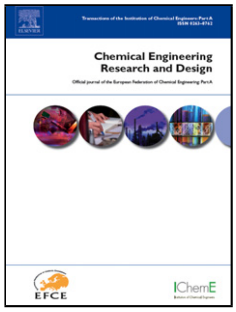


Title: Model-based design of experiments in the presence of structural model uncertainty: an extended information matrix approach

Author: Marco Quaglio Eric S. Fraga Federico Galvanin

PII: S0263-8762(18)30225-9
DOI: https://doi.org/doi:10.1016/j.cherd.2018.04.041
Reference: CHERD 3158

To appear in:

Received date: 15-9-2017
Revised date: 20-4-2018
Accepted date: 25-4-2018

Please cite this article as: Marco Quaglio, Eric S. Fraga, Federico Galvanin, Model-based design of experiments in the presence of structural model uncertainty: an extended information matrix approach, *<![CDATA[Chemical Engineering Research and Design]]>* (2018), https://doi.org/10.1016/j.cherd.2018.04.041

Model-based design of experiments in the presence of structural model uncertainty: an extended information matrix approach

Marco Quaglio[a], Eric S. Fraga[a], Federico Galvanin[a,*]

[a]*Department of Chemical Engineering, University College London (UCL), Torrington Place, WC1E 7JE London, United Kingdom*

Abstract

The identification of a parametric model, once a suitable model structure is proposed, requires the estimation of its non-measurable parameters. Model-based design of experiment (MBDoE) methods have been proposed in the literature for maximising the collection of information whenever there is a limited amount of resources available for conducting the experiments. Conventional MBDoE methods do not take into account the structural uncertainty on the model equations and this may lead to a substantial miscalculation of the information in the experimental design stage. In this work, an extended formulation of the Fisher information matrix is proposed as a metric of information accounting for model misspecification. The properties of the extended Fisher information matrix are presented and discussed with the support of two simulated case studies.

Keywords: model identification, maximum likelihood, design of experiments, Fisher information

1. Introduction

Many chemical and biochemical systems of interest in chemical engineering are too complex for allowing the identification of the *exact* mathematical laws governing the phenomena. The identification of comprehensive model structures is hindered by observability limits (e.g. impossibility of measuring some physical quantities) and/or practical limits (e.g. excessive experimental cost) [1]. Due to these limitations, the aim of the scientist is recast in terms of identifying the model structure that represents an optimal compromise between model identifiability and model descriptive capabilities [2]. The identification of such compromise may be extremely challenging and it may result in the construction of model structures that embody a certain degree of misspecification. Whenever experimental evidence highlights the presence of model misspecification, the following research activities may focus on finding the answer to the following questions:

1. what is the best way of planning the future experimental activities to estimate parameters in a model affected by misspecification?

*Corresponding author
Email address: f.galvanin@ucl.ac.uk (Federico Galvanin)

2. is it possible to define data driven criteria to diagnose the source of model misspecification and provide guidance for improving the model structure?

The objective of this work is to pave the way to the development of a framework for guiding both the modelling and the experimental activities whenever there is a high uncertainty on how to describe a physical system. Specifically, this work is concerned with parameter estimation and experimental design problems in the presence of misspecified model structures.

In the field of linear regression, where models are algebraic expressions that are linear in both the parameters and the variables, the effect of fitting a misspecified model to experimental data is well studied [3, 4]. In a linear modelling framework there are two types of misspecification [3]: *1*) the inclusion of extraneous variables in the model; *2*) the omission of relevant variables from the model. The effect of omitting a variable generally produces a bias in the parameter estimates, i.e., there is a discrepancy between the expected value of the estimates and their true value [3]. In nonlinear regression, model misspecification types span over a much wider spectrum and cannot be classified exhaustively within the two aforementioned categories. Furthermore, true values for the parameters may not exist and the statistical concepts of biased and accurate estimates are not applicable in classical terms. The parameter estimation problem in nonlinear misspecified models has already got the attention of the scientific community [5–7]. However, despite the contribution of many scientists in the field of regression and experimental design, a general framework for the identification of misspecified model structures is yet to be established.

A variety of model-based design of experiments (MBDoE) techniques were proposed in the literature for designing experiments with the aim of improving the statistical quality of the parameter estimates. Conventional MBDoE methods for parameter precision are based on the solution of an optimisation problem where the objective function to maximise is a metric of information. Usually the design metric is a scalar quantity (e.g. the determinant) of the *expected* Fisher Information Matrix (FIM) [8]. Once the experiment is performed, data are collected and included in the parameter estimation problem and the *observed* FIM can be computed. The existing MBDoE frameworks implicitly assume that the model structure adopted at the experimental design stage is *exact* [9–12], i.e. the expected value for the model residuals is assumed to be null. Few works have been proposed in the scientific literature to address the problem of optimal experimental design in conditions of high system uncertainty. Specifically, the main sources of uncertainty that were considered in the available scientific literature are: the presence of significant, unknown measurement noise [13, 14] or the presence of significant unknown random inputs to the system [14]. However, the problem of the MBDoE under structural model uncertainty has not received much attention from the scientific community.

Fisher information measures the sensitivity of the model responses to a variation in the values of the model parameters [8]. The fitting of data with high Fisher information content is a fundamental requirement for identifying parametric models, whether a misspecification is present in the model structure or

not. Fisher information is required to reduce the volume of the confidence region associated to the parameter estimates and concomitantly reduce the uncertainty on the model predictions [15]. Minimising the uncertainty on the model outputs is fundamental not only when the model is correct, but also in the presence of an incorrect parametrisation to help the diagnosis of the misspecification [5]. Furthermore, whenever multiple competing model structures are proposed, reducing the uncertainty on their predicted responses is necessary to prompt their mutual discrimination and determining which is the best model out of the set of candidates [16–18].

In this work, it is shown that whenever the model is nonlinear and the parametrisation is misspecified, there is significant discrepancy between the *expected* and the *observed* FIM. In such conditions, the employment of the *expected* FIM as information metric leads to an inaccurate prediction of the information across the design space, which in turns may lead to a suboptimal experimental design. The discrepancy in nonlinear, misspecified models is due to two aspects: *1*) both *expected* and *observed* FIM are functions of the parameter values and there may be a significant difference between the initial parameter estimates (employed to compute the *expected* FIM), and the parameter estimates optimised after the execution of the experiment (used to compute the *observed* FIM); *2*) high residuals in misspecified model structures result in the rising of an accidental term in the observed FIM, namely the information of *deviation*, which is not considered in conventional design metrics.

A framework for the MBDoE under structural model uncertainty is proposed in this manuscript, where an *extended* FIM is employed as information metric. In the *extended* FIM, an additional term is included to model the *deviation* and provide a more accurate quantification of the information across the experimental design space. It is shown that the *extended* FIM reduces to the *expected* FIM when the model structure is exact. The properties of the *extended* FIM are illustrated through two case studies simulated in silico.

2. Methodology

2.1. Problem definition

An approximated mechanistic model is proposed to describe a system. In general, the candidate model is described by a set of differential and algebraic equations and it is given in (1) in its standard reduced form [15]. For simplicity of notation and without loss of generality it is assumed that the model involves only one measurable output variable $\hat{y}$.

$$\begin{aligned} \mathbf{f}(\dot{\mathbf{x}}, \mathbf{x}, \mathbf{u}, t, \boldsymbol{\theta}) &= \mathbf{0} \\ \hat{y} &= g(\mathbf{x}, \mathbf{u}, t, \boldsymbol{\theta}) \end{aligned} \tag{1}$$

In (1), g is a scalar function, $\mathbf{f}$ is a N_f-dimensional array of model equations, $\mathbf{x}$ is an N_x-dimensional vector of state variables, $\mathbf{u}$ is an N_u-dimensional vector of control input variables, t is time and array $\boldsymbol{\theta} \in \Theta$ represents a set of N_θ non-measurable model parameters. $\mathbf{0}$ is the N_f-dimensional null vector. The

estimation of the model parameters requires the fitting of experimental data. It is assumed that the proposed model satisfies the requirements for structural identifiability, i.e. values for the model parameters can be uniquely identified [19]. A popular method for estimating non-measurable quantities in a parametric model is the maximum likelihood estimator. A number of preliminary experiments is performed, leading to the collection of a dataset Ψ_0 consisting of N measurements: $\Psi_0 = \{y_i |\ i = 1, ..., N\}$. We assume that measurements are affected by Gaussian uncorrelated noise with standard deviations σ_i. The computation of the maximum likelihood estimate $\hat{\boldsymbol{\theta}}$ then requires the maximisation of the likelihood function L or, indifferently, its natural logarithm $\Phi = \ln L$ (2).

$$\Phi(\boldsymbol{\theta}|\Psi_0) = \frac{1}{2}\sum_{i=1}^{N} -\ln(2\pi\sigma_i^2) - \left(\frac{g_i(\boldsymbol{\theta}) - y_i}{\sigma_i}\right)^2 \tag{2}$$

$$\hat{\boldsymbol{\theta}} = \arg\max_{\boldsymbol{\theta}\in\Theta} \Phi(\boldsymbol{\theta}|\Psi_0) \tag{3}$$

In (2) g_i represents the model prediction for the measurement y_i. The characterisation of the parameter estimates requires the computation of a confidence region in the parameter space, due to the fact that fitted experimental data are affected by measurement errors. For a wide class of maximum likelihood estimates, the covariance matrix $\mathbf{V}_0$ of the parameter estimates is well approximated by the inverse of the observed Fisher Information Matrix (FIM) $\mathbf{H}$.

$$\mathbf{V}_0 \simeq \mathbf{H}^{-1} \tag{4}$$

Where $\mathbf{H}$ is defined as the negative Hessian of the log-likelihood function Φ evaluated at the maximum likelihood estimate $\hat{\boldsymbol{\theta}}$ (5).

$$\mathbf{H} = -\nabla\nabla^T \Phi(\hat{\boldsymbol{\theta}}|\Psi_0) \tag{5}$$

The quality of the approximation (4) improves as the variance of the measurement errors decreases and the fitting of the model gets better [15]. From (4) it is possible to perform tests on the statistical significance of the parameter estimates and also diagnose potential problems of model identifiability. If one is willing to enhance the precision on the parameter estimates, i.e., reducing the volume of the confidence region in the parameter space, then it is necessary to collect new data and include them in the parameter estimation problem.

2.1.1. Model-based Design of Experiments

The precise estimation of the model parameters relies on the fitting of measurements collected at experimental conditions in which model predictions are sensitive to a parameter change [20]. This sensitivity can be interpreted as the information that measurable model variables bring regarding the value of non-measurable model parameters and it is quantified by the Fisher Information Matrix (FIM) [8]. A variety of Model-based Design of Experiments (MBDoE) methods have been proposed in the literature for driving the design of trials

with the aim of collecting the most valuable information, assuming a limited amount of resources for performing the experiments [9–12]. A class of MBDoE methods for parameter precision is based on the computation of the expected covariance matrix of the model parameters $\mathbf{V_\theta}$ as a function of the expected FIM $\hat{\mathbf{F}}$ and the preliminary information available $\mathbf{H}$, according to (6).

$$\mathbf{V_\theta} \simeq \mathbf{C}^{-1} = \left[\mathbf{H} + \hat{\mathbf{F}}\right]^{-1} \tag{6}$$

In (6), the information predictor is denoted with the symbol $\mathbf{C}$ as the sum of preliminary information $\mathbf{H}$, defined as in (5), and the information $\hat{\mathbf{F}}$ expected from the experiment (or experiments) to be designed[1]. Assume that the experimental budget allows for the design of a single additional experiment with a number N_d of sampling points. In this situation, under the assumption of uncorrelated Gaussian errors with known standard deviations σ, the expected FIM has the form [8]:

$$\hat{\mathbf{F}} = \sum_{i=1}^{N_d} \frac{1}{\sigma_i^2} \nabla g_i \nabla g_i^T \Big|_{\theta=\hat{\theta}} \tag{7}$$

The expected FIM $\hat{\mathbf{F}}$ is a function of the experimental conditions, i.e., the control input variables $\mathbf{u}$ and the sampling times t_k with $k = 1, ..., N_d$. The MBDoE problem is then recast in terms of minimising the expected confidence region of the parameters after the conduction of the experiment to be designed. In order to summarise the multidimensional nature of $\mathbf{V_\theta}$ into a scalar quantity, different measures ψ of $\mathbf{V_\theta}$ were proposed in the literature as objective functions to be minimised for the optimal MBDoE. The most popular design criteria are [9]:

- *A-optimal*: the objective function is $\psi = \mathrm{Tr}(\mathbf{V_\theta})$ and it is equivalent to minimising the volume of the rectangular hyper-box that contains the expected confidence ellipsoid;
- *D-optimal*: where the objective function chosen for minimisation is $\psi = \mathrm{Det}(\mathbf{V_\theta})$ and it corresponds to minimising the volume of the expected confidence ellipsoid in the parameter space (notice that this is equivalent to maximising $\psi^{-1} = \mathrm{Det}(\mathbf{C})$);
- *E-optimal*: this criterion aims at minimising the largest eigenvalue of $\mathbf{V_\theta}$ and it is equivalent to minimising the longest axis of the expected confidence ellipsoid;

[1] Although this is not common in the MBDoE literature, in this work the symbol $\mathbf{C}$ is introduced to denote the information predictor as it is defined by the classic MBDoE theory; this is primarily done for practical reasons, to make the distinction between classic and alternative design metrics easier in the rest of the manuscript.

- *modified E-optimal*: the criterion involves the maximisation the ratio between the smallest and the largest eigenvalues of $\mathbf{V}_{\boldsymbol{\theta}}$ and has the effect of reducing the structural correlation among model parameters [21];

If the model (1) is structurally exact then it is reasonable to adopt $\hat{\mathbf{F}}$ as information metric at the experimental design stage. In fact, in the presence of a correctly specified model structure, the expected value for the model residuals is null (i.e. $E[\hat{y} - y] = 0$) and the following equality holds:

$$E[-\nabla\nabla^T\Phi] = \mathbf{F} = \sum_{i=1}^{N} \frac{1}{\sigma_i^2} \nabla g_i \nabla g_i^T \quad (N \to \infty) \tag{8}$$

Hence, if it is assumed that the maximum likelihood estimate $\hat{\boldsymbol{\theta}}$ is close to the true parameter value $\boldsymbol{\theta}^*$, then (7) represents a very good approximation of the distribution of the information across the experimental design space. The quality of the approximation improves as $\hat{\boldsymbol{\theta}}$ approaches $\boldsymbol{\theta}^*$.

If the model (1) is incorrectly specified, true values for the model parameters may not exist and the parameter estimate $\hat{\boldsymbol{\theta}}$ may not approach any parameter value as the experimental campaign proceeds, i.e. the concept of accuracy in the parameter estimates loses its significance. However it is still possible to define confidence intervals for the parameter estimates by computing the covariance matrix given the current amount of observed Fisher information according to (4). The fitting of data carrying valuable Fisher information is a fundamental requirement even in the presence of a misspecified parametrisation [17]. In fact, a reduction in the confidence region of the parameter estimates results in a reduction of the uncertainty on the model prediction $\hat{y}$. A reduced uncertainty on the model response is required to distinguish statistically the distribution associated to the model prediction from the distribution of the measurement and support the detection of the incorrect model parametrisation. Hence, whenever a modeller is asked to design a model-based experimental campaign for identifying a parametric model, the aim shall be the collection of high Fisher information regardless of the correct or misspecified nature of the model. However, two crucial issues arise in the design stage if the model is incorrectly specified:

Issue 1 one cannot assume zero as the expected value for the model residuals, i.e., $E[\hat{y} - y] \neq 0$;

Issue 2 the estimate $\hat{\boldsymbol{\theta}}$ adopted for computing (6) may vary significantly when the experiment is performed and additional experimental data are included in the parameter estimation problem.

As a consequence of *Issue 1*, if the proposed model is nonlinear in the parameters (i.e. ∇g is a function of $\boldsymbol{\theta}$), then a discrepancy is present between $\mathbf{F}$ and the observed FIM $\mathbf{H}$, namely the information of deviation $\mathbf{D}$.

$$\mathbf{H} = \mathbf{F} + \mathbf{D} \tag{9}$$

$$\mathbf{D} = \sum_{i=1}^{N} \frac{1}{\sigma_i^2}(g_i - y_i)\nabla\nabla^T g_i \tag{10}$$

If the model is misspecified, the deviation term $\mathbf{D}$ does not tend to the zero matrix as the number of fitted measurements increases. As a consequence of *Issue 2*, even if the deviation term $\mathbf{D}$ were negligible, the information predictor $\mathbf{C}$, computed at the design stage, may be significantly different from the observed FIM $\mathbf{H}$ (after the execution and fitting of the designed experiment) because of an important variation in the values of parameters. In the following sections, a framework is proposed to address the problems associated to *Issue 1*, i.e. the presence of a significant deviation component in the information matrix. In future studies, more robust design frameworks will be proposed and tested for addressing also *Issue 2*, i.e. situations in which there is a high uncertainty on the parameter values [22, 23].

2.2. Proposed framework for the MBDoE under structural model uncertainty

Most models in chemical and biochemical engineering are derived from simplifying hypotheses. Approximated models may not be capable of realising negligible residuals across the experimental design space. From this limitation comes the necessity of developing more accurate design criteria that take into account the expected model accuracy across the space of experimental conditions. In Figure 1, a framework is proposed to account for model misspecification in experimental design metrics. The procedure starts from the availability of a candidate model and the execution of a preliminary campaign of experiments. Assume that the model is known to be approximated. Starting from the whole dataset available, the procedure splits into two parallel branches. In fact, the available dataset is used for two purposes:

1. setting up a parameter estimation problem for computing a preliminary instance $\hat{\boldsymbol{\theta}}$ of the model parameters;
2. identifying a support model in the form:

$$\hat{z} = h(\mathbf{u}, t) \tag{11}$$

the support model (11) has the primary purpose of offering a more accurate representation of the data than the approximated model. Its structure does not have to reflect necessarily the internal mechanisms of the system. Hence, the support model may be a data driven empirical model, e.g. a response surface. The discrepancy between the support model predictions and the experimental data shall be small for the whole available dataset.

The covariance matrix of the parameter estimates is then computed according to Eq. (4) and the statistical significance of the preliminary parameter instance $\hat{\boldsymbol{\theta}}$ is checked. In this work, the statistical quality of each parameter estimate $\theta_i \in \hat{\boldsymbol{\theta}}\ \forall\, i = 1, ..., N_\theta$ is assessed through a t-test with 95% of significance. The t-test is employed to evaluate if the available dataset is sufficiently informative

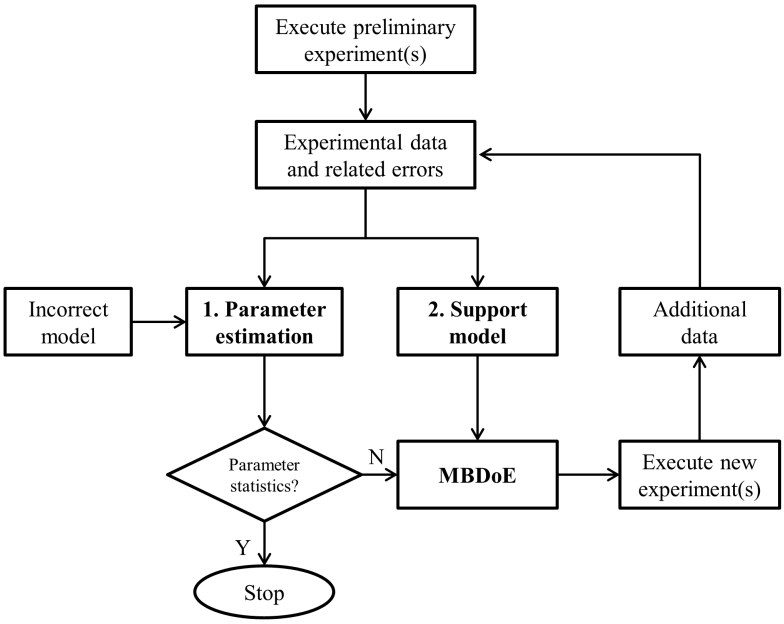


Figure 1: Proposed framework for model identification. Boldface blocks represent fundamental steps in the framework. The procedure starts from the execution of a preliminary experiment and a mechanistic model proposed to describe the experimental observations. The available dataset is used for two purposes: *1*) computing an instance of model parameters for the mechanistic model; *2*) identifying a support model (e.g. a response surface) characterised by a good fitting across the explored design space. The response difference between the instance of the mechanistic model and the support model provides a prediction of model residuals that can be used at the following experimental design stage.

to falsify the hypothesis that parameter estimates are distributed as normal random variables with zero mean. In other words, the t-test is employed to falsify the hypothesis that a certain parameter is *irrelevant* for fitting the data [24]. It is known that the assumption of normality of the parameter estimate distributions is typically not satisfied if the model is nonlinear in the parameters, even in the case of exact model structure [1]. However, it is also recognised that in many situations the assumption of normality is an acceptable approximation of the actual distribution [15, 25].

If some parameter estimates are found to be statistically unacceptable, additional experimental data have to be collected and included in the likelihood function. The location of optimal experimental conditions to investigate shall be identified through MBDoE methodologies. In the proposed framework, it is possible to include knowledge about the expected model residuals in the information metrics adopted at the design stage. Expected residuals are quantified as the response difference between the candidate mechanistic model and the support model.

2.2.1. An extended metric of information

Suppose that a proposed model structure is falsified by some experimental observations. If one is willing to complete the identification of the available model shrinking the confidence region of its parameter estimates, then the following experimental effort shall take into account that the model residuals cannot be expected to be null. In this work, an extended formulation $\mathbf{E}$ of the FIM is proposed as information predictor when structural uncertainty in the model equations is present.

$$\mathbf{E} = \hat{\mathbf{F}} + \hat{\mathbf{D}} + \mathbf{H} = \sum_{i=1}^{N_d} \frac{1}{\sigma_i^2} \nabla g_i \nabla g_i^T + \sum_{i=1}^{N_d} \frac{1}{\sigma_i^2} (g_i - E[y_i]) \nabla \nabla^T g_i + \mathbf{H} \qquad (12)$$

In (12) the first sum, i.e. $\hat{\mathbf{F}}$, represents the expected FIM employed in a conventional MBDoE framework. The second sum $\hat{\mathbf{D}}$ quantifies the predicted information of deviation. Matrix $\hat{\mathbf{D}}$ is evaluated at the most likely value of the parameters, i.e. $\hat{\boldsymbol{\theta}}$, and the measurements y_i are substituted by a measurement expectation $E[y]$, which is approximated through the support model, i.e. it is assumed that $E[y] \simeq \hat{z}$. Notice that because of the presence of $\hat{\mathbf{D}}$ in (12), the extended FIM is not positive semidefinite and may therefore admit negative eigenvalues. For this reason, $\mathbf{E}$ shall not be interpreted as the inverse of a posterior covariance matrix for the parameters. Thus, the inversion of $\mathbf{E}$ loses significance and may also result in critical numerical problems because of changes in the sign of its determinant. Design criteria based on the extended FIM shall be based on the maximisation of a certain direct scalar measure of $\mathbf{E}$ to avoid the numerical issues caused by the inversion of the matrix[2].

[2]In this work, the form of the deviation term $\hat{\mathbf{D}}$ is derived from theoretical considerations

Notice that the proposed formulation of $\mathbf{E}$ in (12) is compatible with the conventional information predictor $\mathbf{C}$. In fact, in the case of a correctly specified model, the predicted information of deviation $\hat{\mathbf{D}}$ approaches the zero matrix as $\hat{\boldsymbol{\theta}}$ approaches the true value of parameters $\boldsymbol{\theta}^*$. The non-convergence of the deviation component of the information to the zero matrix is an indication of model structure misspecification [5].

3. Case studies and Results

The properties of the extended formulation of the FIM (12) are illustrated with the support of two case studies simulated in silico: a biomass model describing baker's yeast growth [19] and a model describing the behaviour of a bacterial population under antibacterial treatment [26, 27]. For each case study, two models structures are postulated: *i*) a structure to simulate the physical system, which is employed to perform the in silico experiments and *ii*) a proposed, misspecified model structure. In the following, the model used to simulate the in silico experiments will be also referred as the *true* model for practical reasons, although nothing such as the true model may exist in reality [28]. Once a preliminary instance of the model parameters for each of the structurally incorrect models is obtained, both case studies involve an experimental design stage. Different information metrics for optimal experimental design are employed:

1. *Conventional D-optimal Design*: The posterior covariance is approximated as $\mathbf{V}_{\boldsymbol{\theta}} \simeq \left[\mathbf{C}\right]^{-1}$ and Det($\mathbf{C}$) is adopted as design metric to be maximised.
2. *Extended D-optimal Design*: matrix $\mathbf{E}$ (12) is assumed as information predictor and Det($\mathbf{E}$) is employed as design metric to be maximised. In order to reduce the amount of uncertainty that is present in the problem, it is chosen to employ the true model for the computation of $E[y]$ in $\mathbf{E}$.

Two independent scenarios are then considered: 1) the experiment designed through the conventional D-optimal approach is carried out; 2) the experiment designed with the extended D-optimal is performed. The accuracy in the prediction of the information and the parameter statistics are used as indices for comparing the performance of the two considered information metrics. A χ^2-test with 95% of significance is also performed at every stage of the model identification procedure [29]. This is reported to assess whether the fitted data are sufficient to detect the misspecification of the candidate model through a discrepancy between the distribution of model residuals and the expected distribution of measurement errors.

The results presented in the following sections were obtained employing scripts implemented in Python 2.7 (the scripts are available as additional material). The in silico experiments and the integration of the dynamic systems

on the observed FIM under model misspecification. However, different formulations of $\hat{\mathbf{D}}$ will be studied in future works with the aim of obtaining an extended FIM that satisfies the property of being positive semidefinite.

for the computation of the information metrics were performed using the *lsoda* library from the package *scipy* [30]. The computation of the Hessian matrix for evaluating the deviation term of the information was performed through the package *numdifftools* [31]. Parameter estimation was performed employing the software gPROMS ModelBuilder 5.0 [32].

An additional scenario was considered for the bacterial population model where an algebraic, linear response surface is employed as support model instead of the *true* model for the computation of $E[y]$ in $\mathbf{E}$. Since the results in this additional case were found to be similar to the aforementioned scenario 2, where the *true* model was employed, it was chosen to omit it from the manuscript and it is reported in Appendix A.

3.1. Case study 1: Baker's yeast growth model

The candidate model with incorrect structure involves the set of differential equations (13) and (14) with a Monod-type kinetic (15).

$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = (r - u_1 - \theta_4) \cdot x_1 \tag{13}$$

$$\frac{\mathrm{d}x_2}{\mathrm{d}t} = -\frac{r \cdot x_1}{\theta_3} + u_1 \cdot (u_2 - x_2) \tag{14}$$

$$\text{Candidate model: Monod} \rightarrow r = \frac{\theta_1 \cdot x_2}{\theta_2 + x_2} \tag{15}$$

where $x_1(t)$ represents the biomass concentration [g/L], $x_2(t)$ is the substrate concentration [g/L], $u_1(t)$ is the dilution factor (range 0.05-0.20 h^{-1}), $u_2(t)$ is the substrate concentration in the feed (range 5-35 g/L) and $\boldsymbol{\theta} = [\theta_1, \theta_2, \theta_3, \theta_4]$ is a set of four non-measurable kinetic parameters.

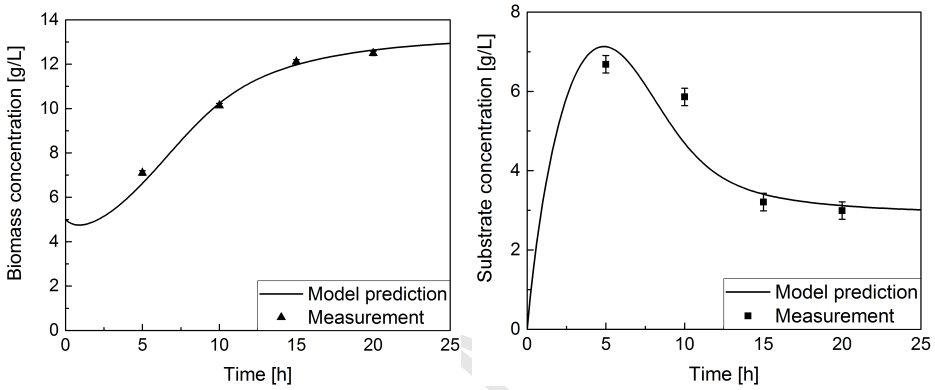
$$\text{True model: Cantois} \rightarrow r = \frac{\theta_1 \cdot x_2}{\theta_2 \cdot x_1 + x_2} \tag{16}$$

The physical biomass system is instead assumed to be described by the true model involving (13) and (14) with a Cantois-type kinetic (16). The true values for the parameters referring to the true model structure are reported in Table 1 together with a synthetic description of their physical significance. The true model is employed for generating experimental data *in silico* assuming that measurements of x_1 and x_2 are affected by Gaussian noise with variance $\sigma_1^2 = 0.01$ and $\sigma_2^2 = 0.05$ respectively.

A preliminary experiment is performed adopting: $u_1 = 0.13\ h^{-1}$ and $u_2 = 35.0$ g/L as time-invariant controls; $x_1(0) = 5.0$ g/L and $x_2(0) = 0.01$ g/L as initial values for the differential variables. Both biomass concentration x_1 and substrate concentration x_2 are sampled at 5.0 h, 10.0 h, 15.0 h and 20.0 h, thus leading to the generation of a preliminary dataset Ψ_0 involving 8 measurements. Measurements obtained *in silico* from the execution of the preliminary experiment are reported in Table 2. The candidate kinetic model, i.e. the Monod-type

Table 1: Assumed true values for the parameters in the true baker's yeast growth model.

Parameter	Description	Value
θ_1	Biomass growth rate kinetic coefficient	0.310
θ_2	Biomass growth inhibition coefficient	0.180
θ_3	Substrate consumption rate	0.550
θ_4	Biomass death rate coefficient	0.050



(a) (b)

Figure 2: Case study 1: Baker's yeast growth model; experimental data obtained from the simulation of the preliminary experiment with sampling every 5.0 h. Predictions of the candidate model, i.e., Monod-type kinetic, after data fitting. Model predictions and measurements are given for (a) biomass concentration and (b) substrate concentration.

kinetics, is fitted to the dataset Ψ_0 to obtain a preliminary instance of the model parameters $\hat{\boldsymbol{\theta}}_0$ adopting a maximum likelihood approach.

Model profiles obtained simulating the preliminary experiment with the candidate model are given for biomass and substrate concentration in Figure 2. The instance $\hat{\boldsymbol{\theta}}_0$ is given in Table 3 with the related t-values and the sum of squared residuals associated to the identified parameter instance, i.e. χ^2_{sample}. The t-value of reference t_{ref} is also given in the table. This represents a t-value with 95% of significance derived from a Student's distribution with degree of freedom equal to the number of fitted measurements minus the number of estimated parameters. A t-value larger than t_{ref} is interpreted as an index of satisfactory parameter precision. The information content of the preliminary dataset Ψ_0 was sufficient to estimate satisfactorily only parameter θ_3 while the estimation of θ_1, θ_2 and θ_4 is still poor, thus justifying the design of a new trial with the aim of improving parameter statistics. As one can see from Table 3, the χ^2_{sample} is larger than χ^2_{ref}. A failed χ^2-test after the fitting of the preliminary experiment highlights the misspecification of the candidate model.

It is assumed that the experimental budget only allows for a single dynamic

Table 2: Case study 1: Baker's yeast growth model; measurements obtained from preliminary experiment adopting time-invariant controls $u_1 = 0.125\ h^{-1}$ and $u_2 = 35.0$ g/L. Initial conditions for biomass concentration and substrate concentration are set to $x_1(0) = 5.0$ g/L and $x_2(0) = 0.01$ g/L.

Preliminary experiment		
Sampling time [h]	Biomass concentration [g/L]	Substrate concentration [g/L]
5.0	7.098	6.683
10.0	10.135	5.860
15.0	12.108	3.209
20.0	12.491	2.993

experiment in which both the biomass concentration and substrate concentration are sampled at regular intervals of 5.0 h, i.e., the sampling times are fixed at $t_s = (5.0, 10.0, 15.0, 20.0)$. For the experimental design purpose, it is assumed that the design space is two-dimensional, identified by dilution factor u_1 and substrate concentration in the feed u_2 (both treated as time-invariant controls). Initial conditions for the differential variables are fixed at $x_1(0) = 5.0$ g/L and $x_2(0) = 0.01$ g/L.

The normalised distribution of Det($\mathbf{C}$) in the design space is given in Figure 3a. The conventional *D-optimal* design criterion leads to the design of a trial in the top-right corner of the design space, i.e. the region at high dilution factor and high substrate concentration in the feed. The predicted information in this point of the design space is $\text{Det}(\mathbf{C}) = 1.47 \cdot 10^{16}$. The normalised distribution of Det($\mathbf{E}$) is instead given in Figure 3b. As one can see from a comparison of Figure 3a and 3b, the information distribution in the design space is significantly different for the two considered criteria. The optimal design conditions for the extended *D-optimal* case are obtained in the bottom-left corner of the design space, thus for the lowest values of dilution factor and substrate concentration in the feed. The information predicted by the extended design in the optimal conditions is $\text{Det}(\mathbf{E}) = 3.11 \cdot 10^{14}$.

The model instances obtained in the two scenarios are given in Table 5. In both scenarios the information content of the additional experiment was sufficient to provide a precise estimation of all model parameters, i.e. t-values above t_{ref}. The observed information after the fitting of the additional experiment in the conventional case is $\text{Det}(\mathbf{H}) = 1.31 \cdot 10^{19}$. In the extended case, the observed information was instead $\text{Det}(\mathbf{H}) = 8.73 \cdot 10^{15}$. Evaluating the information on a $\log_{10}$ scale, the conventional design underestimated the information content of the designed experiment by -18.23% while in the extended case it was underestimated only by -10.00%. Design points and performance of the two methods in predicting the information content of the experiments are summarised in Table 4.

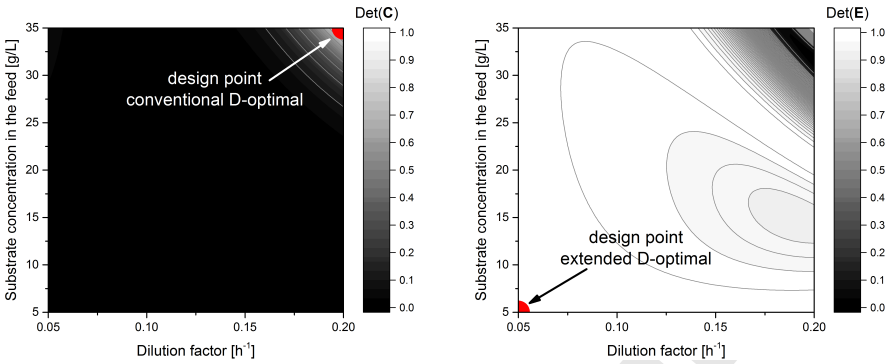


Figure 3: Case study 1: Baker's yeast growth model; normalised design metric distributions in the bi-dimensional design space identified by dilution factor u_1 and substrate concentration in the feed u_2 in the case of : (a) conventional *D-optimal* design; (b) extended *D-optimal* design. White areas represent regions with high predicted information content. Red dots indicate the optimal design points.

Table 3: Case study 1: Baker's yeast growth model; parameter estimation results obtained from the preliminary experiment. t-values quantifying parameter precision and the sum of squared residuals χ^2_{sample} quantifying the goodness of fit are given.

Model Instance After Preliminary Experiment		
Parameter	Value	95% t-value* $t_{ref} = 2.13$
θ_1	0.531	0.612*
θ_2	7.854	0.327*
θ_3	0.474	4.057
θ_4	0.019	0.374*
χ^2-test** (95% $\chi^2_{ref} = 9.49$)		
χ^2_{sample} =59.251**		

*a t-value lower than the reference indicates that the information given by the experiments may not be sufficient to estimate the parameter precisely
**a χ^2_{sample} larger than χ^2_{ref} tends to indicate a bad fit

Table 4: Case study 1: Baker's yeast growth model; design point, predicted information, information observed after the execution of the designed experiment and prediction error. Predicted information is quantified as the determinant of the predictor (i.e. Det(**C**) for conventional *D-optimal* and Det(**E**) for extended *D-optimal*), computed in the design point. The observed information is quantified as the determinant of **H** after the execution and fitting of the experiment.

	Conventional *D-optimal*	Extended *D-optimal*
Design point $[u_1, u_2]$	[0.20, 35.0]	[0.05, 5.0]
Predicted information	$1.47 \cdot 10^{16}$	$3.11 \cdot 10^{14}$
Observed information	$1.31 \cdot 10^{19}$	$8.73 \cdot 10^{15}$
Prediction error*	-18.23%	-10.00%

*error evaluated as $(\log_{10}(\text{predicted}) - \log_{10}(\text{observed}))/\log_{10}(\text{predicted})$

Table 5: Case study 1: Baker's yeast growth model; parameter estimates after the fitting of the designed experiment. The two scenarios considered in this case study are given in the table: experiment designed adopting a conventional *D-optimal* approach and experiment designed adopting an extended *D-optimal* approach. t-values quantifying parameter precision and the sum of squared residuals χ^2_{sample} quantifying the goodness of fit are given for both cases.

Model Instance After Designed Experiment					
Conventional *D-optimal*			Extended *D-optimal*		
Parameter	Value	95% t-value* $t_{ref} = 1.78$	Parameter	Value	95% t-value* $t_{ref} = 1.78$
θ_1	0.326	33.569	θ_1	0.386	7.653
θ_2	1.491	8.560	θ_2	3.345	2.716
θ_3	0.555	21.984	θ_3	0.524	33.111
θ_4	0.057	5.284	θ_4	0.041	6.869
χ^2-test** (95% $\chi^2_{ref} = 21.02$)			χ^2-test** (95% $\chi^2_{ref} = 21.02$)		
$\chi^2_{sample} = 137.57$**			$\chi^2_{sample} = 82.45$**		

*a t-value lower than the reference indicates that the information given by the experiments may not be sufficient to estimate the parameter precisely
**a χ^2_{sample} larger than χ^2_{ref} tends to indicate a bad fit

Table 6: Assumed true values for the parameters in the true bacterial growth model.

Parameter	Description	Value
θ_1	Concentration to achieve 50% of max kill-rate	2.29
θ_2	Growth rate constant for bacterial population	1.50
θ_3	Maximum kill rate constant	4.71
θ_4	Sigmodicity constant for bacterial population	2.83
θ_5	Maximum population size on $\log_{10}$ scale	9.87
θ_6	Maximal adaptation of the population	5.85
θ_7	Adaptation rate of the population	$9.5 \cdot 10^{-3}$

3.2. Case study 2: Bacterial population growth model

The true model describing a bacterial population growth is assumed to involve the set of equations proposed by Tam *et al.* [26]. The time response of the bacterial burden $N(t)$ expressed in [cfu/mL] is modelled through equations (17-20).

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \log_{10}(e) \cdot (G(x) - K(C_A)) \tag{17}$$

$$G(x) = \theta_2 \cdot [1 - 10^{x-\theta_5}] \tag{18}$$

$$K(C_A) = \frac{\theta_3 \cdot C_A^{\theta_4}}{C_A^{\theta_4} + (\alpha \cdot \theta_1)^{\theta_4}} \tag{19}$$

$$\text{True model: } \alpha = 1 + \theta_6 \cdot (1 - e^{-C_A \cdot \theta_7 \cdot t}) \tag{20}$$

where $x = \log_{10}(N)$ quantifies the bacterial concentration on a $\log_{10}$ scale. G and K are the growth and kill rate respectively. α is a function describing bacterial adaptation to the antibacterial treatment over time. C_A is the antibiotic concentration introduced in the system (range 0-16 as mg/L). The model involves a set of 7 parameters $\boldsymbol{\theta} = [\theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \theta_6, \theta_7]$. True values of parameters $\boldsymbol{\theta}^*$ are assumed equal to the values obtained by Tam *et al.* by measuring the response of the bacterial variety *Pseudomonas aeruginosa* when treated with *meropenem*. The assumed true parameter values are reported in Table 6 with a brief description of their physical significance. The true model is employed for generating experimental data in silico assuming that measurements of x are affected by Gaussian noise with variance $\sigma^2 = 4 \cdot 10^{-4}$.

The candidate model with incorrect structure is instead assumed to be described by the set of equations (17-19) considering (21) as adaptation function.

$$\text{Candidate model: } \alpha = 1 + \theta_6 \cdot (1 - e^{-\theta_7 \cdot t}) \tag{21}$$

Two preliminary experiments are performed setting: $C_A = 0.25$ mg/L in the first experiment and $C_A = 4.00$ mg/L in the second experiment. Initial inoculum

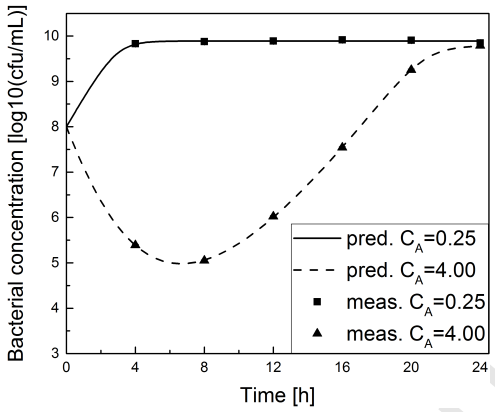


Figure 4: Case study 2: Bacterial population growth system; bacterial concentration profiles predicted by the candidate model after fitting the preliminary experiments. Experimental samples for the time-kill experiment at $C_A = 0.25$ mg/L (squares) and for the time-kill experiment at $C_A = 4.0$ mg/L (triangles).

is set at $x(0) = 8.0$ $\log_{10}$(cfu/L). In both trials the bacterial concentration is sampled every 4.0 h over an experimental time-frame of 24.0 h obtaining a preliminary dataset Ψ_0 consisting of 12 measurements. Analogously to the previous case study, the preliminary dataset is fitted with the candidate model through a maximum likelihood approach to obtain a preliminary parameter instance $\hat{\boldsymbol{\theta}}_0$. The preliminary parameter instance $\hat{\boldsymbol{\theta}}_0$ is reported in Table 7 with the respective t-values statistics. The information content of the preliminary experiments was sufficient to estimate precisely parameters θ_2, θ_3, θ_4 and θ_5. The t-values for the remaining parameters, i.e. θ_1, θ_6 and θ_7, are below the reference value t_{ref}, thus justifying the design of an additional trial for improving parameter precision. As one can see from Table 7, the quality of fitting achieved by the candidate model after the preliminary experiments is good even if the model structure is misspecified, i.e. the identified model passes the χ^2-test with 95% of significance. A visual proof of the goodness of fit is given in Figure 4, where experimental data are plotted together with the respective time-kill curves predicted by the incorrect model for the two preliminary trials.

The following analysis focuses on the design of an optimal trial to improve parameter precision. It is assumed that the experimental budget allows for the execution of an experiment in which the bacterial concentration is sampled at regular intervals of 4.0 h, i.e. the sampling times are fixed at $t_s = (4.0, 8.0, 12.0, 16.0, 20.0, 24.0)$. Initial inoculum is fixed at $x(0) = 8.0$ $\log_{10}$(cfu/L). A one-dimensional design space is assumed in which the antibiotic concentration C_A has to be optimised as time-invariant control. The distribution of the two considered design metrics, i.e. Det($\mathbf{C}$) for the conventional D-optimal and Det($\mathbf{E}$) for the extended D-optimal are reported in the graph in Figure 5. As one can see from the graph, the two curves follow a similar trend,

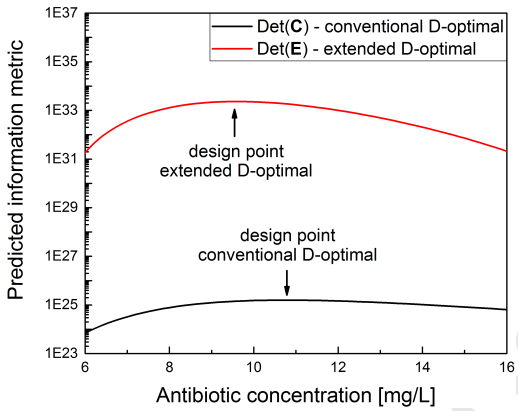


Figure 5: Case study 2: Bacterial population growth system; information metrics distribution in the considered monodimensional design space identified by the antibiotic concentration C_A [mg/L]: for conventional D-optimal (black); for extended D-optimal (red).

but the extended D-optimal predicts and information that is 7-8 orders of magnitude higher than the conventional D-optimal. The discrepancy between the two design metrics is due to the fact that a significant information of deviation is predicted across the design space. The conventional D-optimal suggests the conduction of the additional experiment setting $C_A = 10.776$ mg/L, predicting the collection of an amount of information equal to $\text{Det}(\mathbf{C})=1.58 \cdot 10^{25}$. The extended D-optimal instead leads to the design of a trial at $C_A = 9.565$ mg/L, where the respective information design metric is much higher, i.e. $\text{Det}(\mathbf{E})=2.33 \cdot 10^{33}$.

The parameter instances obtained in the two scenarios are reported in Table 8. In both scenarios, the information content of the additional experiment was sufficient to obtain satisfactory parameter estimates according to the chosen significance of the t-test (95%). From Table 8 it is also possible to appreciate that the fitting of the additional experiment leads to the failure of the χ^2-test with 95% of significance, highlighting the misspecification of the candidate model structure. In this second case study, the conventional D-optimal outperforms the extended D-optimal in terms of accuracy in predicting the information of the additional experiment. The information observed after the additional experiment is performed is: $\text{Det}(\mathbf{C})=5.55 \cdot 10^{21}$ for the conventional case; $\text{Det}(\mathbf{E})=1.08 \cdot 10^{21}$ for the extended case. Evaluating the information on a $\log_{10}$ scale, the extended design overestimates the information content of the experiment by 36.97% while the overestimation in the conventional design is only 13.71%. The performance of the two designs is summarised in Table 9.

Table 7: Case study 2: Bacterial population growth model; parameter estimation results obtained from the preliminary experiments. t-values quantifying parameter precision and the sum of squared residuals χ^2_{sample} quantifying the goodness of fit are given.

Model Instance After Preliminary Experiment		
Parameter	Value	95% t-value* $t_{ref} = 1.79$
θ_1	1.487	1.320*
θ_2	1.524	9.504
θ_3	4.005	4.612
θ_4	2.605	3.750
θ_5	9.890	488.1
θ_6	10.018	1.168*
θ_7	$3.8 \cdot 10^{-2}$	1.268*
χ^2-test** (95% $\chi^2_{ref} = 11.07$)		
χ^2_{sample} =8.718		

*a t-value lower than the reference indicates that the information given by the experiments may not be sufficient to estimate the parameter precisely
**a χ^2_{sample} larger than χ^2_{ref} tends to indicate a bad fit

3.3. Results discussion

Two case studies were considered in this work for testing the performance of an extended FIM (12) on the design of experiments for parameter precision in the presence of model misspecification. In the first case study on the baker's yeast model, the extended D-optimal design provided a more accurate prediction of the information than a conventional D-optimal design metric (see Table 4). In the second case study on the bacterial population model, the extended design was instead less accurate than the conventional design (see Table 9). The reason is in the fact that the formulation of the extended FIM is evaluated at the most likely parameter estimate available, i.e. $\hat{\boldsymbol{\theta}}_0$. Thus, the extended formulation (12) does not take into account that, if the model is misspecified, the introduction of additional experimental data in the parameter estimation problem may result in a significant variation in the model parameter estimates.

The shift of the maximum likelihood estimate in the extended D-optimal case, can be appreciated in the graphs of Figure 7 for the baker's yeast growth model and in Figure 8 for the bacterial population model. As one can see from Figure 7, parameter estimates in the Baker's yeast case after the additional experiment is performed (black squares in the graphs) are within the 95% confidence range associated to the preliminary parameter estimate (red ellipsoids)[3].

[3]The only parameter pair that is outside the respective prior confidence region is θ_1-θ_2. However both estimates for θ_1 and θ_2 after the extended D-optimal are within 2 standard deviations of the confidence range of their respective preliminary estimates.

Table 8: Case study 2: Bacterial population growth model; parameter estimates after the fitting of the designed experiment. The two scenarios considered in this case study are given in the table: experiment designed adopting a conventional *D-optimal* approach and experiment designed adopting an extended *D-optimal* approach. t-values quantifying parameter precision and the sum of squared residuals χ^2_{sample} quantifying the goodness of fit are given for both cases.

Model Instance After Designed Experiment					
Conventional *D-optimal*			Extended *D-optimal*		
Parameter	Value	95% t-value* $t_{ref} = 1.78$	Parameter	Value	95% t-value* $t_{ref} = 1.78$
θ_1	0.677	9.515	θ_1	0.820	12.144
θ_2	2.222	10.033	θ_2	2.058	10.958
θ_3	6.213	14.799	θ_3	6.154	14.649
θ_4	0.999	11.474	θ_4	1.021	11.387
θ_5	9.345	492.2	θ_5	9.929	534.5
θ_6	116.0	6.227	θ_6	398.5	2.289
θ_7	$1.37 \cdot 10^{-2}$	3.781	θ_7	$3.45 \cdot 10^{-3}$	2.053
χ^2-test** (95% $\chi^2_{ref} = 19.67$)			χ^2-test** (95% $\chi^2_{ref} = 19.67$)		
$\chi^2_{sample} = 166.48$**			$\chi^2_{sample} = 153.32$**		

*a t-value lower than the reference indicates that the information given by the experiments may not be sufficient to estimate the parameter precisely
**a χ^2_{sample} larger than χ^2_{ref} tends to indicate a bad fit

Table 9: Case study 2: Bacterial population growth model; design point, predicted information, information observed after the execution of the designed experiment and prediction error. Predicted information is quantified as the determinant of the predictor (i.e. **C** for conventional *D-optimal* and **E** for extended *D-optimal*), computed in the design point. The observed information is quantified as the determinant of **H** after the execution and fitting of the experiment.

	Conventional *D-optimal*	Extended *D-optimal*
Design point $[C_A]$	[10.776]	[9.565]
Predicted information	$1.58 \cdot 10^{25}$	$2.33 \cdot 10^{33}$
Observed information	$5.55 \cdot 10^{21}$	$1.08 \cdot 10^{21}$
Prediction error*	13.71%	36.97%

*error evaluated as $(\log_{10}(\text{predicted}) - \log_{10}(\text{observed}))/\log_{10}(\text{predicted})$

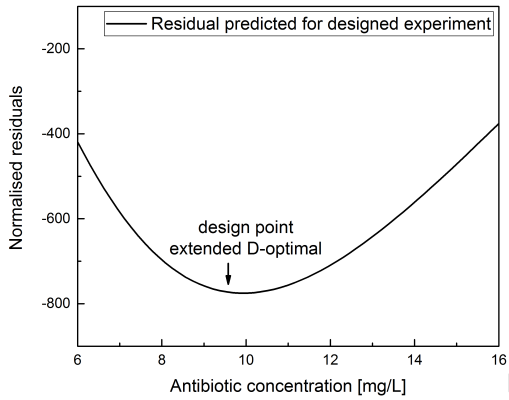


Figure 6: Case study 2: Bacterial population growth system; normalised residuals predicted for the designed experiment.

Instead, as one can see from Figure 8, in the bacterial population case there is a much more significant difference between the parameter estimates before and after the fitting of the additional experiment. This important parameter variation is the cause of the significant discrepancy between the information prediction provided by $\mathbf{E}$ and the information observed after performing the experiment in the bacterial population case. It will be object of future work to test the extended FIM in a robust design framework [22, 23, 33, 34] to take into account also the uncertainty on the location of the parameter estimate point in the parameter space.

Still with reference to the bacterial population case, as one can see from Figure 5, there is an important difference between the two considered metrics of information, i.e. Det($\mathbf{C}$) and Det($\mathbf{E}$). The difference is caused by the presence of a significant component of deviation $\hat{\mathbf{D}}$ in the predicted information. The predicted deviation is function of the predicted model residuals in the design points. As one can see from Figure 6, the predicted normalised residual is nearly -800 in proximity of the experiment designed by the extended D-optimal. The execution of an experiment at those conditions was then expected to result in a significant worsening of the fitting and in an important shift of the parameter estimates in the parameter space. The predicted information of deviation, together with the predicted residuals represent indices of model inappropriateness and may be employed for defining further design criteria, e.g. criteria for designing experiments with the aim of falsifying the model structure or discriminating among competing proposed models [16–18, 35]. The study of the extended FIM may also provide useful insights for diagnosing the cause of mismatch between the candidate model and the experimental observations. Exploring these applications of the extended FIM will be object of future studies.

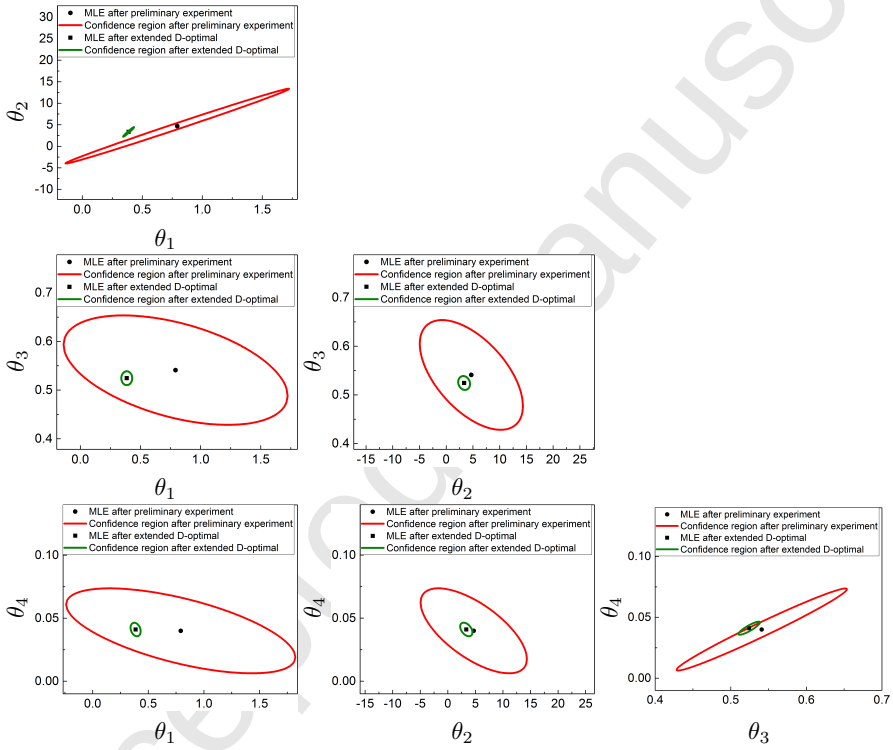


Figure 7: Case study 1: Baker's yeast growth model; 95% confidence ellipsoids and maximum likelihood estimates referring to the candidate model with incorrect structure, i.e. the Monod-type kinetics. Maximum likelihood estimates and corresponding ellipsoids are plotted for two cases: after the fitting of the preliminary experiment (red); after the fitting of the additional experiment designed through extended D-optimal (green).

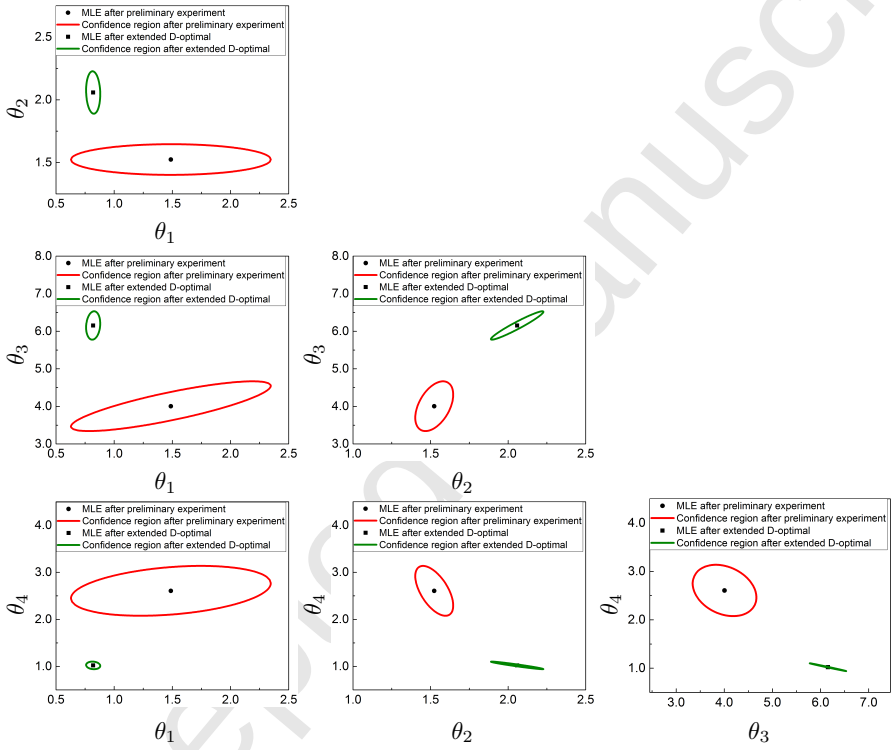


Figure 8: Case study 2: Bacterial population growth model; 95% confidence ellipsoids and maximum likelihood estimates referring to the candidate model with incorrect structure, i.e. assuming an adaptation function that is independent from antibiotic concentration. Maximum likelihood estimates and corresponding ellipsoids are plotted for two cases: after the fitting of the preliminary experiment (red); after the fitting of the additional experiment designed through extended D-optimal (green). Parameters θ_5, θ_6 and θ_7 are not represented in the figure for space limitations.

4. Conclusion

An extensive literature is available on the optimal Model-Based Design of Experiments (MBDoE) for parameter precision. These methods are based on the maximisation of a certain scalar measure of the expected Fisher Information Matrix (FIM). Conventional methodologies implicitly assume that the model employed for experimental design and data fitting is structurally exact and model accuracy is therefore not considered at the experimental design stage. However, in many cases it may be inappropriate to assume that the model structure is correct.

In the present manuscript, it was shown that in the presence of nonlinear misspecified models, conventional MBDoE methodologies lead to a substantial miscalculation of the information at the design stage, i.e. significant discrepancy between expected information and information observed after the execution of the experiment. This discrepancy is interpreted as an indication of the incorrect model parametrisation.

The inaccurate prediction of the information is linked to two causes: *1*) high model residuals lead to the rising of an incidental term in the observed FIM, namely the information of *deviation*, which is always neglected in the conventional MBDoE; *2*) the value of the model parameters adopted for predicting the information in the design stage may vary significantly once the experiment is performed and the additional data are fitted. A framework for the optimal MBDoE for parameter precision in the presence of structural model uncertainty is proposed in this work to account for the expected model accuracy at the design stage. An extended formulation of the FIM was also proposed including a term for predicting the information of *deviation*, i.e. for addressing the first cause of discrepancy. The performance of the extended FIM was tested in silico and compared to a conventional D-optimal design on two case studies, where experimental design was performed with misspecified model structures:

- In the first case study on a baker's yeast growth model, an initial instance of the model parameters was obtained fitting a preliminary experiment. The fitting of the preliminary experiment highlighted the incorrect structure of the model. An additional experiment was then designed adopting two different information metrics. A D-optimal design with the extended FIM provided a more accurate prediction of the information than a conventional D-optimal design based on the expected FIM.

- In the second case study on a bacterial population growth system, a preliminary instance for the model parameters was obtained fitting the experimental data from two time-kill curves. The fitting of the preliminary experiments was statistically satisfactory despite the known model misspecification. In the design stage, a conventional D-optimal design provided a more accurate prediction of the information with respect to the extended D-optimal.

In the second case study, the low accuracy of the extended FIM (i.e. high difference between information predicted at the design stage and information

observed once the experiment is performed) is related to the second cause of discrepancy. In fact, the current formulation of the extended FIM does not consider that a significant variation in the values of parameters may occur when the data collected in the designed experiment are fitted. It will be object of future works to develop more robust and accurate information metrics to support the MBDoE in the presence of misspecified model structures.

A high discrepancy between predicted and observed information indicates a likely model misspecification even if the parameter fitting is satisfactory. Thus, the information of *deviation* represents an index of inappropriate model parametrisation. Its accurate prediction may lead to the definition of metrics for further design criteria, e.g. design criteria for model structure falsification or model discrimination among a set of competing models. Furthermore, the extended FIM may represent a useful tool for diagnosing the reasons of the mismatch between experimental observations and model predictions, leading to the construction of tools for amending the incorrect model parametrisation. The investigation of these potential applications of the extended FIM is going to be the focus of future research activities.

Acknowledgements

The authors want to express great appreciation to the anonymous reviewers for their extremely constructive and valuable comments.

Financial support for the work presented in this manuscript was offered by the Hugh Walter Stern PhD Scholarship, Centre for Nature Inspired Chemical Engineering, University College London.

References

[1] A. Raue, C. Kreutz, T. Maiwald, J. Bachmann, M. Schilling, U. Klingmller, J. Timmer, Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood, Bioinformatics 25 (2009).

[2] D. Bonvin, C. Georgakis, C. C. Pantelides, M. Barolo, M. A. Grover, D. Rodrigues, R. Schneider, D. Dochain, Linking Models and Experiments, Industrial & Engineering Chemistry Research 55 (2016).

[3] P. Rao, Some Notes on Misspecification in Multiple Regressions, The American Statistician 25 (1971).

[4] R. R. Hocking, A Biometrics Invited Paper. The Analysis and Selection of Variables in Linear Regression, Biometrics 32 (1976).

[5] H. White, Maximum Likelihood Estimation of Misspecified Models, Econometrica 50 (1982).

[6] A. White, M. Tolman, H. D. Thames, H. R. Withers, K. A. Mason, M. K. Transtrum, The Limitations of Model-Based Experimental Design and Parameter Estimation in Sloppy Systems, PLOS Computational Biology 12 (2016).

[7] F. Galvanin, M. Barolo, F. Bezzo, Online Model-Based Redesign of Experiments for Parameter Estimation in Dynamic Systems, Industrial & Engineering Chemistry Research 48 (2009).

[8] E. Walter, L. Pronzato, Identification of parametric models from experimental data, Springer, 1997.

[9] D. Espie, S. Macchietto, The optimal design of dynamic experiments, AIChE Journal 35 (1989).

[10] V. Prasad, D. G. Vlachos, Multiscale Model and Informatics-Based Optimal Design of Experiments: Application to the Catalytic Decomposition of Ammonia on Ruthenium, Industrial & Engineering Chemistry Research 47 (2008).

[11] J.-L. Dirion, C. Reverte, M. Cabassud, Kinetic parameter estimation from TGA: Optimal design of TGA experiments, Chemical Engineering Research and Design 86 (2008).

[12] F. Galvanin, E. Cao, N. Al-Rifai, A. Gavriilidis, V. Dua, A joint model-based experimental design approach for the identification of kinetic models in continuous flow laboratory reactors, Computers & Chemical Engineering 95 (2016).

[13] F. Galvanin, M. Barolo, G. Pannocchia, F. Bezzo, Online model-based redesign of experiments with erratic models: A disturbance estimation approach, Computers & Chemical Engineering 42 (2012).

[14] D. Telen, B. Houska, F. Logist, E. Van Derlinden, M. Diehl, J. Van Impe, Optimal experiment design under process noise using Riccati differential equations, Journal of Process Control 23 (2013).

[15] Y. Bard, Nonlinear Parameter Estimation, Academic Press, 1974.

[16] G. E. P. Box, W. J. Hill, Discrimination among Mechanistic Models, Technometrics 9 (1967).

[17] G. Buzzi-Ferraris, P. Forzatti, C. Paolo, An improved version of a sequential design criterion for discriminating among rival multiresponse models, Chemical Engineering Science 45 (1990).

[18] M. Schwaab, J. Luiz Monteiro, J. Carlos Pinto, Sequential experimental design for model discrimination: Taking into account the posterior covariance matrix of differences between model predictions, Chemical Engineering Science 63 (2008).

[19] S. P. Asprey, S. Macchietto, Statistical tools for optimal dynamic model building, Computers & Chemical Engineering 24 (2000).

[20] G. E. P. Box, H. L. Lucas, Design of Experiments in Non-Linear Situations, Biometrika 46 (1959).

[21] K. J. Versyck, J. F. V. Impe, On the unicity of optimal experimental design solutions for parameter estimation of microbial kinetics, in: 1997 European Control Conference (ECC), 1997, pp. 3509–3514.

[22] S. Asprey, S. Macchietto, Designing robust optimal dynamic experiments, Journal of Process Control 12 (2002).

[23] S. Korkel, E. Kostina, H. G. Bock, J. P. Schloder, Numerical methods for optimal control problems in design of robust optimal experiments for nonlinear dynamic processes, Optimization Methods and Software 19 (2004).

[24] G. Franceschini, S. Macchietto, Model-based design of experiments for parameter precision: State of the art, Chemical Engineering Science 63 (2008).

[25] E. L. Lehmann, J. P. Romano, Testing Statistical Hypotheses, Springer Texts in Statistics, 3 ed., Springer-Verlag, New York, 2005.

[26] V. H. Tam, A. N. Schilling, M. Nikolaou, Modelling timekill studies to discern the pharmacodynamics of meropenem, Journal of Antimicrobial Chemotherapy 55 (2005).

[27] F. Galvanin, C. C. Ballan, M. Barolo, F. Bezzo, A general model-based design of experiments approach to achieve practical identifiability of pharmacokinetic and pharmacodynamic models, Journal of Pharmacokinetics and Pharmacodynamics 40 (2013).

[28] G. E. P. Box, Science and Statistics, Journal of the American Statistical Association 71 (1976).

[29] S. D. Silvey, Statistical Inference, CRC Press, 1975.

[30] E. Jones, T. Oliphant, P. Peterson, et al., SciPy: Open source scientific tools for Python, 2001.

[31] J. Perktold, numdiff package, www.pypi.python.org/pypi/numdifftools, 2014.

[32] Process Systems Enterprise, gPROMS, www.psenterprise.com/gproms, 1997-2017.

[33] A. Mesbah, S. Streif, A Probabilistic Approach to Robust Optimal Experiment Design with Chance Constraints, IFAC-PapersOnLine 48 (2015).

[34] D. Telen, D. Vercammen, F. Logist, J. Van Impe, Robustifying optimal experiment design for nonlinear, dynamic (bio)chemical systems, Computers & Chemical Engineering 71 (2014).

[35] I. Stamati, S. Akkermans, F. Logist, E. Noriega, J. Van Impe, Optimal experimental design for discriminating between microbial growth models as function of suboptimal temperature: From in silico to in vivo, Food Research International 89 (2016).

Appendix A. Additional case study with linear support model

In the present Appendix, an additional case study is proposed, where the experimental design is performed through an extended D-optimal criterion employing a data driven surrogate model as the support model. This additional case is reported to assess the sensitivity of the extended design metric to the choice of the support model. The considered system is the bacterial population under antibacterial treatment presented in Section 3.2. The assumptions made in Section 3.2 regarding the model structures are briefly recalled here. The *true* model employed to perform the in silico experiments is described by equations (17-20) in Section 3.2. The assumed true values for the parameters are reported in Table 6. The proposed model that needs to be identified is assumed to be described by the set of equations (17-19) and includes a misspecified adaptation function (21). As in case study 2 (see Section 3.2), the preliminary instance for the parameters of the incorrectly specified model is computed from the fitting of two time-killing curves at different antibiotic concentrations: $C_A = 0.25$ mg/L in the first experiment and $C_A = 4.00$ mg/L in the second experiment. Preliminary parameters are reported in Table 7 together with relevant statistical indices for assessing the quality of the estimate. As one can see from Table 7, parameter θ_1, θ_6 and θ_7 did not pass the 95% t-test, thus justifying the design of additional trials to improve their statistical quality.

Analogously to case study 2 in Section 3.2, it is assumed that the experimental budget allows for performing an additional experiment where the only design variable is the antibiotic concentration C_A as time-invariant control. Sampling times are fixed at $t_s = (4.0, 8.0, 12.0, 16.0, 20.0, 24.0)$. Initial inoculum is fixed at $x(0) = 8.0$ $\log_{10}$(cfu/L). Two scenarios are here considered in which the design is performed employing an extended D-optimal criterion, but adopting different support models:

- *Scenario A*: the *true* model is employed as support model to compute the term E[y] in **E** (this scenario was already considered in Section 3.2);
- *Scenario B*: a linear response surface is adopted as support model for computing an approximation of E[y] in **E**.

With reference to *Scenario B*, the linear response surface model in the form $\hat{z} = h(C_A, t)$ was identified from the preliminary dataset and it is reported in (A.1).

$$\mathrm{E}[y] \simeq \hat{z} = 8.24 - 0.72 \cdot C_A + 0.13 \cdot t \tag{A.1}$$

The response surface was identified using the regression tool available in the software Origin (OriginLab, Northampton, MA) adopting a weighted least squares method. The design metrics related to the two considered scenarios are plotted in Figure A.9. The optimal design in *Scenario A* is achieved for an antibiotic concentration $C_A = 9.565$ mg/L. In *Scenario B*, the optimum point is

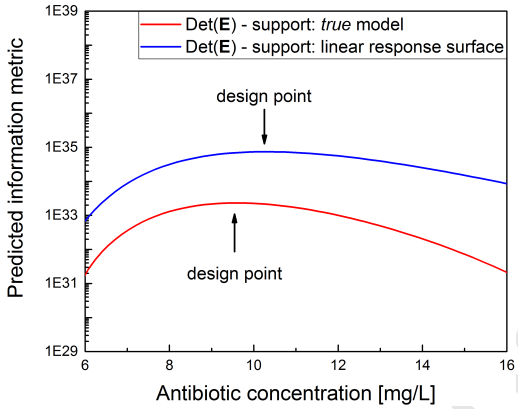


Figure A.9: Bacterial population growth system; information metrics distribution in the considered monodimensional design space identified by the antibiotic concentration C_A [mg/L] in: *Scenario A* with extended D-optimal employing the *true* model as support model (red); *Scenario B* with extended D-optimal employing a linear response surface as support model (blue). Arrows highlight optimal experimental design points according to the different criteria.

achieved at $C_A = 10.240$ mg/L. In Table A.10, the parameter estimates obtained after the execution of the designed experiments in the two scenarios are reported. As one can see, the employment of a linear response surface does not affect significantly the result. The two considered design metrics suggest the execution of a trial at similar conditions and consequently the model instances identified after the experiments are performed do not differ significantly in parameter estimates and fitting quality. In Table A.11, a summary of the quality of the information prediction offered by the two design criteria in the design points is reported. For both scenarios, the information at the design points is significantly overestimated (see Table A.11). However, the prediction error (evaluated on a $\log_{10}$ scale), is not significantly affected by the choice of the support model: it increases from 36.97% in *Scenario A* to 39.27% in *Scenario B*.

Table A.10: Bacterial population growth model; parameter estimates after the fitting of the designed experiment. Two scenarios considered in this case study are given in the table: experiment designed adopting an extended *D-optimal* approach employing the *true* model as support model; experiment designed with an extended D-optimal approach employing a linear response surface as support model. t-values quantifying parameter precision and the sum of squared residuals χ^2_{sample} quantifying the goodness of fit are given for both cases.

Model Instance After extended D-optimal Experiment					
Scenario A support model: *true* model			*Scenario B* support model: linear response surface		
Parameter	Value	95% t-value* $t_{ref} = 1.78$	Parameter	Value	95% t-value* $t_{ref} = 1.78$
θ_1	0.820	12.144	θ_1	0.741	8.611
θ_2	2.058	10.958	θ_2	2.155	9.905
θ_3	6.154	14.649	θ_3	6.200	13.963
θ_4	1.021	11.387	θ_4	1.004	10.780
θ_5	9.929	534.5	θ_5	9.932	519.6
θ_6	398.5	2.289	θ_6	167.5	2.861
θ_7	$3.45 \cdot 10^{-3}$	2.053	θ_7	$0.89 \cdot 10^{-2}$	2.132
χ^2-test** (95% $\chi^2_{ref} = 19.67$)			χ^2-test** (95% $\chi^2_{ref} = 19.67$)		
$\chi^2_{sample} = 153.32$**			$\chi^2_{sample} = 160.50$**		

*a t-value lower than the reference indicates that the information given by the experiments may not be sufficient to estimate the parameter precisely
**a χ^2_{sample} larger than χ^2_{ref} tends to indicate a bad fit

Table A.11: Case study 2: Bacterial population growth model; additional scenario employing a linear response surface as support model for the extended D-optimal. Design point, predicted information, information observed after the execution of the designed experiment and prediction error are reported. Predicted information is quantified as the determinant of the predictor (i.e. **C** for conventional *D-optimal* and **E** for extended *D-optimal*), computed in the design point. The observed information is quantified as the determinant of **H** after the execution and fitting of the experiment.

	Scenario A support model: *true* model	*Scenario B* support model: linear response surface
Design point [C_A]	[9.565]	[10.240]
Predicted information	$2.33 \cdot 10^{33}$	$7.42 \cdot 10^{34}$
Observed information	$1.08 \cdot 10^{21}$	$1.50 \cdot 10^{21}$
Prediction error*	36.97%	39.27%

*error evaluated as $(\log_{10}(\text{predicted}) - \log_{10}(\text{observed}))/\log_{10}(\text{predicted})$

TITLE: Model-based design of experiments in the presence of structural model uncertainty: an extended information matrix approach

HIGHLIGHTS:

- Conventional MBDoE may lead to suboptimal trial design if the model is not exact
- A framework for the MBDoE under structural model uncertainty is proposed
- An extended Fisher information matrix (FIM) is proposed as suitable design metric
- The extended formulation of the FIM is tested on two simulated case studies
- A difference between extended and conventional FIM is an index of inexact structure