Novel Anticorrelation Criteria for Model-Based Experiment Design: Theory and Formulations

Gaia Franceschini and Sandro Macchietto
Dept. of Chemical Engineering, Imperial College London, South Kensington Campus, SW7 2AZ London, U.K.

DOI 10.1002/aic.11429
Published online February 21, 2008 in Wiley InterScience (www.interscience.wiley.com).

Model-based experiment design techniques are becoming an essential tool for the rapid development and refining of process models. One of the areas where an effective design can be most useful is the identification of the kinetic parameters of a model. When complex kinetic networks (i.e., parallel, consecutive reactions) are involved, parameter correlations play a significant role because they often prevent the solution of experiment design calculations, make parameter identification more difficult, and decrease the statistical validity of the resulting models. It is therefore important to obtain estimates of the parameters as uncorrelated as possible and this article presents new optimal experiment design criteria that include explicit measures of correlation as objective function or as constraints and are able to target the experiments to the improvement of specific parameter(s). Through an illustrative application to an epoxidation example, the new approach proposed is demonstrated to be very successful, highly flexible, and more effective than the standard experiment design criteria in both reducing the uncertainty regions of the parameters and improving the reliability of the estimates. © 2008 American Institute of Chemical Engineers *AIChE J,* 54: 1009–1024, 2008
Keywords: kinetics, model-based experiment design, nonlinear dynamics, parameter correlation, parameter identification

Introduction

The use of mechanistic dynamic mathematical models is a key and well-established activity in process engineering; its main advantage is the possibility of gaining a better understanding of the different phenomena, which occur within the system under investigation. By expressing the underlying phenomena in a compact mathematical form, these detailed models can be used to improve product, process, and plant performance in a wide range of applications. Therefore, building high quality and validated models of process systems cannot be ignored in many applications such as model-based product and process design, control, and optimization.

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 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 with the maximum precision and to validate their estimates and the model statistically against experimental data. However, collecting the required data can be costly, both in terms of time and resources (materials, equipment, labor, analytics ...). Therefore, there is a need to develop such models in a systematic way to maximize the information obtained from each experiment and to minimize the number of analyses, the cost of materials, and the time required. From this point of view, the technique of *Model-based design of experiments* is an important link between the experimental and the modeling world. Using progressively

Correspondence concerning this article should be addressed to G. Franceschini at g.franceschi03@imperial.ac.uk.

improved approximations to the model and its parameters, it aims at obtaining the maximum information from the experimental apparatus being modeled by devising experiments that will yield the most informative data, in a statistical sense, for use in parameter estimation, and model validation.

Early developments in experiment design considered mainly steady-state models (both linear and nonlinear 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,[1] Box and Hunter,[2,3] Draper and Hunter,[4–6] Box,[7] Hill et al.,[8] and Hunter et al.[9] The extension of experiment design concepts to dynamic experiments/models has been a slow process[10] although already in 1977 the potential benefits of these techniques for dynamic studies were amply recognized.[11] Since then, several studies have successfully applied model-based experiment design techniques to a wide range of systems and/or have tried to improve the experiment design method by developing new objective functions or novel and more efficient algorithms for the numerical solution of the underlying optimization problem.[12–21] One of the areas where an effective experiment design can be most useful is the identification of the kinetic parameters of a model. As highlighted in a previous publication by the authors[22] and by many others, this problem can be very much complicated by the large number of parameters often involved in kinetic mechanisms and by their significant interactions. Reaction networks constituted of parallel, sequential, competitive, or consecutive steps are all examples of kinetic models characterized by highly correlated parameters, which often prevent successful experiment design and/or parameter identification. The specific issue of correlation has not been properly addressed in the literature yet (see the section on parameter correlation and experiment design) and this article presents a novel approach to the experiment design of complex kinetic models capable of reducing parameter correlations while maintaining the same aims of traditional designs (improving the precision of the parameters). The theory on which the novel experiment design criteria are based is illustrated after the introduction and the four formulations proposed are then discussed in detail. An illustrative three-parameter example is introduced in the Results section to clarify the concepts described and highlight the effectiveness and flexibility of the proposed approach in reaching the desired goals (correlation reduction and increase in the information content of all or selected parameters). Two subsequent publications[23,24] will present more complex applications and a thorough discussion of some of the issues, which are merely noted in this work (such as the choice of the most appropriate bounds and criteria, the potential rotation of the ellipsoid during the design, and the preliminary analyses required for a reasoned application of the criteria). Franceschini and Macchietto[23] have also proposed a comprehensive algorithm and a set of recommendations to help the user in adopting the novel approach.

The next section contains a brief overview of model-based experiment design and of the issue of parameter correlation. The negative effects caused in parameter estimation and experiment design procedures by highly correlated parameters are highlighted, and a critical survey of the very few works published on the subject is presented.

Model-based experiment design formulation

In what follows, a general deterministic model described by a set of (possibly mixed) differential and algebraic equations (DAEs) is considered:

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

where t is time, $\mathbf{f}$ is a n_{eq}-dimensional set of differential and algebraic equations, which is assumed to have continuous first partial derivatives with respect to its arguments. $\mathbf{x}(t)$ is a n_{s}-dimensional vector of time dependent state variables, $\dot{\mathbf{x}}(t)$ is an n_{diff}-dimensional vector of differential variables, $\mathbf{u}(t)$ is a n_{u}-dimensional vector of time-varying controls or inputs to the process, $\mathbf{w}$ is a n_{w}-dimensional vector of constant controls or inputs to the process, $\boldsymbol{\theta}$ is a p-dimensional vector of model parameters to be determined, and $\mathbf{y}(t)$ is an n_{resp}-dimensional vector of measured response variables that are functions of the state variables, $\mathbf{x}(t)$. In most cases, $\mathbf{h}(\mathbf{x}(t))$ will simply be a "selector" function, selecting those state variables that are in fact measured. For dynamic experiment design purposes, the number of measurements for each response variable $\widehat{y}_i$ is assumed to be finite and defined by a fixed number n_{sp_i} of samples, taken at sampling times $\mathbf{t}_i^{\text{sp}}$.

Model-based design of experiments aims at assisting a modeler/experimenter in devising experiments that will yield the most informative data, in a statistical sense, for use in parameter estimation and model validation. In mathematical terms, given an initial model and current values of its parameters, the aim is to minimize the expected inference region of the new parameters, that is, to make the elements of the parameters variance–covariance matrix small. An experiment design calculation thus involves minimizing some metrics of this matrix or of its inverse, the information matrix, by choosing a set of experiment decision variables (length, time-varying and time invariant controls, initial conditions, sampling times, etc.), which are collected in the so-called design vector ϕ, subject to equality or inequality constraints defining the allowable experimental conditions and (expected) responses.[12] Various real-valued functions have been suggested as suitable metrics for the "size" of the parameters variance–covariance matrix or of the information matrix. The most common criteria are three:

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

Because 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), all these criteria have a geometrical interpretation. The D-optimal criterion aims at minimizing 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 (see Walter and Pronzato,[25] for a detailed discussion of experiment design criteria and their interpretation).

The joint confidence regions provide a reasonable way to assess the reliability of parameter estimates, with one qualification. Linear approximations to the inference regions are easily obtained from a first-order Taylor series approximation to the expectation function[26] and are therefore typically used as a basis for estimating the above criteria. However, as pointed out by several authors,[27–29] these linearization techniques apply only approximately to nonlinear models and in case of highly nonlinearity can be quite unreliable. Alternative techniques have been developed for establishing confidence regions for nonlinear models such as profiling[27] or other methods based on the curvature measures of Bates and Watts[30,31] (see Benabbas et al.[32] for an application of these curvature measures to model-based experiment design). In this work, only linear approximations to joint confidence regions will be adopted, although the alternatives outlined above could be used just as easily.

Parameter correlation and experiment design

Model-based experiment design techniques aim at improving the precision of the parameter estimates through a set of optimally designed experiments. The method assumes that if the (predicted) information content of the new experiment is enhanced, the accuracy of the estimates, which is assessed by means of standard statistical tests, such as the *t* test (see Asprey and Naka[26] for a detailed discussion on statistical tests for parameter estimation), will improve. The standard criteria for experiment design (A-, D-, and E-optimal) represent different methods for evaluating this information content by means of simple scalar metrics. However, the accuracy of a parameter estimate is given not just by its individual *t* test: the relationships between the different parameters of the model and in particular their correlations are also very important. Correlations between parameters represent a well-known, significant problem in estimation. The search of an optimum in the estimation objective function (typically, the maximum likelihood) can be seriously hindered if the parameters are correlated. In this case, they give rise to badly conditioned optimization problems with elongated valley surfaces in the objective function, which can create severe difficulties to most optimizers.[33] Moreover, when the parameters are highly correlated, 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.[34] In addition to convergence problems in the estimation, which can hinder the solution of the design of experiments as well, correlations generate another very significant difficulty, because, if the parameters are highly correlated, the estimates obtained may be inaccurate.[35] The third but no less important problem caused by parameter correlation involves the reliability of the statistical tests by means of which the accuracy of the estimates is assessed. The *t* test requires a series of hypotheses to be satisfied to give reliable results. The two most important hypotheses are the normality of the samples subjected to test and their statistical independence. The latter is the more significant of the two: the *t* test is more robust against deviations from normality than against departures from the sample independence hypothesis.[36] In case of dependent (or partially dependent) samples, the results of the test can be inaccurate and unreliable. The concept of statistical independence is strongly related to that of correlation: in normal distributions, lack of correlation implies statistical independence.[37] Only if the parameters are uncorrelated, it is therefore possible to establish confidence intervals and statistical tests for each component individually and obtain reliable results. Figure 1 illustrates the concept graphically: Figure 1a represents the case of two highly correlated parameters while in Figure 1b the correlation coefficient is zero.

The ellipses in Figure 1 correspond to the joint 95% confidence region for the true parameters (θ_1 and θ_2) and enclose pairs (θ_1, θ_2) which the data regard as jointly reasonable for the parameters (the correlations between parameters are taken into account). The individual 95% confidence intervals (always calculated by parameter estimation software) for θ_1 and θ_2 separately are appropriate for specifying ranges for the individual parameters irrespective of the value of the other parameter. The joint message of individual confidence intervals (the dashed rectangular regions in Figure 1) can be very misleading in case of highly correlated parameters, as it can be seen in Figure 1a. Entire sections of the rectangle contain points (such as points A or B), which are wrongly indicated as reasonable values for (θ_1, θ_2). If the parameters

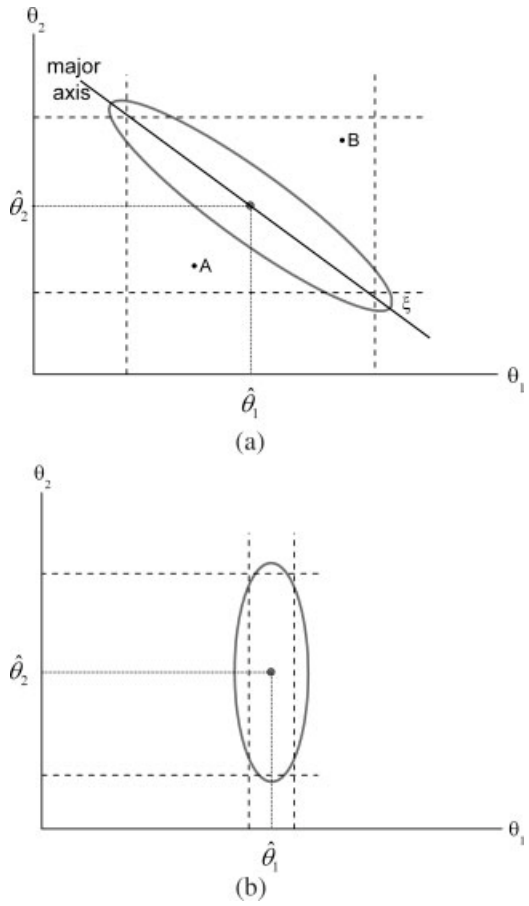

Figure 1. Individual confidence intervals and joint confidence region for (a) highly correlated parameters and (b) uncorrelated parameters. $\hat{\theta}_1$ and $\hat{\theta}_2$ are the estimated values of the true parameters θ_1 and θ_2.

are uncorrelated (Figure 1b), then the rectangular region defined by the individual confidence intervals will better approximate the true joint region, although the latter is the correct one.[38] Moreover, when the parameters are correlated, it is difficult to determine how well each individual parameter estimate is identified. From Figure 1a, it is only possible to affirm that there is a relative lack of precision associated with the value $\theta_1 \cos \xi + \theta_2 \sin \xi$ (a measurement parallel to the major axis of the ellipse), while the value of $-\theta_1 \sin \xi + \theta_2 \cos \xi$ is well determined (a measurement perpendicular to the major axis of the ellipse). ξ is the angle between the major axis of the ellipse and the x-axis (see Figure 1a). In case of Figure 1b, because the parameters are uncorrelated, the single estimates can be evaluated individually: estimate θ_2 is found to be more poorly determined than estimate θ_1.[39]

In the last 20 years, several studies have highlighted the problems, which can affect an estimation procedure when parameters are highly correlated,[40–43] but only a few of them have tried to propose and implement a solution based on

- model reparameterization and/or variable separation,[44–47]
- well-designed experiments,[42,48]
- independent estimation of as many parameters as possible.[49]

The rest of these works simply noted the problem and concluded with a generic recommendation of trying to avoid correlated parameters as much as possible.[50]

Few papers in the literature have identified a suitable experiment design procedure as a possible way of overcoming the correlation problem. Box and Hunter[3] suggested that for a two-parameter model the volume criterion (D-optimal design) minimizes 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 derives directly from the definition of the determinant of a (2×2) matrix but cannot, however, be extended to models with three or more parameters. For this reason, Pritchard and Bacon[42] proposed a new criterion alternative to the traditional D-optimal design, which has a measure of the overall extent of the correlation present among the parameters as objective function to be minimized (i.e., a scalar measure of "size" for the correlation matrix **C**). The measure proposed as more effective is the root square of the individual correlations between pair of parameters:

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

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. The very large correlations between the pre-exponential factors and the activation energies of the Arrhenius' equations were however not improved, and the authors concluded that even a correlation-specific experiment design could do little to reduce these correlations, which are largely due to the form of the Arrhenius' expression. Pritchard's criterion was then successfully applied by Agarwal and Brisk[51] to a steady-state model for an ethylene hydrogenation reaction and by Issanchou et al.[52] to an alkaline heterogeneous hydrolysis reaction (at the steady state). In both studies, a correlation decrease was achieved to the detriment of the quality of parameter identifiability because the sizes of the uncertainty regions were substantially higher than in the D-optimal case.

To obtain uncorrelated estimates, Bernaerts et al.[34] adopted the modified E-optimal design first introduced by Mehra.[53] This criterion uses as objective function, the condition number ($\overline{\Lambda}$) of the information matrix, that is, the ratio between the largest and the smallest eigenvalue. For a two-parameter model, a perfect circular shape of the confidence ellipsoid ($\overline{\Lambda} = 1$) indicates that both estimates are identified with the same precision, and the parameters are uncorrelated. The criterion was successfully applied to a bacterial growth model but this modified E-optimal approach, as the D-optimal criterion of Box and Hunter,[3] is effective in reducing the correlations only for two-parameter models.

Novel Anticorrelation Design Criteria: Main Principles

As the short review presented in the previous section has highlighted, the experiment design criteria aiming at reducing parameter correlations published so far are limited to two-parameter models or have been applied only to steady-state processes. The novel approach proposed and presented in this article is far more general and can be applied to very large class of nonlinear dynamic models in the form of Eq. 1, DAE systems, and with a generic number p of parameters.[54]

First, new scalar metrics are developed that allow parameter correlation to be explicitly taken into account even for multiple parameter models. Second, as the works of Agarwal and Brisk[51] and Issanchou et al.[52] have revealed, an experiment design criterion, which aims only at reducing parameter correlations is likely to produce large confidence regions for the parameters because the information content of the experiment is not included in the design. For this reason, most of the criteria proposed in this article aim at finding the best possible tradeoff between reduction in the parameter correlation and increase in the information content of the experiment. Finally, when dealing with complex kinetic networks, it is often highly useful to design experiments specifically targeted at improving a selected parameter or group of parameters of interest,[22] and this work shows how the novel criteria may be used to achieve this. They exploit some concepts of principal component analysis[55–57] to reach this goal (see next section), and the simultaneous reduction in the parameter correlation makes this experiment targeting much more effective.

Association between eigenvalues and parameters

For a dynamic experiment, the information matrix can be calculated according to the following definition, first derived by Zullo[58]:

$$\mathbf{M}(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}) = \sum_{r=1}^{n_{\mathrm{resp}}} \sum_{s=1}^{n_{\mathrm{resp}}} \sigma_{rs} \mathbf{Q}_r^T \mathbf{Q}_s \tag{3}$$

where n_{resp} is the number of model responses, $\hat{\boldsymbol{\theta}}$ is the vector of the best available estimates of the model parameters, ϕ is

Table 1. Information Matrix and Its Principal Component Analysis at the Base Point and at an Optimal Point (No Parameter Correlations) for the Epoxidation Example (the Optimal Point is That Obtained in the First Iteration of Case 2 in the Results Section)

	Principal Direction 1	Principal Direction 2	Principal Direction 3	Information Matrix
Base point				
Eigenvalues	$\lambda_3 = 0.12e^3$	$\lambda_2 = 0.68e^1$	$\lambda_1 = 0.11$	$\begin{bmatrix} 0.1845 & -1.9955 & -2.192 \\ & 59.861 & 56.321 \\ & & 66.597 \end{bmatrix}$
	$0.2478e^{-1}$	0.7473^{-2}	-0.999	
Eigenvectors	-0.6855	0.72802	$-0.1155e^{-1}$	
	-0.7277	-0.68552	$-0.2346e^{-1}$	
Relative importance	0.06	0.01	99.93	
	46.99	53	0.01	
	52.95	46.99	0.05	
Optimal point				
Eigenvalues	$\lambda_3 = 0.12e^3$	$\lambda_2 = 0.68e^1$	$\lambda_1 = 0.135e^1$	$\begin{bmatrix} 1.346 & -0.03 & -0.082 \\ & 6.733 & 0.0048 \\ & & 116.53 \end{bmatrix}$
	$0.707\ e^{-3}$	$-0.559e^{-2}$	0.999	
Eigenvectors	$-0.445e^{-4}$	0.999	$0.559e^{-2}$	
	-1	$-0.484e^{-4}$	$0.7077e^{-3}$	
Relative importance	0	0	100	
	0	100	0	
	100	0	0	

the design vector, and σ_{rs} is the element (r, s) of the inverse of the variance–covariance matrix of the experimental measurements. $\mathbf{Q}_r$ is defined as

$$\mathbf{Q}_r = \left[\frac{\partial y_{ri}}{\partial \theta_j}\right] \qquad i = 1, \ldots, n_{sp};\ j = 1, \ldots, p \qquad (4)$$

and is the matrix of the first-order sensitivity coefficients of the rth model response, computed at each of the n_{sp} sampling times. $\mathbf{Q}_s$ is the sensitivity matrix of the sth model response.

According to the theory of principal component analysis, an explicit connection between parameters and eigenvalues can be identified by diagonalizing the information matrix $\mathbf{M}$ in the following way:

$$\mathbf{M} = \overline{\mathbf{E}}\mathbf{\Lambda}\overline{\mathbf{E}}^{\mathrm{T}} \qquad (5)$$

where $\mathbf{\Lambda}$ is a diagonal matrix formed by the eigenvalues of $\mathbf{M}$, and $\overline{\mathbf{E}}$ is the matrix of the corresponding normed eigenvectors. The new parameters $\mathbf{\Psi} = \overline{\mathbf{E}}^{\mathrm{T}}\ \boldsymbol{\theta}$ (θ is the vector of the model parameters) are called principal components and are a linear combination of the original ones. From the inverse of the information matrix (the parameter variance–covariance matrix) a hyperellipsoid can be obtained in the parameter space, which represents the true joint confidence region of the parameters (see Asprey and Naka,[26] for more details). The eigenvectors of the information matrix define the orientation of this ellipsoid with respect to the parameter axes (each eigenvector identifies a principal direction), and the relative lengths of the axes of the ellipsoid are given by the eigenvalues of $\mathbf{M}$. Therefore, these eigenvalues quantify the effectiveness and importance of the parameters, which contribute to the corresponding principal directions and thus the precision with which these parameters can be obtained.

As Figure 1 in the introductory section illustrates, if there are no correlations between the parameters, the confidence ellipsoid is parallel to the axes.[38] In such a situation, each of the principal directions of the information matrix (or of the variance–covariance matrix) is dominated by a specific parameter. This derives directly from the condition of parallelism: only one eigenvector component for each principal direction is significantly different from zero if the ellipsoid and the parameter axes are essentially parallel. For example, Table 1 (optimal point) shows the eigenvalue–eigenvector decomposition of a 3×3 information matrix obtained after an experiment design, which essentially eliminates any correlation between the three parameters (see first iteration of case 2 in the Results section). The relative importance is calculated according to Perger et al.[59] as the square of each eigenvector component and indicates how significant the parameters are in each of the principal directions.

As it can be seen from the table, parameter k_3 controls the first principal direction (the one with the maximum information content, $\lambda_1 \approx 10^2$), whereas parameter k_2 is related to the second direction ($\lambda_2 \approx 7$). The third principal direction (dominated by k_1) shows the smallest eigenvalue ($\lambda_3 \approx 1$) and is therefore not as informative as the other two. After performing the experiment, which corresponds to this information matrix, the estimate of parameter k_3 is expected to be the most precise.

Therefore, if there are no correlations between the parameters, the principal component analysis of the information matrix can easily relate the parameters with the corresponding eigenvalues. This characteristic is exploited in two of the new anticorrelation criteria (ACE and E-AC) for the experiment design (see next section) to target an optimal experiment to a desired parameter or set of parameters. If not all the correlations can be eliminated (because of the model structure, for example), the confidence ellipsoid is no longer parallel to the parameter axes at the end of the design and this can influence the effectiveness of the design criteria in targeting specific parameters. In such a case, some principal directions will be dominated by groups of parameters and therefore minimizing the corresponding eigenvalues will help gather information about these parameter combinations. When all the parameters of the model need improving, this feature does not represent a drawback. However, if the precision of a single specific parameter must be enhanced, a further criterion, the AC-V design is a better one to use. This issue is discussed in detail in Franceschini and Macchietto.[23]

Criteria Formulation

The novel experiment design criteria proposed in this work are based on taking into explicit account the parameter correlation coefficients in the problem formulation. The first criterion seeks only to reduce/eliminate the parameter correlations without taking into account the information content of the data. The other three novel criteria have a double aim

- to find the best possible trade-off between reduction in the parameter correlation and increase in the information content of the experiments and
- to plan, if so desired, experiments specifically targeted at improving a selected parameter or group of parameters (according to the principles explained earlier).

The correlation matrix (**C**) is calculated, by definition, from the elements of the variance–covariance matrix (**V**):

$$C_{ij} = \frac{V_{ij}}{\sqrt{V_{ii}}\sqrt{V_{jj}}} \qquad i,j = 1,\ldots,p \tag{6}$$

Because **V** is the inverse of the information matrix, the correlation coefficients required in the formulation of the novel criteria can be easily computed at each iteration of the experiment design calculations by inversion of the information matrix, **M**.

An experiment design procedure for dynamic systems may be formulated that directly use the correlation matrix in several new ways (see the next sections for more detailed formulations):

1. to minimize all or some of the correlation coefficients:

$$\min_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} f\ (\mathbf{C}(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})) \tag{7}$$

2. to minimize all or some of the correlation coefficients, subject to an acceptable level of information content for the experiment (measured through one or more of the eigenvalues of the information matrix):

$$\min_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} f\ (\mathbf{C}(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})) \tag{8}$$

$$\text{s.t. } \lambda_i - \lambda_i^0 > \varepsilon_i^{\lambda} \qquad i \in \{1,p\} \tag{9}$$

where λ_i indicates an eigenvalue of **M** (associated with a certain parameter) and ε_i^{λ} is a specified lower bound for the increase of λ_i over its initial value λ_i^0, calculated at some base point;

3. to maximize the information content of the experiment (measured through one or more of the eigenvalues of the information matrix) subject to an acceptable value of correlation between individual parameter pairs:

$$\max_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} f\ (\mathbf{M}(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})) = \max_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} \lambda_i(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi}) \qquad i \in \{1,p\} \tag{10}$$

$$\text{s.t. } C_{ij}\big|_{i\neq j} < \varepsilon_{ij}^{C} \qquad i = 1,\ldots,p-1; \quad j = 2,\ldots,p; \tag{11}$$

4. to minimize all or some of the correlation coefficients, subject to acceptable values of the variances of specified parameters (targeted experiments):

$$\min_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} f\ (\mathbf{C}(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})) \tag{12}$$

$$\text{s.t. } V_{ii} < \varepsilon_i^{V} \qquad i \in \{1,p\} \tag{13}$$

where V_{ii} is the variance of parameter i and ε_i^{V} a threshold tolerance value.

In all above formulations 1–4, p is the number of model parameters, ϕ the design vector (see introduction), Φ the design space (identified by the allowable range of all the design variables included in the vector ϕ), and $\hat{\boldsymbol{\theta}}$ the vector of the best currently available estimates. In practice, because the correlation coefficients can be both positive and negative, their square value should be considered in the objective function and in the constraints so as to avoid discontinuities in the optimization, which can hinder the numerical solution. These considerations lead to the following formulations.

Criterion 1: PAC design

The aim of the first novel design is to eliminate or, if that is not possible, to reduce the correlations between the parameters without taking into account the information content of the experiments. Therefore, the design criterion involves only the correlation coefficients and two different formulations can be defined:

- Criterion PAC1: the objective function to be minimized is the sum of the square values of all the correlation coefficients

$$\min_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} \sum_{\mathrm{i}=1}^{\mathrm{p}-1} \sum_{\mathrm{j}=2}^{\mathrm{p}} C_{\mathrm{ij}}^2(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})\big|_{i\neq j}\ ; \tag{14}$$

- Criterion PAC2: the objective function minimized is the largest correlation coefficient (selected based on the values of the correlation matrix **C** at the base point), subject to upper bounds on the acceptable magnitude of each of the other correlation coefficients. A different bound ε_{kl}^{C} can be set for each of the correlation coefficients involved in the constraints:

$$\min_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} C_{ij}^2(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi}) \text{ with } i,j \text{ such that}$$

$$C_{ij} = \max \mathbf{C}\big|_{\text{basepoint}} \text{ and } i,j \in \{1,p\} \tag{15}$$

$$\text{s.t. } C_{kl}^2(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})\Big|_{\substack{k\neq l \\ k,l\neq i,j}} < \varepsilon_{kl}^{C} \qquad k,l \in \{1,p\} \tag{16}$$

The PAC2 criterion can be more advantageous in case of models with a high number of parameters because a sum involving many terms can be a difficult function to minimize (it may be flat or present several minima). When dealing with highly-parameterized models, the two formulations of the PAC criterion can also be combined: the objective function can include the sum of a subset of all correlation coefficients (for example, the largest ones) with the other coefficients subject to the constraints (16).

Criterion 2: ACE design

The PAC criterion takes into account only the correlations between the parameters and tries to reduce them as much as possible; the effect of this minimization on the eigenvalues

of the information matrix and so on the information content of the experiment is not considered. The optimal experiments planned with the PAC criterion are, therefore, not expected to be necessarily informative, although a reduction in the correlations surely enhances the confidence in the statistical assessment of the estimates and should also improve the estimates themselves.

The ACE design formulation combines both aims (increase in the information content and reduction in the parameter correlations) in a single criterion: in this way, a trade-off between the requirements of the PAC criterion and those of the standard methods (such as the E-optimal design) may be achieved. The ACE criterion uses the same objective function and constraints described in the previous section for the PAC design. In addition, one or more additional constraints on the eigenvalues of the information matrix are added to ensure at least a minimum level for the information content of the experiments. Two variants of the criterion can be adopted:

1. ACE1: the information content is expressed by means of a single eigenvalue;
2. ACE2: two or more eigenvalues are involved in the constraints.

The constraints on the eigenvalues are formulated in both cases according to Eq. 9 but the choice of bound ε_i^{λ} depends on the specific variant considered.

Criterion ACE1.

$$\min_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} C_{ij}^2(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi}) \text{ with } i,j \text{ such that}$$

$$C_{ij} = \max \mathbf{C}\big|_{\text{basepoint}} \text{ and } i,j \in \{1,p\}$$

$$C_{kl}^2(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})\Big|_{\substack{k\neq l\\ k,l\neq i,j}} < \varepsilon_{kl}^C \qquad k,l \in \{1,p\}$$

s.t.

$$\lambda_i - \lambda_i^0 > \varepsilon_i^{\lambda} \qquad i \in \{1,p\} \qquad (17)$$

A bound is imposed on one eigenvalue of the information matrix depending on the accuracy wanted for the estimation of a specific parameter. As previously highlighted, when the correlations between the parameters are eliminated (the main aim of the ACE criterion), each eigenvalue represents the information content of the experiment for the parameter, which dominates the principal direction corresponding to that eigenvalue. Therefore, the information content for a specific parameter can be enhanced by bounding from below its corresponding eigenvalue. First, the appropriate eigenvalue to be constrained and then a suitable value of the acceptable bound must be selected.

The smallest eigenvalue of the information matrix (at the base point) is the most logical choice for selection in the constraint: in this way, the design tries to improve the estimate of the most uncertain parameter (as in the E-optimal design). Usually, enhancing the accuracy of this parameter allows a better estimate of some other parameters as well. However, in case of sequential or parallel approaches to the experiment design, it may be very useful to enhance the estimation of some other specific parameters. For example, in a parallel design, each experiment could be planned to increase the information content of a different parameter while reducing the correlations. In a sequential approach, the first step could reduce the correlations and improve the estimate of the most uncertain parameter. After the first parameter estimation, the new most uncertain parameter could be identified, and the next experiment designed to improve the information content for this parameter and so on.

To establish the connection between parameters and eigenvalues and so choose the most appropriate formulation for the constraint, a preliminary eigenvalue–eigenvector decomposition of the information matrix at the current point (base point) should suffice. Very often, the base point information matrix generates an ellipsoid, which is not parallel to the axes (the parameters are correlated before the design); however, it is already possible to identify which parameters or groups of parameters dominate the various principal directions. Table 1 reports, for example, the information matrix at the base point for the case study discussed in the Results section. It can be seen that k_1 is already the dominant parameters for the third principal direction (the most uncertain one) while k_2 and k_3 control with approximately equal contributions the first and second principal direction.

However, the design can possibly cause a rotation of the ellipsoid around its axes and change the association between eigenvalues and parameters in subsequent iterations. In this way, the experiment obtained may turn out to be not so informative for the wanted parameter. If this happens, a constraint can be introduced to prevent an ellipsoid rotation from changing the parameter-eigenvalue connection shown at the base point. If the aim is to have parameter i dominating the principal direction j, it is sufficient to ensure that its relative importance in that direction, imp_{ij}, is greater than a value $\varepsilon_{ij}^{\text{imp}}$ in excess of 50%; the following constraint formulation can therefore be used:

$$\text{imp}_{ij} > \varepsilon_{ij}^{\text{imp}} \text{ with } 55 < \varepsilon_{ij}^{\text{imp}} < 100 \text{ and } i,j \in \{1,p\} \qquad (18)$$

For the constraint on the eigenvalues required by the ACE criterion [Eq. (9)], the bound ε_i^{λ} can be chosen within the range:

$$\left[0, (\lambda_i - \lambda_i^0)\big|_{E-\text{optimal}}\right] \quad i \in \{1,p\} \qquad (19)$$

If the lower bound (0) is adopted, this constraint simply requires the final eigenvalue to be larger than λ_i^0, the value at the base point. The upper bound corresponds to the value of λ_i obtained in a standard E-optimal design. It can be noted that reducing the correlations and increasing the information content of the experiment are often opposite requirements. Therefore, because no constraints on the correlations are imposed when the E-optimal criterion is used, the eigenvalues obtained with this design are the highest possible. The closer the tolerance ε_i^{λ} to the upper bound, the more evident the trade-off with the correlation level will be.

Criterion ACE2.

$$\min_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} C_{ij}^2(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi}) \text{ with } i,j \text{ such that}$$

$$C_{ij} = \max \mathbf{C}\big|_{\text{basepoint}} \text{ and } i,j \in \{1,p\}$$

$$\text{s.t.} \quad C_{kl}^2(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})\Big|_{\substack{k\neq l\\ k,l\neq i,j}} < \varepsilon_{kl}^C \qquad k,l \in \{1,p\} \text{ and}$$

$$n_c^{\lambda} \text{ constraints of the form } \lambda_i - \lambda_i^0 > \varepsilon_i^{\lambda} \qquad i \in \{1,p\} \qquad (20)$$

The objective of this variant is to minimize the correlations and simultaneously increase the information content of

the experiment for more than one parameter. A number of constraints n_c^{λ} of form (9), one for each of the parameters to be improved, is therefore required. The higher this number, the more difficult it is to select bounds resulting in a feasible optimization problem. For this reason, the bounds in this variant typically should be less strict than in the previous case. If constraints on two eigenvalues are used, usually the bound for one of them can follow the criterion described for ACE1, but the second constraint should have a much lower ε_i^{λ} (even ε_i^{λ} approaching zero, which means that a final eigenvalue only slightly larger than the initial one is acceptable). If more than two constraints are used, all the tolerances should be lowered to help defining a feasible optimization problem. An alternative strategy may be to introduce additional constraints on new eigenvalues one at a time with the bound on the next-selected eigenvalue chosen to be slightly larger than in the previous case, in which the same eigenvalue was unconstrained.

Criterion 3: E-AC design

This criterion is a modification of the ACE design: in this case, the objective function requires the maximization of one eigenvalue (i.e., information content), which can be chosen as in the ACE design

$$\max_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} \lambda_i(\boldsymbol{\varphi},\hat{\boldsymbol{\theta}}) \qquad i\in\{1,p\} \tag{21}$$

and the constraints deal with the reduction of the correlation coefficients to values below a certain threshold:

$$C_{ij}^2(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})\Big|_{i\neq j} < \varepsilon_{ij}^C \qquad i=1,\ldots,p-1; j=2,\ldots,p \tag{22}$$

In this way, it is easier to control the trade-off between information content of the experiments and parameter correlations. The modeler/experimenter can choose a maximum acceptable degree of correlation between the parameters (e.g., 10–15%) and, then, the optimizer will find the largest value of the selected λ compatible with the constraints. The less stringent the constraints on the correlation coefficients, the larger the eigenvalue will be. An upper bound for the obtainable λ is the value achieved with the standard E-optimal design (no constraints on the correlations) and a lower bound is the value found with the PAC criterion (which does not take into account the information content), resulting in the following inequality:

$$\lambda_i\big|_{PAC} < \lambda_i < \lambda_i\big|_{E-\text{optimal}} \qquad i\in\{1,p\}. \tag{23}$$

Criterion 4: AC-V design

The novel AC-V criterion presents the same structure as the ACE design; the correlation coefficients are partly involved in the objective function (the largest ones) and partly bounded in the constraints. As in the ACE design, additional constraints may be included to improve the information content of the experiment. Unlike the above-mentioned criterion, where these constraints work on one or more eigenvalues of the information matrix [Eq. (9)], in the AC-V design, it is the variance of one or more parameters that is bounded in the constraints:

$$\begin{aligned}
&\min_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} C_{ij}^2(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi}) \text{ with } i,j \text{ such that}\\
&\qquad C_{ij} = \max \mathbf{C}\big|_{\text{basepoint}} \text{ and } i,j\in\{1,p\}\\
&\text{s.t.}\quad C_{kl}^2(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})\Big|_{\substack{k\neq l\\ k,l\neq i,j}} < \varepsilon_{kl}^C \qquad k,l\in\{1,p\} \text{ and}\\
&\qquad n_c^V \text{ constraints of the form } V_{ii} < \varepsilon_i^V \quad i\in\{1,p\}
\end{aligned} \tag{24}$$

where V_{ii} is the variance of the ith parameter, ε_i^V a specified upper bound for the variance V_{ii}, and n_c^V is the number of constraints of this type required. In this way, no association between parameters and eigenvalues needs to be established to use the criterion, and therefore this design is very suitable for cases where residual parameter correlations are expected due to model structure (a further discussion on this issue will be presented in a subsequent publication).

To identify a suitable value for the bound ε_i^v, the relationship between the standard deviation of a parameter and its t value can be adopted[37]:

$$t_i = \frac{\hat{\theta}_i}{X_i(0.95)} \quad \text{with} \tag{25}$$

$$X(\alpha) = t\left(\frac{1+\alpha}{2}, n-n_p\right)\sqrt{V_{ii}} \tag{26}$$

In the above-mentioned equations, $\hat{\theta}_i$ is the current best estimate of the ith parameter, α is the probability level (typically $\alpha = 95\%$), n the number of measurement data available, and t the statistical Student's t distribution. From these equations, a value for the bound ε_i^v is easily calculated after choosing a desired predicted t value (precision of the estimate) for the parameter, which is the target of the optimal experiment.

As an alternative, the formulation of the E-AC design may be adopted, resulting in the V-AC criterion; the objective function minimizes the variance of a certain parameter/s while all the correlation coefficients are bounded in the constraints:

$$\begin{aligned}
&\min_{\boldsymbol{\varphi}\in\boldsymbol{\Phi}} V_{ii}(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi}) \text{ with } V_{ii}\in\mathbf{V}(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})\\
&\text{s.t. } C_{ij}^2(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi})\big|_{i\neq j} < \varepsilon_{ij}^C \quad i=1,\ldots,n_p-1; j=2,\ldots,n_p.
\end{aligned} \tag{27}$$

Further combinations of the above criteria and constraints could of course be adopted.

Application to a Three-Parameter Model

To illustrate the effectiveness and flexibility of the novel criteria described, an illustrative three-parameter model is used. All the cases presented in this section comprise two experiments, which are designed sequentially (one experiment at each design iteration) so as to demonstrate the suitability of the novel anticorrelation approach in a sequential experiment design procedure (the most commonly used design strategy). The required experimental data were simulated using the true values of the parameters (see below) and

a normally distributed random error with a specified variance–covariance matrix (see below) was added to the simulated data to reproduce the uncertainty typical of real measurements. Finally, the parameters were estimated and their estimates statistically assessed. The results of these tests are reported in the following sections after a brief description of the example used.

Case study

The case study chosen to test the new criteria for the experiment design is a three-parameter model, describing a system of consecutive/parallel reactions:

$$\begin{aligned} r_1 &= A + B \xrightarrow{k_1} C \\ r_2 &= C + D \xrightarrow{k_2} E \cdot \\ r_3 &= C + F \xrightarrow{k_3} G \end{aligned} \tag{28}$$

This reaction network represents the first step in the chemical production of an environmentally friendly lubricant called HISM, starting from OME (oleic acid methyl esters), under investigation at the university of Aachen in the group of Prof. Liauw.[60,61] The first step depicted in Eq. 28 constitutes the main process: the epoxidation reaction of the oleic acid methyl esters (A) with hydrogen peroxide (B) to form the epoxide (C). Reactions 2 and 3 are secondary reactions: they involve the desired product C and create unwanted byproducts (E and G) causing a decrease in the overall process yield (C is the main reagent in the second step of the lubricant production). The effect of these side reactions can be reduced by working in a controlled environment but can never be completely eliminated, because the coreagents D and F are respectively water and hydrogen ions and they are inevitably present as impurities in the starting materials. The kinetics of this process is still unknown and the subject of an experimental research program. Some assumptions about the orders of the reactions and the values of the parameters are therefore made here to use this interesting example as a case study.

All the three reactions are assumed to be of second order (first order in each of the reactants), and the epoxidation is considered faster than the side reactions. The following equations are used to model the kinetics of this process:

$$r_i = k_i \, c_j \, c_k \qquad i = 1, \ldots, 3; \; j,k \in \{1,7\} \tag{29}$$

where c_j and c_k are the concentrations (in mol/l) of the two reagents of each reaction. Because the reactions are of second order, the kinetic constants k_i are expressed in (l/mol h).

As pointed out by Pritchard and Bacon,[42] a kinetic network including parallel reactions is always subject to high correlations between its parameters, and this example is therefore an excellent benchmark to test the performance of the new anticorrelation criteria.

Analysis of the System. The process is studied in a fed-batch reactor (depicted in Figure 2), which is assumed to be isothermal and well mixed. Not all the seven components are present initially in the reactor, as it can be seen by the following initial quantities, which are adopted for this process:

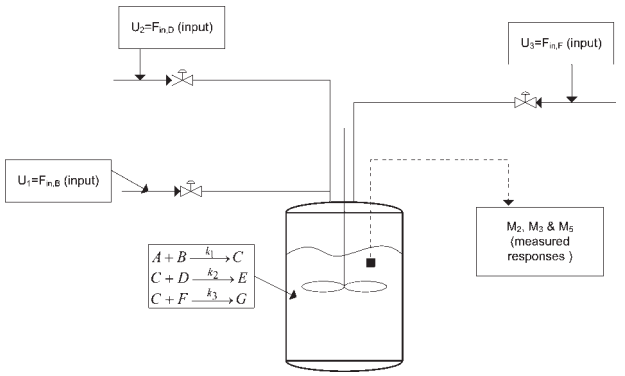

Figure 2. Schematic illustration of the fed-batch reactor used for the epoxidation process.

$$\mathbf{M}^0 = \left[M_{\mathrm{A}}^0, M_{\mathrm{B}}^0, M_{\mathrm{C}}^0, M_{\mathrm{D}}^0, M_{\mathrm{E}}^0, M_{\mathrm{F}}^0, M_{\mathrm{G}}^0\right] = \left[y_{\mathrm{A}}^0, 0, 0, 0.1, 0, 0.1, 0\right] \tag{30}$$

where the symbol M_i represents the moles of the various components (not to be confused with the information matrix). M_{A}^0 is the initial amount of component A (OME), which is a design variable and is optimized in each experiment design. The other initial quantities are kept fixed for experiment design purposes; the initial moles of components D and F are set to 0.1 to model their presence as impurities in the starting materials.

Three distinct molar flow rates (mol/h) enter the reactor, each controlled by its own valve and containing only one pure component, respectively, B, D, and F. This allows implementing different feeding policies for each of the inputs and so a great versatility for the experiment design can be achieved. These three input flow rates (u_1, u_2, and u_3) are the time-varying control variables $\mathbf{u}(t)$ and are modeled as piecewise constant functions over four time intervals. Three switching times for each control are therefore adopted. Based on our experience, a discretization of the control variables over four intervals is sufficient to obtain a good design in this application. Additionally, the initial amount of the first component (M_{A}^0) is included in the design vector as mentioned earlier. Three variables are assumed to be measured, the amounts of components B, C, and F in the reactor, and the number of sampling times n_{sp} is chosen equal to six (assuming a limited analytics budget). The three responses are assumed to be sampled at the same time (i.e., the same sampling times are used for the three responses). A total of 28 variables is therefore optimized in each experiment design. Table 2 reports all the design variables with their range and initial guess; this information is included in the input file required by the experiment design software, which is an in-house software developed within the research group. The software applies an optimal control approach to the experiment design problem using the control vector parameterization technique (CVP) for the mathematical representation of the time-varying inputs of the process.[62] The resulting NLP problem is then solved using a Reduced-Space Successive Quadratic Programming (SRQPD) method based on the work originally reported in Chen et al.[63] The software uses a null-range space reduction method and is very robust with respect to both NLP degeneracy and noisy functions. Our

Table 2. Initial Guess and Range for the Design Variables of the Case Study

Variable	Symbol	Initial Guess	Lower Bound	Upper Bound
Initial amount of component A (mol)	y_1^0	10	1	10
Sampling times (h)	t_{sp}	[1,5,6,12,15,18]	0.5	20
Switch time for the first control (h)	τ_{sw1}	[3,5,8]	0	20
Switch time for second control (h)	τ_{sw2}	[1,2,8]	0	20
Switch time for third control (h)	τ_{sw3}	[4,6,8]	0	20
Flowrate of component B (mol/h)	u_1	[1,1,1,1]	0	2
Flowrate of component D (mol/h)	u_2	[0.5,0.5,0.5,0.5]	0	2
Flowrate of component F (mol/h)	u_3	[0.3,0.3,0.3,0.3]	0	2
Experiment duration* (h)	τ	18	0.5	20

*The initial guess of the experiment duration equals the initial guess of the last sampling time.

experience shows that the occasional convergence problems encountered are due more to the ill-conditioned nature of some formulations than the NLP solver adopted.

Additional constraints are also included in the design to take into account particular limitations of the experimental procedure or of the apparatus. In particular, the following are formulated:

- the earliest time at which a measurement could be taken is equal to 0.5 h;
- the minimum time between consecutive measurements is again equal to 0.5 h;
- the minimum time between consecutive control switching times is equal to 1 h.

Regarding the three measurable responses (the amounts of components B, C, and F in the reactor), the variance-covariance matrix Σ of the experimental data is assumed to be diagonal (independent measurements) and following a constant variance model:

$$\Sigma = \begin{bmatrix} 0.07 & 0 & 0 \\ 0 & 0.00505 & 0 \\ 0 & 0 & 0.1025 \end{bmatrix}. \tag{31}$$

Matrix Σ represents a realistic case with medium–high measurement errors for the responses. Very often in practice, the available measurement devices cannot deliver good quality data, and this has a significant effect on the reliability of the parameter estimation based on these measurements. Here, this variance–covariance matrix is used in both the experiment design and the parameter estimation steps. This mimics a situation where a measurement error analysis has been performed before the model identification. The true values of the parameters (required to simulate the experimental data) are assumed to be $\mathbf{k}_{true} = [2.5, 0.7, 0.5]$, and the following set of initial guesses for the parameters is adopted for the experiment design: $\mathbf{k} = [5, 1.4, 1]$. These parameters show a deviation from the true values of 100%; they were all chosen to be equidistant from the true values so that differences in the precision obtained after the estimation could not be ascribed to better or worse initial guesses.

Criteria assessment: test results

This section presents the results obtained after the parameter estimation was carried out using the data from the (simulated) optimal experiments. The performance of the novel criteria is assessed against three main goals: effectiveness in eliminating/reducing correlations, effectiveness in selectively enhancing the information content of desired parameter(s), and suitability for a sequential experiment design approach. As mentioned earlier, two experiments were designed sequentially; the parameter values obtained after the first estimation were used as initial guesses for the second design iteration. According to a standard sequential experiment design approach, the second estimation was performed using the data from both optimal experiments. Some designs were also performed using the standard criteria (E-, D- and A-optimal) so as to compare their performance with that of the novel anticorrelation approach.

The parameter estimation results were assessed by means of two statistical tests: the *t*- and the χ^2 test (see Hines et al.[64] and Asprey and Naka,[26] for a detailed description of the tests). The *t* test (see Eqs. 25, 26) is used to establish the statistical significance of the parameter estimates, whereas the χ^2 test (Lack-Of-Fit test) is used to check whether or not the model explains the observed data in a satisfactory way. The χ^2 value, which is tested by reference to a χ^2 distribution, was calculated as

$$\chi^2 = \frac{S_r(\hat{\boldsymbol{\theta}})}{\sigma^2} \tag{32}$$

where S_r is the sum of squares of residuals (the deviations between experimental data and simulated profiles) and σ^2 is the error variance of the experimental measurements.

Preliminary Analysis. Before starting a design with the novel anticorrelation criteria, a preliminary eigenvalue–eigenvector analysis of the information matrix at the base point (initial conditions) is performed to obtain an insight into the degree of parameter correlation and the ellipsoid orientation. In particular, this is used to identify the parameters which dominate the various principal directions so as to select the appropriate eigenvalue for the criteria and to plan experiments targeted at specific parameters. Table 1 shows the base point information matrix and the results of its eigenvalue–eigenvector decomposition for this case study. From the table, it can be noted that the third principal direction (the one affected by the highest uncertainty) is essentially dominated by parameter k_1. An experiment maximizing the eigenvalue of this direction, that is, λ_1, should therefore be designed if the precision of parameter k_1 is to be improved. The first and second directions tend to be controlled by the pair k_3 and k_2. In each direction, the influence of both parameters is not negligible. Furthermore, k_2 and k_3 are highly correlated

Table 3. Results of the Parameter Estimation for the E-Optimal Design (First Iteration Only)

Iteration	Parameter	Estimated Value	95% CI	95% t Values	Reference t Value	Correlation Matrix	χ^2 Test
1	k_1	2.38	0.374	6.37	1.75	$\begin{bmatrix} 1 & 0.0251 & -0.0104 \\ & 1 & -0.974 \\ & & 1 \end{bmatrix}$	14.67 vs 24.996
	k_2	0.598	0.203	2.95			
	k_3	0.592	0.18	3.29			

($C_{23} = -0.83$), as it can be seen by the base point correlation matrix:

$$\mathbf{C}\big|_{bp} = \begin{bmatrix} 1 & 0.12 & 0.25 \\ & 1 & -0.83 \\ & & 1 \end{bmatrix} \tag{33}$$

A design maximizing λ_2 or λ_3 while simultaneously reducing the correlation between the parameters k_2 and k_3 is therefore suitable and we would expect such a design to improve both k_2 and k_3.

Standard Experiment Design. From the base point, application of the standard D- and A-optimal criteria resulted in convergence problems at the first design iteration and therefore yielded no results. With the E-optimal design, the calculations were successfully performed and after the first experiment and subsequent estimation, the new parameters and statistics reported in Table 3 were obtained. All the parameters show adequate t values but the correlation between k_2 and k_3 is very high (even higher than the initial one), which makes the results of the test for these two parameters quite unreliable. A second design was then tried with the new estimated parameters reported in Table 3 as initial guesses but no convergence was reached. It is very likely that the high k_2–k_3 correlation hindered the success of the optimal design calculations. Because the standard criterion failed in the second iteration, no direct comparison can be performed with the optimal experiments obtained with the novel anticorrelation criteria, which were all successful (see below). As noted, the optimization failures with the standard design criterion are typically due to very badly conditioning resulting from this problem formulation. The next section reports the most significant of the tests performed; all the four novel criteria were used at least once.

Anticorrelation Experiment Design. Table 4 contains a summary of the various cases tested and described in this section. The anticorrelation criteria and the formulations (objective function and constraints) adopted in both design iterations are reported.

The first case tested (Case 1) used the PAC criterion (variant PAC2, Eqs. 15, 16) in the first experiment design iteration. As already mentioned, this criterion aims at reducing all the parameter correlations (by means of suitable objective function and constraints), but does not take into account the predicted information content of the measurements. The experiments thus designed are therefore not expected to be particularly informative (likely less informative than the E-optimal design). Figure 3 reports the optimal experiment conditions (control profiles and sampling times) obtained for this case. The expected response profiles are also indicated. The case study was chosen intentionally because it is known a priori that the structure of its kinetic scheme allows the three reactions to be studied individually, if necessary. If, for example, the second and third flow rates (which contain only components D and F, respectively) are switched off for all the duration of the experiment, it should be possible to isolate the effects of the first reaction. If only the third flow rate is switched off, the influence of the second reaction on the desired product C can be investigated. Therefore, for this example, an appropriate feeding policy can allow the experimenter to analyze each single aspect of the process in detail. Because the correlation coefficient C_{23} at the base point [see matrix (33)] is very high, an experiment choice based on experience and insight alone and aimed at obtaining separate k_2 and k_3 estimates could be to turn on the two controls, u_2 and u_3, at different times during the process. As seen in Figure 3, a rather more complex and less easy to predict feeding policy was calculated by the optimal experiment design. This is a clear example of what is typically observed that experiment design techniques are usually more powerful than even an experienced experimenter.

Table 5 shows the parameters estimated after the designed experiment of Figure 3 was carried out. For this case, because the χ^2 test is satisfied, the model is deemed to fit the experimental data in a satisfactory way. All the correlations between the three model parameters are very substantially eliminated and the criterion is therefore very effective. However, as expected, the optimal experiment is not very inform-

Table 4. Objective Functions and Constraints Used in the Various Cases Tested

Design Iteration	Case	AC Criterion (Variant)	Objective Function	Constraints on Correlation Coefficients*	Other Constraints
1	1	PAC (PAC2)	min C_{23}^2		–
	2	ACE (ACE1)		$C_{12}^2 < 0.01^2$	$\lambda_1 - \lambda_1^0 > 1$
	3	ACE (ACE2)		$C_{13}^2 < 0.01^2$	$\lambda_1 > \lambda_1^0$ and $\lambda_2 - \lambda_2^0 > 10$
	4	AC-V			$V_{11} < 0.61$ (predicted t value of three)
2	1	ACE (ACE1)	min C_{23}^2	$C_{ij}^2 < 0.1^2$	$\lambda_1 - \lambda_1^0 > 2$
	2	E-AC	max λ_2†		–
	3	E-AC			–
	4	V-AC	min V_{22}	$C_{ij}^2 < 0.01^2$	–

*The symbol C_{ij} indicates that this constraint applies to all the three correlation coefficients.
†λ_1 and λ_2 are the smallest and the intermediate eigenvalue of the information matrix.

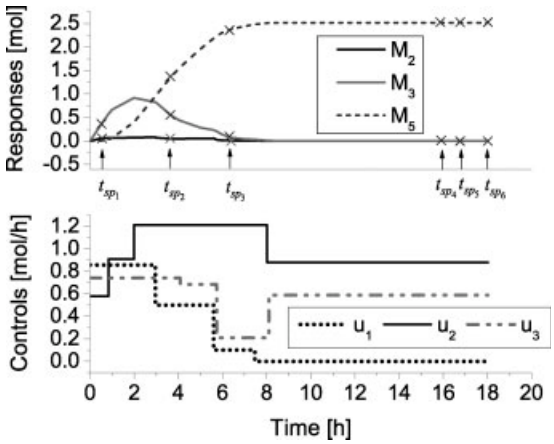

Figure 3. Optimal experimental conditions (controls and sampling times) and expected profiles for the three measured responses (M_2, M_3, and M_5) as calculated by the experiment design for the first iteration of case 1.

ative and therefore not all the parameters can be estimated with sufficient precision. In particular, k_1 presents an insufficient t value (one instead of six as in the standard case, Table 3). This means that the confidence regions involving this parameter are much larger than in the E-optimal case. Nonetheless, as it can be seen in Figure 4a, the elimination of the very high correlation between k_2 and k_3 allows a significant reduction in the area of the corresponding ellipse.

For the second experiment design iteration (Table 5, Case 1 iteration 2), the ACE design was used with a constraint on the smallest eigenvalue aiming at improving the estimation of k_1 while maintaining the correlations to a very low level. As in the first iteration, a complex feeding policy is obtained and the sampling times tend to concentrate in two intervals: one at the beginning of the process (three measurements) and one at the end of the reaction (the other three measurements).

After execution of the experiment and re-estimation of the parameters, Table 5 shows that the criterion is extremely effective: a threefold increase in the t value of k_1 is obtained without a significant rise in the correlation levels. Thank to this improvement, the areas of all the confidence regions are significantly reduced (Figure 4a), in particular, those involving k_1. An improved fit is achieved (see the χ^2 test results in Table 5) after this second iteration.

In the second test (case 2), starting from the same base point, the ACE criterion was directly used in the first design iteration with the aim of improving the precision of the most uncertain parameter (k_1) while eliminating the correlations. Of course, a trade-off must be accepted between correlation reduction and improvement in the information content but a more satisfactory performance of the novel approach is expected in this case. The results obtained are reported in Table 5 and Figure 4b.

It is immediately evident from the results that already after the first iteration no parameter correlations are left and a satisfactory estimation of k_1 is obtained. The t value achieved for k_1 is smaller than in the E-optimal case (because of the requirement to reduce the correlation coefficients) but that of parameter 3 is higher and all the confidence regions exhibit a significant reduction in their area compared with the standard case (Figure 4b). As the t values in Table 5 show, k_2 is the less precisely estimated of the three parameters after the first iteration; therefore, the E-AC criterion with λ_2 as objective function was adopted in the second design iteration. Table 5 shows that a sixfold increase in the t value of k_2 is achieved after the second iteration. In addition, the precision of k_3 is doubled, the confidence regions (Figure 4b) are all further reduced, and the parameters are completely uncorrelated. This is a further confirmation that the novel criteria are very appropriate in a sequential approach, thanks to the flexibility of choosing which eigenvalue to target. For this particular example, the novel anticorrelation approach is significantly more effective than the standard methods (much smaller confidence regions in the first iteration and no correlations) and does not result in any optimization convergence difficulties,

Table 5. Results of the Parameter Estimation for case 1 (PAC and ACE Design in First and Second Iteration, Respectively) and Case 2 (ACE and E-AC Design in First and Second Iteration, Respectively)

Case/Iteration	Parameter	Estimated Value	95% CI	95% t Values	Reference t Value	Correlation Matrix	χ^2 Test
1/1	k_1	2.88	2.88	0.99*	1.75	$\begin{bmatrix} 1 & 0.0554 & 0.0093 \\ & 1 & -0.0265 \\ & & 1 \end{bmatrix}$	13.37 vs 24.996
	k_2	0.72	0.194	3.71			
	k_3	0.64	0.216	2.98			
1/2	k_1	2.7	1.04	2.596	1.692	$\begin{bmatrix} 1 & 0.0005 & -0.0215 \\ & 1 & -0.103 \\ & & 1 \end{bmatrix}$	26.15 vs 47.4
	k_2	0.71	0.144	4.96			
	k_3	0.63	0.124	5.08			
2/1	k_1	2.34	0.578	4.05	1.75	$\begin{bmatrix} 1 & 0.0636 & 0.0365 \\ & 1 & 0.0514 \\ & & 1 \end{bmatrix}$	17.46 vs 24.996
	k_2	0.67	0.276	2.42			
	k_3	0.573	0.084	6.86			
2/2	k_1	2.39	0.554	4.3	1.692	$\begin{bmatrix} 1 & 0.0097 & 0.0866 \\ & 1 & -0.0053 \\ & & 1 \end{bmatrix}$	27.94 vs 47.4
	k_2	0.702	0.055	12.65			
	k_3	0.511	0.039	13.06			

*The asterisk indicates a failed t test.

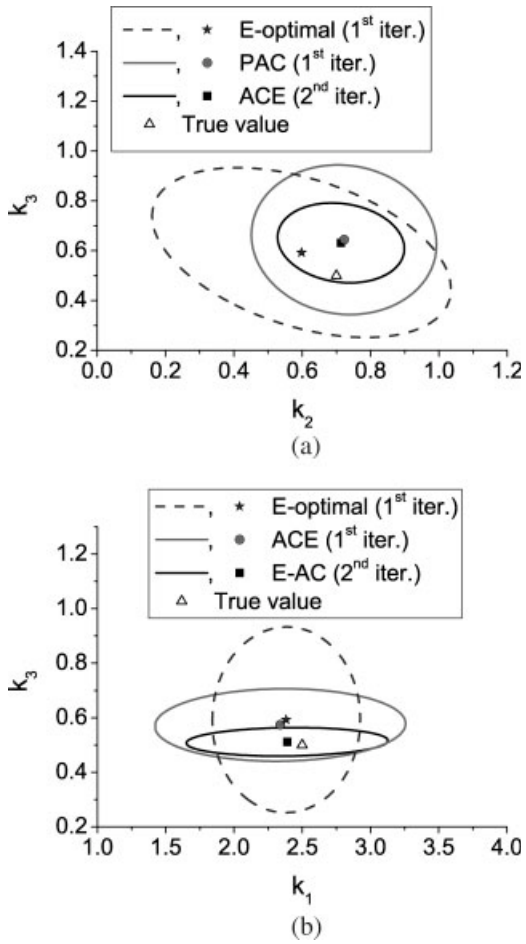

Figure 4. (a) Case 1: confidence ellipse for parameters k_2–k_3; comparison between E-optimal (first iteration) and anticorrelation design (PAC and ACE criteria are used in the first and second iterations, respectively); (b) Case 2: confidence ellipse for parameters k_1–k_3.

Comparison between E-optimal (first iteration) and anticorrelation design (ACE and E-AC criteria are used in the first and second iterations, respectively).

due to the better problem conditioning of the new formulations.

If the ACE criterion is used with λ_2 bound in the constraint, an improvement in the estimation of k_2 is expected, thanks to the flexibility of the novel approach in targeting desired parameters. By not bounding the smallest eigenvalue in the constraint, a low precision in the estimation of the most uncertain parameter (k_1) is likely but such an approach would be ideal if for some reasons a particularly precise estimate of k_2 was required (i.e., k_2 is the most important parameter of the model). This case was tested and the results obtained (not reported here) confirmed the expectations: with respect to case 2, k_2 showed a higher t value after the first iteration of the experiment design but this was paid with a significant decrease in the precision of k_1 (the parameter now exhibited a slightly insufficient t value). The correlations were again almost completely eliminated (only a 14% of correlation remained between parameters 2 and 3), and, despite the low precision of k_1, the approach was demonstrated to be more effective than using standard design criteria (smaller confidence regions).

Unlike the previous cases, which always used the first variant of the ACE design (ACE1), case 3 adopted the ACE2 criterion in the first iteration. The aim was to improve the information content of both k_1 and k_2 simultaneously in the first iteration by bounding the two corresponding eigenvalues ($\lambda_1 > \lambda_1^0$ and $\lambda_2 - \lambda_2^0 > 10$). From the bounds used, it is evident that the improvement of parameter 2 is considered more important than that of k_1 (the constraint is tighter for the corresponding eigenvalue λ_2). This should allow a good precision to be achieved for k_2 but without the drawback of an insufficient t value for k_1. The results obtained are reported in Table 6 and Figure 5a.

From the table, it can be seen that k_1 is well estimated with a sufficient t value (of course lower than in case 2) while the precision of k_2 is doubled. The confidence ellipses show a smaller area than in the standard case with in particular the confidence region of the pair k_2–k_3 significantly improved (see Figure 5a).

The second experiment design iteration for case 3 used the E-AC criterion with the smallest eigenvalue as objective function so as to improve the confidence in the estimation of k_1 (the most uncertain parameter). The t value of this parameter doubles at the second iteration of the design and the precision in the estimation of k_3 is also very much improved (Table 6). As a result, all the confidence regions are significantly reduced (Figure 5a). A 10% correlation remained between each pair of parameters because of the less stringent bounds used in the constraints (0.1 instead of 0.01 as in the first iteration).

As a final test (Case 4), the AC-V criterion was used in the first iteration with the goal of minimizing the correlations while simultaneously obtaining a t value of at least three for the most uncertain parameter k_1 (i.e., $V_{11} < 0.61$). The results shown in Table 6 demonstrate the effectiveness of this design: the correlations are practically eliminated (only a 12% correlation remains between k_2 and k_3), and a t value of 3.7 is reached for the desired parameter. All the t tests are satisfied and, as it can be seen in Figure 5b, the criterion is much more effective than the E-optimal design in obtaining small confidence regions for all the parameters. Because k_2 was the most uncertain parameter after the first iteration, the second design used the V-AC criterion to minimize its variance while keeping the correlations to a low level. As shown in Table 6, an almost double t value is obtained for k_2, and the precision of the other two parameters is improved so that a further reduction in the confidence regions is achieved (Figure 5b).

Criteria assessment: discussion on the results

For all the cases investigated, the various postestimation analyses show the experimental data to be well fitted; the results of the χ^2 test are always satisfactory and the model can therefore be considered adequate to represent the physical system under investigation. This implies that the deviations between experimental data and simulated profiles can be entirely attributed to random errors (measurement errors).

Table 6. Results of the Parameter Estimation for Case 3 (ACE and E-AC Design in First and Second Iteration, Respectively) and Case 4 (AC-V and V-AC Design in First and Second Iteration, respectively)

Case/Iteration	Parameter	Estimated Value	95% CI	95% t Values	Reference t Value	Correlation Matrix	χ^2 Test
3/1	k_1	2.41	1.06	2.26	1.75	$\begin{bmatrix} 1 & 0.037 & 0.059 \\ & 1 & -0.144 \\ & & 1 \end{bmatrix}$	12.46 vs 24.996
	k_2	0.67	0.137	4.87			
	k_3	0.55	0.091	5.96			
3/2	k_1	2.27	0.45	4.97	1.692	$\begin{bmatrix} 1 & 0.106 & 0.116 \\ & 1 & -0.0972 \\ & & 1 \end{bmatrix}$	31.81 vs 47.4
	k_2	0.68	0.12	5.3			
	k_3	0.52	0.03	17.81			
4/1	k_1	2.203	0.599	3.67	1.75	$\begin{bmatrix} 1 & -0.011 & 0.072 \\ & 1 & -0.124 \\ & & 1 \end{bmatrix}$	11.66 vs 24.996
	k_2	0.617	0.274	2.25			
	k_3	0.564	0.115	4.88			
4/2	k_1	2.28	0.451	5.06	1.692	$\begin{bmatrix} 1 & -0.058 & 0.1 \\ & 1 & -0.0612 \\ & & 1 \end{bmatrix}$	26.52 vs 47.4
	k_2	0.686	0.168	4.083			
	k_3	0.574	0.086	6.658			

The results reported in the previous section demonstrate the effectiveness of the novel criteria in eliminating parameter correlations in situations, such as those represented by the case study, when inaccurate initial values of the parameters and not very reliable measurement data require repeated sequential design iterations. After the estimation, the parameters are essentially uncorrelated, except when a looser bound is used in the constraints, as in the second iteration of Case 3 (in this case, it is the user who accepts, a priori, higher correlation coefficients). When the standard E-optimal design was used, the high correlation between k_2 and k_3 (obtained after the first iteration) prevented a second experiment to be designed but, when the novel criteria were adopted, no such problems occurred. This provides a clear demonstration that a criterion able to reduce the correlations between the parameters can be much more effective than the standard experiment design metrics when dealing with highly correlated systems.

The cases investigated highlighted an important trade-off between parameter correlation and information content of the experiment. To reduce the correlations, it is often necessary to accept a less informative experiment. This is particularly evident for the PAC criterion (case 1), which takes into account only the correlations between the parameters with no constraints on information content; the experiments obtained are usually less informative than in the E-optimal case, and this tends to make the confidence regions larger. The ACE design tries to combine the good features of the PAC criterion and of the standard design. The best results are obtained when the smallest eigenvalue is maximized (as in the E-optimal design), subject to constraints on the correlation coefficients. No correlations between the parameters are left, and the confidence regions are much smaller than in the standard case (see Case 2).

The second objective of the tests was to check whether or not it is possible to enhance the information content for a specific parameter while eliminating the correlations and again the results obtained are very satisfactory. By choosing an appropriate eigenvalue to maximize, the information content of the experiment toward the specifically desired param-

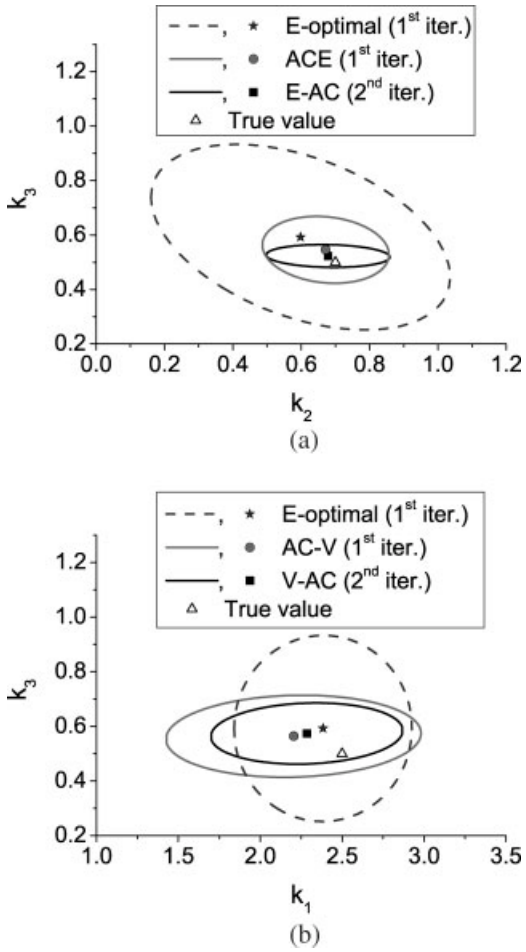

Figure 5. (a) Case 3: confidence ellipses for parameters k_2–k_3; comparison between E-optimal (first iteration) and anti-correlation design (ACE and E-AC criteria are used in the first and second iteration respectively; (b) Case 4: confidence ellipse for parameters k_1–k_3.

Comparison between E-optimal (first iteration) and anti-correlation design (AC-V and V-AC criteria are used in the first and second iteration respectively).

eter can be improved. The cases investigated here showed that the new criteria work very effectively in a sequential procedure because the precision in the estimation of the parameters can be enhanced in a selective and progressive way. When the first experiment is designed, it is preferable to use the smallest eigenvalue or a combination of the two smallest eigenvalues (unless there are some particular requirements on a specific parameter). After the first design, the next most uncertain parameter is identified, and its corresponding eigenvalue should be used in the second iteration and so on. Following this approach, very good results in terms of improved t values and smaller confidence regions were achieved in all the case studies investigated. The ACE, E-AC, and AC-V criteria proved to be very effective in a sequential experiment design procedure while the use of the PAC criterion alone is not particularly recommended. Case 1 showed the PAC design may yield poorly informative experiments as the significant reduction in the correlation coefficients, which can be obtained with this design, is not sufficient to counterbalance the modest increase in the information content. However, the PAC design provides a valuable criterion to use at the preliminary stage to analyze the features of the system under investigation. This will be detailed in a subsequent publication.[23]

Conclusions

A novel experiment design approach and several new formulations have been proposed, which are able to reduce the significant interactions between parameters. This method is capable of dealing with nonstructural parameter correlations, while retaining the same aims of traditional design methods. Four novel criteria have been described, which work directly on reducing the parameter correlation matrix. The first criterion (PAC design) seeks only to reduce/eliminate the parameter correlations without taking into account the information content of the data and has been demonstrated useful only in a preliminary stage of system analysis. The other three criteria achieve a double aim:

- to find the best possible trade-off between reduction in the correlation and increase in the information content of the experiments and
- to plan, if so desired, experiments specifically targeted at improving a selected parameter or group of parameters.

The application of the novel approach to an illustrative three-parameter model describing an epoxidation reaction of practical interest showed that all criteria are very successful in meeting the above goals and more effective than the standard experiment design criteria. In general, the new formulations improve the robustness and capability of model-based design of experiments for precise parameter estimation and the reliability of the resulting parameter estimates. The new anticorrelation criteria proposed in this article are highly flexible in respect to the choice of objective functions and constraints. This flexibility and the capability of targeting the optimal experiments and enhancing the precision of the parameters in a selective and progressive way allow tailoring the desired trade-off between information and correlation in a manner very suitable for a sequential experiment design procedure.

Acknowledgments

The authors gratefully acknowledge Prof. Liauw (RWTH Aachen) and his team for bringing to our attention the case study used in this work and for the useful discussions.

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Manuscript received July 25, 2007, and revision received Dec. 20, 2007.