, because all the terms in the Fourier expansion are mutually orthogonal (Saltelli et al., 2000).

A detailed analysis of these methods and a survey on global sensitivity algorithms is beyond the scope of this review. The aim of this section is simply to raise the issue of the limits of local sensitivity and to introduce global sensitivity methods as a potential alternative. A couple of applications where these techniques have been used as a pre-screening step to optimal experiment design are now presented. Kontoravdi et al. (2005) applied Sobol's methods to a dynamic model of monoclonal antibody-producing mammalian cell cultures. The aim was to identify the parameters that were needed to be accurately determined experimentally and the results showed that only 8 parameters out of 30 were important. All the other parameters had very low sensitivity indices and so they could be kept at their nominal values. A high degree of parameter correlation was also observed and a dynamic GSA was applied to distinct cell growth phases during the batch culture. This analysis provided indications for the most informative sampling times, which could be used as initial guess for the subsequent experiment design. Thanks to this pre-screening step, the experiment design could be limited only to the eight important parameters with a significant reduction in the time and costs of the necessary experimentation. Ho et al. (2006) recently published a similar application of GSA, where the core parameters of a model for antibody-producing GS-NS0 cells under normal and hyperosmotic culture conditions were identified.

Use of GSA for pre-screening of potential models, and to identify which parameters in a model are potentially identifiable, appears to be one of the most promising preliminary test methods in an overall model-based experiment design/model validation procedure (Fig. 1).

5. Model-based experiment design for parameter precision: recent applications

As mentioned in the Introduction, model-based experiment design is becoming a reliable tool for rapid model development and validation and, as such, more widely used. The previous sections have already highlighted many significant and innovative applications. Several other recent applications of model-based experiment design for parameter precision are summarised in Table 2 . It can be seen that many of these studies aim to facilitate and improve kinetic and biological modelling. As noted by Bernaerts and Van Impe (2004), the design

Table 2
Various applications of model-based experiment design for parameter precision

Contribution			Reference
Application	Design criterion	Example used	
Biochemical networks	D-optimal design	Dose–response models (Hill equation)	Bezeau and Endrenyi (1986)
	Standard design criteria	Receptor–ligand reaction models with dynamic positron emission tomography data	Delforge et al. (1989)
	D-optimal design	Population pharmacodynamic models	Duffull et al. (2001)
	D-optimal design	Viral dynamics models	Han and Chaloner (2003)
	Bayesian design (robust design)	HIV dynamics model	Han and Chaloner (2004)
	Standard design criteria	Three-step biochemical pathway	Rodriguez-Fernandez et al. (2006)
	Optimal experiment design to reduce the average variance of model predictions	Epidermal growth factor receptor signalling and down-regulation model	Casey et al. (2007)
Biological processes (fermentation, bio-kinetics, etc.)	Modified E-optimal design	Fed-batch fermentation processes	Baltes et al. (1994)
	Modified E-optimal design	Fed-batch baker's yeast models	Ejiofor et al. (1994)
	Modified E-optimal design	Activated sludge respiration model	Vanrolleghem et al. (1995)
	D-optimal design	Two-step nitrification model	Ossenbruggen et al. (1996)
	D-optimal design	Anaerobic degradation of acetic acid	Merkel et al. (1996)
	D-optimal design	Bigelow growth model	Cunha et al. (1997)
	Modified E-optimal design	Haldane growth model	Versyck et al. (1997)
	D-optimal design	Baranyi bacterial growth model	Grijspeerdt and Vanrolleghem (1999)
	Maximin design (robust design)	Exponential growth models	Imhof (2001)
	Modified E-optimal design	Square root model describing the growth of *Escherichia coli*	Bernaerts et al. (2002)
	D- and E-optimal designs	Biological cardinal models (static growth experiments)	Bernaerts et al. (2005)
	D-optimal design	Model identification of biological networks	Gadkar et al. (2005)
	E-optimal design	Michaelis–Menten enzyme kinetic process	Lindner and Hitzmann (2006)
Chemical kinetics	Modified A-optimal design	Decomposition model of coal pyrolysis	Lohmann et al. (1992)
	D-optimal design	Batch control of crystallisation processes	Fujiwara et al. (2005)
	D-optimal design	Alkaline hydrolysis of *n*-amylacetate (only one measurement per experiment at the steady state)	Issanchou et al. (2005)
	A-optimal design	Toluene nitration model	Yang et al. (2006)
	E-optimal design (design-by-groups approach)	Validation of a non-isothermal biodiesel production model	Franceschini and Macchietto (2007a)
Heat/mass transfer	Maximin design (robust design)	Precise identification of heat transfer model parameters	Emery and Nenarokomov (1998) and Emery (2001)
	D-optimal design	Estimation of temperature -dependent thermal parameters	Dowding and Blackwell (1999)

Table 2 *(contiued)*.

Contribution			Reference
Application	Design criterion	Example used	
	D-optimal design	Estimation of heat and mass transfer parameters in capillary porous media	Dantas et al. (2002)
	D-optimal design (only one parameter)	Diffusion experiments for the binary mixture toluene–cyclohexane	Bardow et al. (2003)
	Modified E-criterion	Optimisation of the temperature sensor position in a hot wire probe	Nahor et al. (2003)
	D-optimal design	Kinetic parameter identification of a dynamic thermal degradation model (thiamine degradation during thermal processing of canned tuna)	Balsa-Canto et al. (2007)
Numerics	Novel approach	Model-based experiment design for ill-posed problems	Bardow (2006)
	E-optimal design: genetic algorithm for the optimisation	Michaelis–Menten enzyme kinetic process	Lindner and Hitzmann (2006)
	Standard design criteria: application of the stochastic optimisation method of Banga et al. (2002)	Three-step biochemical pathway	Rodriguez-Fernandez et al. (2006)
Regression models	Standard design criteria	Estimation of non-linear regression models	Rudolph and Herrendörfer, 1995
	Bayesian D-optimal design	Exponential regression models	Dette and Neugebauer (1997)
	E-optimal designs	Exponential regression models	Dette et al. (2003)
Robust design	Maximin designs	Non-linear models	Müller (1995)
	Bayesian D-optimal design	Exponential regression models	Dette and Neugebauer (1997)
	Bayesian D-optimal designs	Heteroscedastic polynomial models	Dette and Wong (1998)
	Maximin design	Precise identification of heat transfer model parameters	Emery and Nenarokomov (1998) and Emery (2001)
	Maximin designs	Exponential growth models and heteroscedastic polynomial models	Imhof (2001)
	Bayesian design	HIV dynamics model	Han and Chaloner (2004)
	Maximin designs	Dynamic models	Rojas et al. (2007)

of optimal experiments is particularly suitable for biological modelling since experimental data generation for bioprocesses is usually a very time-consuming, labour-intensive and costly job (the underlying systems are also rather complex).

It is worth noting that most applications mentioned in the paper and in Table 2 were carried out by the same researchers who also developed the methods. In spite of their demonstrated benefit, a notable obstacle to the diffusion of the techniques has been the lack of general availability of easy to use, let alone standardised software (say, in the form of a numerical solver library or commercial software). As a consequence, most experimental researchers (who often have little time for complex mathematics and statistics anyway) carry on planning experiments and analysing data in a very traditional, often manual way. A notable improvement in this area is offered by the recent proposal of a DOE facility in a commercial modelling and solution software (Process Systems Enterprise Ltd., 2007). Two demanding industrial applications have been publicly disclosed which also show the scope of the benefits achievable. The first (Shin et al., 2007) deals with the development of a new process for production of terphthaldehyde. Experiments in a laboratory setting were designed to identify and validate a complex reaction chemistry involving around 30 species (kinetic constants and adsorption equilibrium constants). Pilot plant experiments were also designed to assess the performance of the chemistry in catalytic and thermal oxidation reactions in a single reactor tube. The reactions identified turned out to describe the observed data well, yielding accurate parameter values, and the

models were then used to develop and optimise an entire new proprietary process and full plant design. The second application (Baumler et al., 2007) details how model-based DOE is used to support new catalyst development in a leading industrial company. Experiments are first carried out in a micro-reactor environment to estimate kinetic mechanisms and accurate parameters. These are then coupled with full scale reactor models to predict the performance of candidate catalysts in full scale operation and tailor the reactor design to specific catalysts. This methodology was applied to two cases, a high-fidelity methanol synthesis loop, and an undisclosed "common" partial oxidation process, enabling the prediction and optimisation of catalyst activity in a real plant (methanol case), and establishing optimum operational catalyst loading and temperature/throughput trade-offs (partial oxidation case). Substantial benefits are mentioned from both cases.

6. Conclusions

This paper has intended to present a selected overview of model-based experiment design techniques for increasing parameter precision. The theoretical background, the numerical and theoretical issues arising from the use of these methods and examples of practical and interesting applications have been described. These applications have been selected from a wide range of fields: chemical kinetics, process control, biological systems, pharmacodynamics, etc. in order to highlight the growing importance and use of model-based experiment design techniques in process engineering. The advantages obtainable from a reasoned employment of these methods are now well consolidated: optimally designed experiments allow quality information to be extracted from the experimental data with less time and resource consumption. This is particularly important in traditional fields such as kinetic and biological modelling, where the complexity of underlying systems is high and cost and length of experimentation can be heavy.

This paper has reviewed numerous studies aimed at improving experiment design techniques, from the definition of novel objective functions (such as, for example, new metrics to measure the information content of the optimal experiments) to innovative formulations which take into account other issues than the information content of the measurements, such as, for example, parameter correlation, confidence region curvature, missing observations, etc.

The local validity of the sensitivity analysis on which model-based DOE is based has been early identified as a significant limitation of this approach. Robust design techniques have been proposed, from Bayesian to maximin designs, to account for the uncertainties in the model parameters. These novel methods did not find a wide use at the beginning because of the severe computational load required to solve these problems. Recent advances in optimisation techniques (multiple shooting, stochastic algorithms, semi-infinite programming methods) have made even worst-case (maximin) designs more easily accessible.

The number of parameters involved in the mathematical model can represent another limitation for the application of model-based experiment design techniques. The recent improvements in the computation of GSA (another technique which may involve a heavy computational load) have made possible to use this method in a sort of pre-screening step (precursor to optimal experiment design) so as to concentrate the design effort only on the core model parameters.

From the first theoretical studies on model-based experiment design, the method has undergone significant developments, in particular in the last 10 years when the advances in computation have made the use of these techniques possible for more complex applications with reasonable solution times. These methods are now becoming available within commercial software.

A major conclusion is the recognition that the standard criteria, which attempted to capture all the "goodness" of an experiment in a single scalar measure of "information content", are necessarily of limited value. A far richer approach is emerging, where various aspects of interest (directional information about individual parameters, specific correlations, etc.) can be quantified and explicitly included in the optimal design formulations. This involves moving from single objective optimisation to multi-objective optimisation. A pleasing consequence of the dynamic optimisation approach is that such extensions can be easily accommodated through suitable alternative objective functions and constraints. Parametric solutions of the Pareto curves representing trade-offs between conflicting objectives have not yet appeared, but are clearly just around the corner.

A continuous interest and effort of the scientific community to improve and make all techniques more accessible, effective and efficient remain desirable for the future so that model-based experiment design can become a standard tool for experimentalists and industrial applications.

Notation

c	overall curvature of inference region surfaces
Corr	parameter correlation matrix
$\mathbf{f}$	vector of model equations
$\mathbf{M}$	dynamic information matrix
n, n_c	number of experimental measurements and of constraints
n_{diff}, n_s	number of differential and state variables
$n_{\text{eq}}, n_{\text{resp}}$	number of model equations and of responses
$n_{\text{exp}}, n_{\text{exp}}^P$	number of optimal experiments and number of experiments designed in parallel
$n_{\text{sp}}, n_{\text{sw}}$	number of sampling and switching times
$n_u, n_{\bar{w}}$	number of time-varying and time-invariant controls
Of	objective function
p	number of parameters
q_{ij}	sensitivity of response i to parameter j
$\mathbf{Q}, \mathbf{Q}_r$	dynamic sensitivity matrix and dynamic sensitivity matrix of the rth response
r	number of repeated measurements
s^2	estimate of measurement variance
S_r	sum of squares of residuals
t	time

$\mathbf{t}_{sp}$	sampling time vector
$\mathbf{u}$, $\mathbf{U}$	vector of time-varying control variables (input variables) and input space
$\mathbf{V}$	parameter variance–covariance matrix
V_{ii}, V_{ij}	variance of ith parameter and covariance between parameters i and j
$\bar{\mathbf{w}}$, $\mathbf{x}$	vector of time-invariant parameters and of state variables
$\mathbf{y}$, $\widehat{\mathbf{y}}$	vector of measured response variables and of responses simulated by the model
$\mathbf{y^0}$	vector of initial conditions
z_{ij}	level of ith control variable over the jth interval (piecewise constant approximation)
$\hat{\mathbf{Z}}$	residual matrix

Greek letters

$\boldsymbol{\beta}$	vector of variance model parameters
γ	heteroscedastic factor
$\boldsymbol{\eta}$, $\boldsymbol{\eta}_s$	vector of noise (random errors) and of systematic errors
$\boldsymbol{\theta}$, $\boldsymbol{\Theta}$	parameter vector and parameter space
$\hat{\boldsymbol{\theta}}$	vector of the current parameter estimates
$\boldsymbol{\lambda}$	vector of eigenvalues
Λ	condition number
σ^2	measurement variance
$\tilde{\sigma}_{rs}$	element (r, s) of the inverse of $\boldsymbol{\Sigma}_y$
$\boldsymbol{\Sigma}_\theta$	approximation of parameter variance–covariance matrix
$\boldsymbol{\Sigma}_y$	variance–covariance matrix of the measurements
τ	experiment duration
$\boldsymbol{\tau}_{sw}$, $\bar{\boldsymbol{\tau}}_{sw}$	vector of switching times and of intervals for the control variables
$\boldsymbol{\varphi}$, $\boldsymbol{\Phi}$	design vector and design space
ω	measurement standard deviation

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