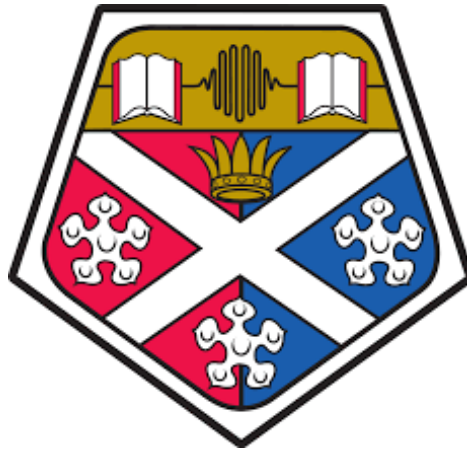


Robust Sampling Time Design for Uncertain Dynamic Systems



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Doctor of Philosophy

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Declaration

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Ke Wang

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Abstract

Data-based modelling of chemical and biochemical systems, where the underlying physical mechanisms are generally well understood, relies on accurate parameter estimation from experimental data. However, parameter estimation for nonlinear dynamic models is often ill-conditioned due to model nonlinearity, parameter correlations, and limited experimental resources. Since model prediction reliability depends critically on data quality, designing informative experiments is essential for accurate model calibration. Optimal experimental design (OED) provides a systematic framework for selecting experimental conditions that maximise data information content for objectives such as identifiability analysis, parameter estimation, and model validation. However, classical OED relies on a nominal model and is therefore sensitive to model uncertainties and process variations, motivating the development of robust experimental design (RED) methods.

This thesis develops robust sampling time design strategies for parameter estimation in nonlinear dynamic systems under parametric and input uncertainties. Challenges associated with large parametric uncertainty and input uncertainty are addressed within an optimisation-based design framework. The main contributions are summarised as follows:

- Developed robust sampling time design methods based on maximin and pseudo-Bayesian criteria for systems with parametric uncertainty. The corresponding problem formulations, numerical solution strategies, and implementation procedures are presented.
- Developed a distribution-based robustness evaluation framework for sampling time design, enabling consistent quantitative assessment using multiple statistical performance

metrics. This framework is applied to compare robust experimental design methods using two nonlinear dynamic systems: an enzyme reaction network and an enzymatic biodiesel production process.

- Proposed a midterm sampling time redesign strategy to overcome key limitations of existing robust design methods. The experimental horizon is divided into sequential zones, within which OED or RED is performed using updated parameter estimates from previously collected data. This enables adaptive experimental design within a single experimental run without repeated trials. Three redesign strategies are developed: equally spaced redesign, auto-updating redesign based on practical identifiability analysis, and condition-triggered redesign activated by predefined operational changes.
- Developed a sampling time design framework based on the misspecified Cramér–Rao bound (MCRB) to address input uncertainty. The proposed framework accounts for changes in pseudo-data dispersion, departures from the assumed measurement distribution, and temporal correlations induced by nonlinear propagation of input uncertainty. A full trajectory (stacked-measurement) MCRB criterion is formulated for sampling time selection. Comparisons with classical FIM-based OED, input-uncertainty-specific methods, and standard RED formulations show that the MCRB-based criterion provides a more appropriate treatment of distributional misspecification under input uncertainty.

This thesis establishes a coherent framework for robust sampling time design for nonlinear dynamic systems under model and input uncertainties. By integrating robust design principles, adaptive experimental strategies, and performance bounds under data-model misspecification, these contributions improve the reliability and practical applicability of MBDoE and provide a foundation for more efficient experimental design in complex systems.

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Nomenclature

Number Sets

Symbol	Description	
$\mathbb{N}^m$	Integer number set	$m \times 1$
$\mathbb{N}_+^m$	Non-negative integer number set	$m \times 1$
$\mathbb{R}^m$	Real number set	$m \times 1$
$\mathbb{R}^{m \times n}$	Real number matrix set	$m \times n$
$\mathbb{R}_+^m$	Non-negative real number set	$m \times 1$
$\mathbb{S}_+^{m \times n}$	Semi-definite symmetry matrix set	$m \times n$

Greek Symbols

Symbol	Description	Set
α	Probability level	$\mathbb{R}_+$
Δ_{θ_j}	Variation of j -th parameter	$\mathbb{R}$
$\Delta_{x_i(t_l)}$	Variation of i -th state at time t_l	$\mathbb{R}$
ξ	Vector of measurement errors	$\mathbb{R}^{N_y}$

ξ_i	Measurement error for i -th output	$\mathbb{R}^{N_y}$
$\boldsymbol{\eta}$	Score function	$\mathbb{R}^{N_p}$
γ	Relative error parameter	$\mathbb{R}_+$
κ	User-set parameter in auto-updating midterm redesign	$\mathbb{R}^+$
λ_{max}	Maximum eigenvalue	$\mathbb{R}$
$\boldsymbol{\mu}$	Expectation of parameter estimator	$\mathbb{R}^{N_p}$
ω	Absolute error parameter	$\mathbb{R}_+$
$\boldsymbol{\Sigma}$	Covariance matrix of measurement error	$\mathbb{R}^{N_y \times N_y}$
σ_i^2	Variance of i -th measurement error	$\mathbb{R}$
Θ	Parameter uncertainty space	-
$\boldsymbol{\theta}$	Vector of model parameters	$\mathbb{R}^{N_p}$
$\boldsymbol{\theta}^L$	Lower bound of parameter uncertainty space	$\mathbb{R}^{N_p}$
$\boldsymbol{\theta}^U$	Upper bound of parameter uncertainty space	$\mathbb{R}^{N_p}$
$\hat{\boldsymbol{\theta}}$	Parameter estimator	$\mathbb{R}^{N_p}$
θ_j	j -th model parameter	$\mathbb{R}$
$\boldsymbol{\theta}_{obs}$	Vector of observation parameters	$\mathbb{R}^{N_{obs}}$
$\boldsymbol{\theta}_{err}$	Vector of error parameters	$\mathbb{R}_+^2$
v	Penalty function	-
φ	Experimental settings	-
ζ	Error function	$\mathbb{R}^{N_p}$

Roman Symbols

Symbol	Description	Set
b	Bias of parameter estimator	$\mathbb{R}^{N_p}$
C	Parameter correlation matrix	$\mathbb{R}^{N_p \times N_p}$
c_{ij}	Correlation coefficient between θ_i and θ_j	$\mathbb{R}$
CI	Confidence interval	-
D	Experimental data	$\mathbb{R}^{N_y}$
D^(k)	k -th set of experimental data	$\mathbb{R}^{N_y}$
$\mathbb{E}\{\cdot\}$	Expectation operator	-
I_{N_p}	Identity matrix	$\mathbb{R}^{N_p \times N_p}$
FIM	Fisher information matrix	$\mathbb{R}^{N_p \times N_p}$
f	A set of state transition functions	$\mathbb{R}^{N_x}$
F	Fisher distribution	-
F	Parametric Jacobian matrix (Chapter 3)	$\mathbb{R}^{N_x \times N_p}$
F_i	Fisher information matrix of i -th state	$\mathbb{R}^{N_p \times N_p}$
h	A set of measurement functions	$\mathbb{R}^{N_y}$
I	Information matrix	$\mathbb{R}^{N_p \times N_p}$
J	Jacobian matrix	$\mathbb{R}^{N_x \times N_x}$
L	Likelihood	$\mathbb{R}$
MSE	Mean squared error	$\mathbb{R}^{N_p \times N_p}$

N	Total number of available data	$\mathbb{N}_+$
N_D	Total number of experimental data sets	$\mathbb{N}_+$
N_{exp}	Number of sub-experiments	$\mathbb{N}_+$
N_m	Number of measurable states to be selected	$\mathbb{N}_+$
N_{obs}	Number of observation parameters	$\mathbb{N}_+$
N_p	Number of parameters	$\mathbb{N}_+$
N_{st}	Number of sampling time points	$\mathbb{N}_+$
N_{sub}	Number of sampling time points to be collected in each sub-experiment in equally divided midterm redesign	$\mathbb{N}_+$
N_T	Number of measurable sampling time points	$\mathbb{N}_+$
N_u	Number of input variables	$\mathbb{N}_+$
N_x	Number of state variables	$\mathbb{N}_+$
N_y	Number of outputs that can be measured	$\mathbb{N}_+$
p	Distribution of model deviations	$\mathbb{R}_+$
PCI	Parameter collinearity index	$\mathbb{R}^+$
RS	Overall effect of parameter	$\mathbb{R}$
S	Sensitivity matrix	$\mathbb{R}^{N_x \times N_p}$
$\bar{\mathbf{S}}$	Relative sensitivity matrix	$\mathbb{R}^{N_x \times N_p}$
$\tilde{\mathbf{S}}$	Normalised relative sensitivity matrix	$\mathbb{R}^{N_x \times N_p}$
$s_{i,j}$	Sensitivity of i -th state w.r.t. j -th parameter	$\mathbb{R}$
$\bar{s}_{i,j}$	Relative sensitivity of i -th state w.r.t. j -th parameter	$\mathbb{R}$

$\tilde{s}_{i,j}$	Normalised relative sensitivity of i -th state w.r.t. j -th parameter	$\mathbb{R}$
$\mathbf{S}_j$	Sensitivity states w.r.t. j -th parameter	$\mathbb{R}^{N_x \times 1}$
t	Time in a continuous model	$\mathbb{R}_+$
T	transpose of a vector	-
t_j	Student-t value for the estimates of j -th parameter	$\mathbb{R}$
$\mathbf{t}_{sp}$	Sampling time points vector	$\mathbb{R}^{N_T}$
$\mathbf{u}$	Vector of input variables	$\mathbb{R}^{N_u}$
$\mathbb{V}\{\cdot\}$	Variance operator	-
V_{ij}	Covariance between i -th and j -th parameters	$\mathbb{R}$
V_{jj}	Variance of the estimates of j -th parameter	$\mathbb{R}$
$\mathbf{x}$	Vector of state variables	$\mathbb{R}^{N_x}$
$\mathbf{x}_0$	Initial condition of state variables	$\mathbb{R}^{N_x}$
$\mathbf{x}_0^L, \mathbf{x}_0^U$	Lower and upper bounds of state initial conditions	$\mathbb{R}^{N_x}$
x_i	i -th state variable	$\mathbb{R}$
$\mathbf{y}$	Vector of outputs	$\mathbb{R}^{N_y}$
y_i	i -th model output	$\mathbb{R}$

Acronyms

CI confidence interval. 151, 162, 165, 170

CRB Cramér–Rao bound. 3, 10, 68, 70, 74, 175, 176, 177, 178, 179, 202, 203, 206, 210, 211, 212, 215

DDM direct differential method. 56, 57

DoE design of experiments. 2, 3, 5, 17, 18, 19, 21, 22

FIM Fisher Information Matrix. 3, 5, 7, 10, 12, 19, 21, 23, 24, 25, 29, 30, 32, 36, 40, 41, 42, 43, 44, 45, 49, 54, 59, 62, 68, 69, 70, 73, 74, 80, 82, 83, 84, 85, 86, 90, 91, 92, 93, 94, 96, 102, 103, 106, 109, 111, 113, 114, 115, 117, 118, 132, 141, 151, 160, 167, 175, 183, 187, 188, 197, 201, 210, 211, 212, 213, 215

GET General Equivalence Theorem. 20

GQ Gaussian quadrature. 95, 96, 97, 113, 114, 115, 117, 126, 127, 128, 136, 140, 141, 207

GSA global sensitivity analysis. 30, 55, 57, 58, 59

IQR interquartile range. 98, 110, 112, 119, 123, 124, 127, 133, 136, 137

KLD Kullback–Leibler divergence. 176, 178, 180, 182

LSA local sensitivity analysis. 55, 57, 124

- LSE** least square estimation. 2, 65, 68, 73
- MBDoE** model-based design of experiments. 3, 4, 5, 6, 7, 8, 9, 19, 20, 21, 22, 27, 28, 40, 44, 73, 82, 213, 215
- MCRB** Misspecified Cramér–Rao bound. 7, 10, 13, 175, 176, 177, 178, 179, 180, 182, 183, 184, 186, 187, 191, 197, 198, 201, 202, 203, 206, 207, 210, 211, 212, 214, 215, 216, 217
- ML** maximum likelihood. 67, 68, 73, 180
- MLE** maximum likelihood estimation. 2, 69
- MML** Misspecified maximum likelihood. 180, 181, 185
- MVU** minimum variance unbiased. 65
- NLP** nonlinear programming. 40, 41
- ODE** ordinary differential equation. 40, 51, 61, 75, 183, 184, 191, 263
- OED** optimal experimental design. 5, 9, 10, 12, 13, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34, 35, 38, 40, 41, 42, 43, 44, 45, 47, 48, 49, 70, 71, 73, 74, 78, 79, 81, 82, 83, 101, 106, 107, 109, 110, 111, 112, 117, 118, 119, 121, 122, 123, 124, 125, 126, 128, 132, 133, 136, 137, 140, 141, 142, 144, 146, 147, 148, 152, 155, 156, 159, 160, 162, 165, 170, 176, 177, 188, 198, 201, 202, 210, 211, 212, 214
- OFAT** One-Factor-at-a-Time. 18
- PDE** partial differential equations. 32, 40, 41
- pdf** probability density function. 53, 90, 179
- PE** parameter estimation. 2, 47, 48, 49, 53, 54, 60, 62, 63, 65, 66, 67, 81, 82
- PSO** particle swarm optimisation. 107, 109, 126, 149, 152, 155, 158, 159, 167, 188

rBias relative bias. 198

RED robust experimental design. 6, 7, 8, 9, 10, 12, 13, 21, 24, 28, 29, 33, 34, 35, 37, 40, 43, 44, 45, 48, 82, 83, 85, 86, 90, 94, 106, 132, 137, 144, 147, 176, 183, 187, 207, 210, 212, 213, 214, 217

RMSE root mean square error. 198, 202, 203, 210

SA sensitivity analysis. 47, 49, 54, 55

SAA sample-average approximation. 97, 113, 114, 115, 117, 126, 127, 128, 140

SDP semi-definite programming. 41, 43, 72, 76, 78, 82, 102, 103, 105, 189

Chapter 1

Introduction

1.1 Research Context and Motivations

Why is design of experiments necessary?

Mathematical modelling plays a crucial role in science and engineering. A reliable mathematical model can be used to explain past observations, guide present decision-making, predict future behaviour under specified experimental settings, and provide insights into system behaviour that may be inaccessible through measurements due to physical or practical constraints (Fowler, 1997).

Models used in practice may be broadly classified as empirical black-box models or physics-based mechanistic models. Black-box models describe input–output relationships without explicitly representing the internal mechanisms of the system and have become increasingly popular with the rapid development of machine learning methods (Bishnu et al., 2023). In contrast, mechanistic models are developed based on the physical laws governing the system. A typical form is the state-space model, represented by a set of differential equations involving state variables and parameters (Bock et al., 2013).

In mechanistic models, the unknown parameters often have physical interpretations. Accurate estimation of these parameters is important for understanding the system and for

ensuring the reliability of the model in practical applications. In many engineering problems, such models are derived from first principles, but some simplifications are usually required to obtain a tractable mathematical description. As a result, more than one candidate model structure may be formulated, which gives rise to the need for model discrimination. In addition, these models often contain unknown parameters that need to be determined from experimental data. Therefore, the modelling process commonly involves two main tasks: model discrimination and parameter estimation (PE) (Franceschini and Macchietto, 2008; Kreutz and Timmer, 2009). This thesis focuses on the latter.

In many practical applications, selecting an appropriate simplified model or determining parameter values relies heavily on measurement data (Ljung, 1999). For parameter estimation, unknown parameter values are typically obtained by fitting the model to experimental data using methods such as least square estimation (LSE) or maximum likelihood estimation (MLE). However, PE is often challenging for complex nonlinear systems. In such systems, the PE problem is usually ill-conditioned, meaning that small changes in the data may significantly affect the estimation results. Furthermore, due to practical limitations in experimental resources, the collected data are often limited in both quantity and quality (Jia and Yue, 2012; Kutalik et al., 2004). It is therefore important to design experiments carefully, since the quality of parameter estimation depends strongly on the informativeness of the measurement data (Banga and Balsa-Canto, 2008). In this context, design of experiments (DoE), first formalised by Fisher (1937), provides a systematic approach to selecting experimental conditions so that the collected data are as informative as possible for parameter estimation (Franceschini and Macchietto, 2008; Geremia et al., 2026).

What is design of experiments?

In this thesis, DoE refers to the design of experiments for mathematical modelling. The aim is to determine experimental settings that generate informative data for model discrimination and parameter estimation, with particular emphasis on parameter estimation in this work.

In a broad sense, DoE includes both statistical design methods, such as factorial design (Box, 2005), and model-based design of experiments (MBDoE) (Franceschini and Macchietto, 2008). Statistical design methods are widely used for empirical modelling, factor screening, and response optimisation. In contrast, MBDoE is particularly suitable for mechanistic dynamic models, where prior structural knowledge of the system can be incorporated explicitly.

In MBDoE, the informativeness of an experiment for parameter estimation is commonly assessed using the Fisher Information Matrix (FIM). Through the Cramér–Rao inequality (Cramér, 1946; Rao, 1992), the inverse of the FIM gives the Cramér–Rao bound (CRB), that is, a lower bound on the covariance matrix of any unbiased estimator. Therefore, a more informative experiment generally corresponds to a more favourable FIM, leading to improved estimation precision. The FIM is constructed from the local parametric sensitivity matrix, which contains the derivatives of the model outputs with respect to the parameters. For dynamic systems, these sensitivities can be computed efficiently by solving the sensitivity equations together with the state equations (Leis and Kramer, 1988; Turányi, 1990), or by using automatic differentiation techniques (Griewank and Walther, 2008). Consequently, scalar functions of the FIM are widely used in the formulation of DoE problems (Franceschini and Macchietto, 2008; Ljung, 1999).

Accordingly, the classical MBDoE approach for achieving precise parameter estimation is to identify the experimental settings that maximise a chosen FIM-based design criterion (Banga and Balsa-Canto, 2008). This methodology has been widely applied in chemical and biochemical systems. The design settings refer to the variables or factors that can be manipulated during an experiment and can be broadly categorised into two types. The first is the input strategy, which includes the initial values of state variables and controllable external variables that may be either time-dependent or time-invariant. The second is the observation strategy, which involves selecting sampling time points for measurement collection and determining which state variables should be measured (i.e., the measurement set).

Application areas of MBDoE

MBDoE has been applied in a wide range of scientific and engineering fields where experiments are costly and data collection must be highly informative for model calibration. Its main objective is to identify experimental conditions that maximise the information content of the collected data while making efficient use of limited experimental resources. Below, several major application areas of MBDoE are outlined, together with typical examples and associated challenges.

A primary and historically significant application of MBDoE lies in chemical and biochemical engineering, where experiments are often expensive, time-consuming, and safety-critical. In these fields, MBDoE is used to design dynamic experiments that provide rich information for estimating kinetic constants, adsorption coefficients, and activation energies. This helps reduce the number of required experiments while improving the predictive capability of the resulting models. Such applications have been demonstrated in areas ranging from catalytic systems to polymerisation kinetics (Deussen and Galvanin, 2022; Franceschini and Macchietto, 2008; Galvanin et al., 2013; Geremia et al., 2026; Sangoi et al., 2024; Yu, 2018; Yue et al., 2013).

In systems biology, biological networks are characterised by high complexity, strong nonlinearity, and often a large number of poorly identifiable parameters. MBDoE strategies are therefore employed to design *in silico* and *in vitro* experiments that optimally stimulate biological systems. These experiments aim to elucidate regulatory pathways, discriminate between competing network structures, and accurately estimate key biological parameters while accounting for practical experimental constraints (Chakrabarty et al., 2013; He et al., 2010; Jia and Yue, 2012; Kreutz and Timmer, 2009; Liepe et al., 2013; van Sluijs et al., 2022; Yue et al., 2008).

Furthermore, MBDoE has demonstrated significant value in fields such as pharmaceuticals and biomedicine (Galvanin et al., 2013; Ghosh and García Muñoz, 2026; Musuamba et al., 2012; Retout et al., 2001, 2002), geophysics (Curtis, 2004; Maurer et al., 2009, 2017; Strutz and Curtis, 2024), and many other disciplines. The application scope of MBDoE is therefore broad and highly interdisciplinary. Its growing adoption reflects the increasing

need to make experimentation more efficient and informative, moving practice away from trial-and-error approaches towards a more rigorous, model-guided process.

Issues faced by design of experiments

In classical MBDoE, the FIM plays a central role, and scalar criteria derived from it are commonly used as design objectives. According to the Cramér–Rao inequality, the inverse of the FIM provides a lower bound on the covariance of parameter estimation under a given experimental strategy. Although the classical FIM-based optimal experimental design (OED) has proven effective in many studies, it does present several limitations.

Firstly, the FIM is derived from local sensitivities, which can be significantly affected by parametric uncertainties, particularly in nonlinear systems (Fedorov and Leonov, 2013; Pronzato and Walter, 1985; Walter and Pronzato, 1997). If the initial parameter estimates are highly unreliable, the local FIM-based design may become ineffective for evaluating the quality of parameter estimation (Atkinson, 2007). On the other hand, if the initial parameter estimates are already considered sufficiently reliable, the motivation for conducting DoE primarily for parameter estimation becomes less compelling, although the FIM still provides a meaningful measure of estimation quality. Therefore, classical DoE methods are generally more reliable when the system is linear, or approximately linear, with respect to the parameters in the region of interest (Fedorov and Leonov, 2013). Alternatively, they are particularly useful in situations where preliminary studies or experiments have already provided rough parameter estimates, but more accurate estimates are required for specific parameters. This refinement can naturally be achieved through sequential design strategies (Ryan et al., 2016).

In addition, practical uncertainties also pose challenges for classical FIM-based MBDoE (Hosseini et al., 2020). The Cramér–Rao inequality is established under assumptions regarding the statistical distribution of measurement noise. In practice, uncertainties such as input uncertainty may violate these assumptions and lead to mismatches between the assumed and actual statistical models (Dijkstra, 1984; Vuong, 1986). For example, input uncertainty can

propagate nonlinearly to the measurements through the system dynamics, often resulting in complex and unknown relationships between inputs and outputs (Wang and Yue, 2024).

Other challenges include model structural uncertainty, computational cost, and trade-offs in multi-criteria decision-making. These issues are beyond the scope of this work; a more detailed discussion can be found in the literature review in Chapter 2.

Why is the development of robust experimental design methods increasingly critical?

Classical MBDoE faces several challenges related to uncertainties. These challenges motivate the development of robust experimental design (RED) methods to improve design reliability under uncertain conditions and to make this technique more broadly applicable to complex systems. RED aims to maintain acceptable performance in the presence of uncertainty, which has attracted increasing attention from researchers.

For parametric uncertainty, commonly used RED approaches include the maximin design, which maximises the information content for the worst-case parameter scenario, and the pseudo-Bayesian design, which maximises the expected information content over the entire uncertainty space (Asprey and Macchietto, 2002; Franceschini and Macchietto, 2008). However, the maximin design may become overly conservative, as it is based on the worst-case parameter scenario, which may be highly unlikely to occur in practice (Mesbah and Streif, 2015). In contrast, the pseudo-Bayesian method may perform poorly for certain initial parameter guesses because it maximises the information content only on average (Fedorov and Leonov, 2013; Ryan et al., 2016). In addition, both approaches require assumptions about the parameter uncertainty space, and these assumptions can influence the resulting design. Maximin designs are often affected by the boundary of the prescribed uncertainty set, while pseudo-Bayesian designs depend directly on the assumed distribution over that space. In practice, however, such uncertainty descriptions may not always be easy to specify reliably. This also makes iterative design strategies appealing, since parameter uncertainty can be progressively refined as new experimental data become available (Bubel et al., 2024; Galvanin et al., 2009; Ryan et al., 2016).

Unlike uncertainty in parameter knowledge, which affects the model used for design rather than the physical execution of a given experiment, input uncertainty directly alters the actual inputs applied to the system and hence influences the resulting measurements. As a result, it may change the effective statistical distribution of the data and invalidate the assumptions underlying the classical FIM-based formulation. In fields with well-developed industrial capabilities, input uncertainty can often be mitigated through the use of high-precision experimental equipment, although this may substantially increase experimental costs. Consequently, addressing input uncertainty when developing RED methods is particularly valuable for experiments conducted under restricted operational conditions or with limited financial resources. Recent studies have emphasised the importance of explicitly accounting for input uncertainty in experimental design, for example by selecting robust measurement sets (Wang and Yue, 2021), adopting robust optimal input design strategies in engineering applications (Hosseini et al., 2020), or utilising the Misspecified Cramér–Rao bound (MCRB) to design robust sampling strategies (Wang et al., 2024).

Taken together, these challenges highlight the limitations of classical MBDoE when uncertainty is significant. They motivate the development of robust experimental design methods that explicitly account for uncertainty while remaining practical for nonlinear dynamic systems. This forms the main motivation for the work presented in this thesis.

1.2 Research Questions

Uncertainties are inherent in both mathematical modelling and the practical execution of experiments, which may impair the applicability and reliability of MBDoE. This research aims to enhance and further develop methods within the RED framework. To achieve this objective, the study is guided by the following research questions:

1. What types of uncertainties significantly affect model-based experimental design, and how do they influence the reliability of parameter estimation? (Chapters 2–3)

2. What are the limitations of existing RED methods, such as the maximin and pseudo-Bayesian design strategies, when applied to nonlinear dynamic systems with parametric uncertainty? (Chapter 4)
3. How can RED strategies be further developed to improve robustness to parametric uncertainty while enhancing parameter estimation quality in nonlinear dynamic systems? (Chapter 5)
4. How can MBDoE be extended to account for input (practical) uncertainty that leads to misspecification in measurement distributions? (Chapter 6)

1.3 Aims and Objectives

This research aims to contribute to the theory and practice of robust model-based experimental design under uncertainty, specifically addressing challenges associated with parametric uncertainty and input (practical) uncertainty. The study focuses on sampling time design for complex nonlinear dynamic systems, as this design variable offers numerical convenience while preserving the normal operation of the system during experimentation.

To achieve this aim, the following research objectives are pursued:

1. Identify and analyse the main sources of uncertainty that affect model-based experimental design, with particular emphasis on parametric (model) uncertainty and input (practical) uncertainty. (Chapter 2 and early Chapter 3)
2. Evaluate the capabilities and limitations of existing robust experimental design methods, particularly the maximin and pseudo-Bayesian design strategies, when applied to nonlinear dynamic systems with parametric uncertainty. (Chapter 4)
3. Develop improved experimental design strategies that enhance robustness to parametric uncertainty while improving parameter estimation quality in sampling time design for nonlinear dynamic systems. (Chapter 5)

4. Extend MBDoE methods to account for input uncertainty by incorporating misspecified statistical models and robust information criteria. (Chapter 6)
5. Demonstrate and assess the robustness and effectiveness of the proposed experimental design approaches through representative dynamic-system case studies. (Chapters 4–6)

1.4 Research Contributions

The main contributions of this PhD work can be summarised as follows. These contributions address the limitations of existing model-based experimental design methods when dealing with parametric and practical uncertainties, and develop corresponding methodological and computational approaches for RED.

1. **Systematic formulation and assessment of robust sampling time design strategies.**

The mathematical formulations of two common RED methods, the maximin design and the pseudo-Bayesian design, are established for nonlinear dynamic systems with parametric uncertainty. Corresponding numerical approaches for solving these robust sampling-time design problems are developed and presented in detail. In addition, the relative strengths and limitations of the two methods are systematically analysed using two benchmark case studies, an enzyme reaction system and a biodiesel production system, which differ in application domain, problem dimension, and system complexity. The results clarify the trade-offs between robustness, estimation quality, and computational tractability in robust sampling time design.

2. **Development of an adaptive midterm redesign framework.** A midterm sampling-time redesign framework is proposed for complex nonlinear dynamic systems with limited prior knowledge of parameter values. The experiment is divided into several stages (midterms), and OED is performed at each stage using parameter estimates updated from the previous stage. This adaptive redesign framework reduces the need for strong prior assumptions on parameter values, as the parameters can be progressively refined using observations collected during each experimental stage.

Within this redesign framework, three redesign strategies are developed: an equally divided midterm strategy for straightforward implementation, an auto-updating strategy that determines the redesign frequency according to the achieved information gain, and a condition-triggered redesign strategy tailored to experiments involving condition shifts, in which the parameter estimates and experimental design are updated whenever the operating conditions change. Case studies on enzyme kinetics and biodiesel production demonstrate that the proposed framework improves estimation robustness compared with static RED, achieves estimation performance close to nominal OED, and reduces worst-case performance loss across uncertainty scenarios. These results suggest that adaptive midterm redesign provides a practical compromise between robustness and estimation quality.

3. **Extension of sampling time design to input uncertainty using the MCRB.** To address the limitations of classical FIM/CRB-based criteria under input-induced model misspecification, this thesis adopts the MCRB as a performance bound for sampling time design. Input uncertainty is shown to alter pseudo-data dispersion, violate the assumed Gaussian error model, and introduce temporal correlations across sampling times. A trajectory-level (stacked-measurement) MCRB-based criterion is formulated to capture the covariance structure of the measurement vector. The resulting design is compared with classical OED, input-uncertainty-specific methods, and standard RED approaches adapted to this setting. The enzyme reaction case study demonstrates that the MCRB-based design provides a more appropriate and balanced criterion under distributional misspecification.

1.5 Thesis Organisation

This PhD thesis investigates model-based RED through two complementary case studies: a relatively compact enzyme reaction benchmark and a more industrially relevant biodiesel production system with greater model complexity. To address the limitations of the most

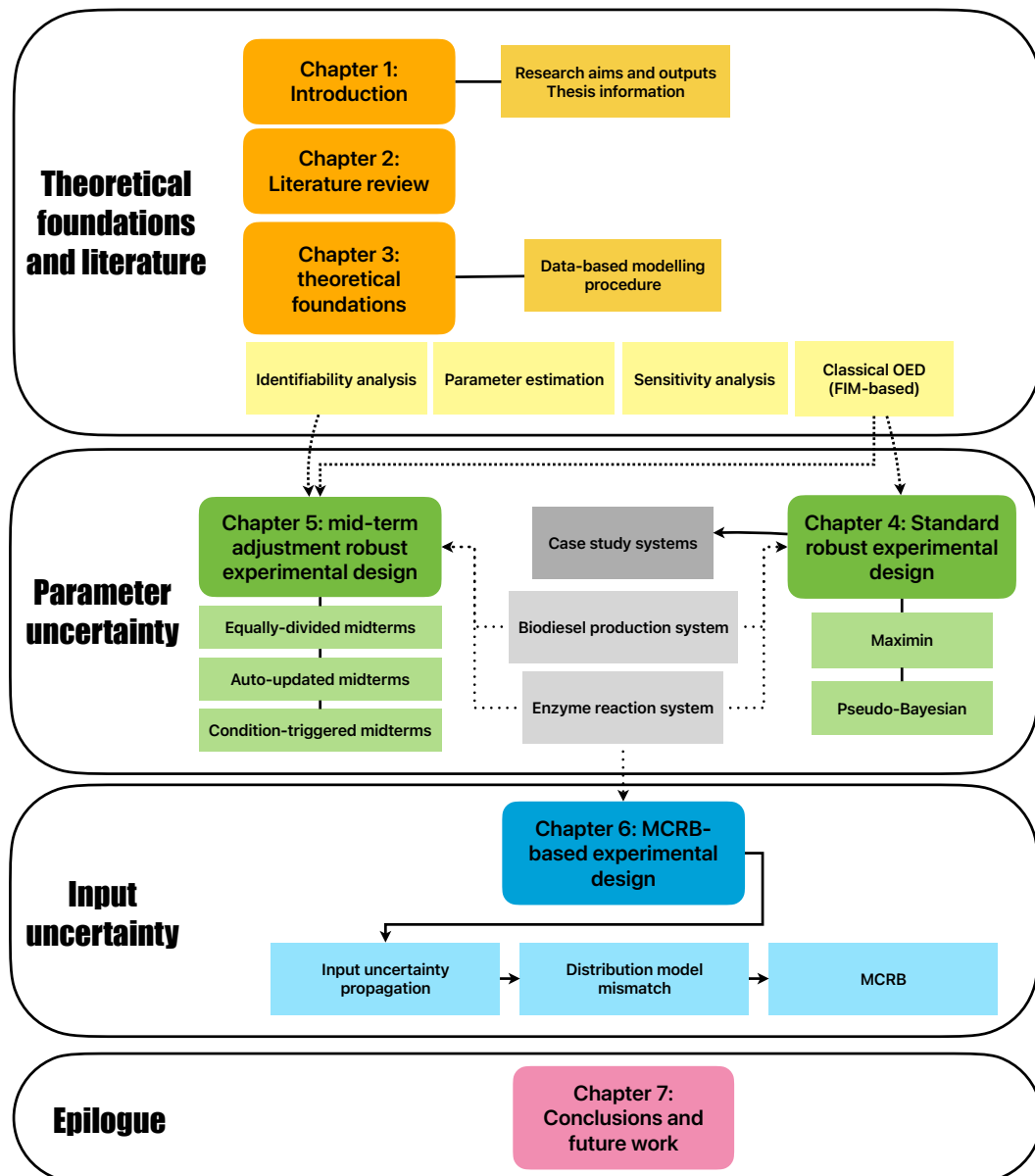


Fig. 1.1 Conceptual flow of the thesis

commonly used RED methods, several model-based robust sampling time design approaches are proposed to handle both parametric and input uncertainty. The conceptual flow of the thesis is illustrated in Fig. 1.1, showing the relationship between the methodological developments and the case-study applications presented in the subsequent chapters. The organisation of this thesis is outlined below.

Chapter 2 provides a comprehensive literature review on OED and RED, presenting the current state of the art in experimental design methods under uncertainty.

Chapter 3 presents the theoretical foundations and mathematical preliminaries related to OED. The chapter begins with a data-based modelling procedure to illustrate the role and benefits of OED. The mathematical description of dynamic systems is then introduced, together with interpretations of all components in the model. Parametric sensitivity analysis is presented as it provides valuable information about system behaviour and can help reduce the dimensionality of OED problems. This is followed by identifiability analysis, which is an essential step in data-based modelling and should be performed before OED to ensure the validity of the experimental design. Parameter estimation methods are then introduced to demonstrate how parameters are inferred from experimental data in dynamic systems. Finally, the FIM and the Cramér–Rao inequality are presented to explain the commonly used criteria for evaluating the information content of experimental data for parameter estimation. Based on these concepts, the general mathematical formulation of classical OED for parameter estimation is established, including input design, sampling time design, and measurement set selection.

Chapter 4 introduces robust sampling time design. Two common RED methods, the maximin design and the pseudo-Bayesian design, are presented for addressing parametric uncertainty. The numerical optimisation methods used to solve these RED problems are also described. In addition, two benchmark case-study systems, the enzyme reaction system and the biodiesel production system, are introduced. The RED methods are implemented on both case studies to evaluate their robustness for parametric uncertainty and their computational efficiency. For the biodiesel system, both Exp. 5 and Exp. 8 are considered to examine

whether the performance trends of the robust designs are retained when a prescribed operating-condition change is introduced.

Chapter 5 presents an adaptive midterm experimental redesign framework for parametric uncertainty. A midterm experimental redesign framework is proposed, in which the entire experimental time span is divided into several stages (midterms). The sampling strategy is redesigned at the beginning of each stage using updated parameter estimates obtained from data collected in previous stages. This adaptive midterm framework is particularly suitable for nonlinear systems with large parametric uncertainty, as parameter estimates are progressively updated based on experimental observations. Three strategies for determining the redesign stages are proposed: equally divided, auto-updating, and condition-triggered. The proposed adaptive redesign framework is evaluated on the two case studies introduced in Chapter 4, and the resulting design performance and robustness are analysed and compared. For the biodiesel case study, Exp. 8 is used because its prescribed operating-condition change provides the setting required to evaluate the condition-triggered redesign strategy.

Chapter 6 investigates sampling time design under input uncertainty using the MCRB. The effect of input uncertainty is analysed through the distributional misspecification it induces in the measurement model, including changes in pseudo-data dispersion, departures from the assumed Gaussian error model, and temporal correlations between measurements at different sampling times. Based on the MCRB framework, a stacked-measurement sampling time design criterion is formulated and applied to the enzyme reaction system. The proposed design is compared with classical OED, existing input-uncertainty-specific methods, including sample-covariance-based design and smallest covariance deviation design, and standard RED methods adapted to input uncertainty.

Chapter 7 concludes the thesis by summarising the main findings and discussing potential directions for future research.

1.6 List of Publications

- Wang, K. and Yue, H. (2026), 'Evaluating Robust Sampling-Time Design: A Comparative Analysis of Maximin and Pseudo-Bayesian Approaches', *Computers & Chemical Engineering*. <https://doi.org/10.1016/j.compchemeng.2026.109907>.
Expanded materials are included in Chapter 4.
- Wang, K. and Yue, H. (2025), 'Robust sampling time design under parametric uncertainty: a mid-term redesign approach', submitted to *Journal of Process Control*, (Ref. No. JPROCONT-D-25-00969) (under review).
Expanded materials are included in Chapter 5.
- Wang, K. and Yue, H. (2024), 'Sampling time design with misspecified Cramer-Rao bounds under input uncertainty', *IFAC-PapersOnLine*, 58(14), 622–627, DOI 10.1016/j.ifacol.2024.08.406.
Expanded materials are included in Chapter 6.
- Wang, K. and Yue, H. (2021), 'Robust measurement selection design for experimental systems with input uncertainty', 2021 26th International Conference on Automation and Computing (ICAC), pp. 1–6, DOI 10.23919/ICAC50006.2021.9594201.
Expanded materials are included in Chapter 6.
- Wang, K. and Yue, H. (2020), 'Robust sampling time designs for parametric uncertain systems', *IFAC-PapersOnLine*, 53(2), 622–627, DOI 10.1016/j.ifacol.2020.12.505.
Expanded materials are included in Chapter 4.
- Wang, K. and Yue, H. (2019), 'Auto-updating of sampling time redesign for system identification under parameter uncertainty', 2019 25th International Conference on Automation and Computing (ICAC) pp. 1–6, DOI 10.23919/ICAC.2019.8895129.
This publication won the *Best Student Paper* and the expanded materials are included in Chapter 5.

- Wang, K., Yue, H. and Yu, H. (2018), ‘Optimal input design for reduction of parameter correlations’, 2018 24th International Conference on Automation and Computing (ICAC) pp. 1–6, DOI 10.23919/IConAC.2018.8749035.

This input design was developed in early stage of the PhD and applied to the enzyme reaction system.

Chapter 2

Literature Review

Design of experiments (DoE), also referred to as experimental design, is a systematic methodology for determining experimental settings using mathematical and statistical tools, while providing a scientific framework for analysing and interpreting experimental data (Ryan and Morgan, 2007). It supports the derivation of valid, objective, and meaningful conclusions from experimental observations (Montgomery, 2017). DoE is typically implemented prior to experimentation to ensure that appropriate data are collected for specific design objectives under constraints of time and resources. The importance of DoE in data collection is highlighted in the well-known statement from Fisher (1937): *"To consult a statistician after an experiment is finished is often merely to ask him to conduct a post-mortem examination. He can perhaps say what the experiment died of."*

DoE is closely linked to mathematical modelling, which has been a cornerstone of scientific and industrial research for centuries. By guiding the selection of informative experiments, DoE enables efficient modelling even for systems where experimentation is time-consuming and resource-intensive.

2.1 Development of Design of Experiments – A Brief Historical Review

Although experimentation has always been an integral part of scientific research, the systematic planning of experiments did not receive significant attention until the early twentieth century. Early experimental approaches were largely empirical and often relied on trial and error (Ryan and Morgan, 2007). One commonly used strategy was the so-called "best-guess approach", which depended heavily on the experimenter's experience and intuition but could not guarantee optimal outcomes (Montgomery, 2017). Another widely adopted approach was One-Factor-at-a-Time (OFAT), in which a single factor is varied while all other factors are kept constant. Although straightforward to implement, OFAT is inefficient and fails to reveal potential interactions among factors in multifactor systems (Box, 2005; Fisher, 1925; Montgomery, 2017).

Modern DoE was established by Sir Ronald Aylmer Fisher during the 1920s through his work on agricultural productivity at the Rothamsted Experimental Station in England. In 1925, Fisher published *Statistical Methods for Research Workers* (Fisher, 1925), which systematically introduced statistical methodology into scientific experimentation and laid the foundation for the development of DoE. This work introduced key statistical tools, including analysis of variance (ANOVA), which enables the analysis of multifactor experiments by detecting both main effects and interaction effects. These methods directly addressed the limitations of OFAT-based experimentation.

Fisher further advanced the field with the publication of *The Design of Experiments* (Fisher, 1937), which established the fundamental principles of modern experimental design, including randomisation, replication, blocking, and factorial design. These principles form the theoretical foundation of classical experimental design and remain central to statistical experimentation today (Box, 1980; Wu, 2021). Examples of traditional DoE methods are illustrated in Figure 2.1.

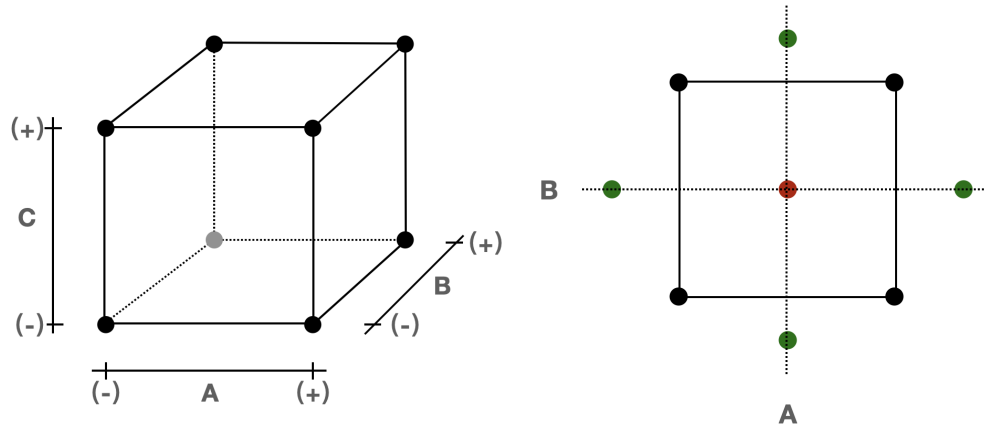


Fig. 2.1 Traditional DoE methods. Left: full factorial design for a system with three factors, where the black and grey points represent the factorial design points and the grey point denotes the hidden corner. Right: central-composite design for a system with two factors, where the black, green, and red points represent factorial, axial, and centre points, respectively.

Following the Second World War, DoE attracted increasing attention from industry and manufacturing. In process optimisation, Response Surface Methodology (RSM) was introduced by Box and Wilson (1951) to handle systems with significant nonlinear effects, extending factorial design approaches that were primarily suitable for linear or additive models to nonlinear systems. In quality engineering, the Taguchi method (Taguchi, 1986) incorporated noise factors to improve the robustness of product and process design, and these techniques have been widely adopted in industrial applications. While these classical DoE methods are effective for relatively simple models, they become less suitable for complex, nonlinear, or high-dimensional systems, particularly when experimental resources are limited. These limitations motivated the development of experimental design methods that maximise the information obtained from limited experimental data, leading to the emergence of model-based design of experiments (MBDoe).

MBDoE employs optimisation theory to design experiments that maximise a criterion reflecting the accuracy of parameter estimation or the ability to discriminate between competing models. In this context, optimal experimental design (OED) denotes criterion-based formulations in which the experimental conditions are optimised with respect to a specified design objective. Kiefer (1959) systematically introduced the Fisher Information Matrix

(FIM) into OED theory as a quantitative measure of the information content of an experiment for parameter estimation. This work defined the classical A-, D-, and E-optimality criteria and laid the foundation for the General Equivalence Theorem (GET) for D-optimal design in linear regression models.

Subsequently, the application of OED was extended to nonlinear and dynamic systems. Early studies on parametric sensitivity analysis for nonlinear kinetic models (e.g., Mezaki and Kittrell (1967)) highlighted the challenges in such systems. Fedorov (Fedorov, 1972) systematically integrated the work of Kiefer and other researchers, extending OED to nonlinear systems and further demonstrating the applicability of the GET to A-, D-, and E-optimal criteria. He also developed exchange-based algorithms for solving the resulting design problems. A major advance in dynamic experimental design was later made by Espie and Macchietto (1989), who formulated the design of transient experiments as an optimal control problem. Atkinson and Doney (1992) subsequently presented an engineering-oriented reformulation of the Kiefer–Fedorov theoretical framework, making OED more algorithmic and computationally practical. However, many early approaches for nonlinear systems relied on local linear approximations. For nonlinear dynamic systems, experimental design is particularly challenging because the information content of an experiment depends on the time evolution of the system states and parameter sensitivities. Evaluation of candidate designs generally requires repeated simulation of the dynamic model and its sensitivity equations, while experimental variables such as inputs, initial conditions and sampling times can influence different regions of the system trajectory. Consequently, MBDoE for nonlinear dynamic systems is both computationally demanding and strongly dependent on the assumed model and parameter values (Balsa-Canto et al., 2008; Bauer et al., 2000; Bock et al., 2013; Franceschini and Macchietto, 2008).

Since the 2000s, MBDoE has been widely applied in various scientific and engineering fields, including pharmaceuticals and biomedicine (Galvanin et al., 2013; Ghosh and García Muñoz, 2026; Musuamba et al., 2012; Retout et al., 2001, 2002), chemical and biochemical engineering (Franceschini and Macchietto, 2008; Kozachynskyi et al., 2024; Yu, 2018; Yue et al., 2013), and geophysics (Curtis, 2004; Maurer et al., 2009, 2017; Strutz

and Curtis, 2024). Research interest has also expanded toward increasingly complex models, including systems described by ordinary differential equations (Bandara et al., 2009; Bauer et al., 2000; Bock et al., 2013), partial differential equations (Alexanderian et al., 2016; Herzog et al., 2018; Neitzel et al., 2019; Uciński, 2020), and implicit models (Duarte et al., 2022; Kunert et al., 2016).

In addition, increasing attention has been paid to the impact of model uncertainty on experimental design for nonlinear systems. Since classical FIM-based design criteria are local measures that depend on initial parameter estimates, robust experimental design (RED) has become an important research direction in the literature (Asprey and Macchietto, 2002; Rojas et al., 2007; Wang et al., 2024). Fully Bayesian OED has also attracted significant interest for systems exhibiting complex or multimodal relationships between experimental data and model predictions (Huan and Marzouk, 2013; Strutz and Curtis, 2024). Sequential OED (Bubel et al., 2024; Cavagnaro et al., 2010; Dror and Steinberg, 2008; Drovandi et al., 2014; Pandita et al., 2021; Sürer et al., 2024) further improves experimental efficiency by allowing the results of earlier experiments to inform the design of subsequent experiments.

More recently, with the rapid development of data-driven artificial intelligence techniques such as machine learning and reinforcement learning, OED has increasingly been combined with these techniques. For example, Quaglio et al. (2020) integrated statistical DoE methods with artificial neural networks (ANNs) to select appropriate kinetic models. To overcome the limitation that classical statistical DoE may yield poorly informative experiments, Sangoi et al. (2022) incorporated OED into the ANN-based kinetic model recognition framework, and (Sangoi et al., 2024) further extended and formalised this approach.

Overall, OED represents a transition from predefined classical experimental plans to computationally driven, criterion-based design frameworks. Rather than replacing classical experimental designs, optimal design can be viewed as their theoretical extension. It enables the construction of highly informative experiments tailored to complex nonlinear models and specific modelling objectives under constrained resources. In the following sections, the development of MBDoE and RED is reviewed in more detail.

2.2 Model-Based Design of Experiments (MBDoE)

Mathematical models provide a way to understand and represent real-world systems. Although all models are inherently imperfect due to simplification and approximation, many remain useful for scientific analysis and decision-making (Box and Draper, 1987). Based on the available knowledge of the system, models can generally be categorised into two forms: mechanistic models and empirical models. The development of DoE has followed different paths for these two types of models.

For empirical models, the objective is typically to identify cause–effect relationships from experimental data through statistical analysis. This approach is often referred to as statistical DoE (Lee, 2019) or black-box experimental design (Franceschini and Macchietto, 2008). In contrast, mechanistic models incorporate prior knowledge of the underlying physics governing the system. In such cases, MBDoE is preferred because it can explicitly exploit information about the system dynamics.

MBDoE is commonly used to design experiments for tasks such as model discrimination and parameter estimation, where the unknown parameters often have clear physical interpretations. Within this framework, OED refers more specifically to criterion-based formulations in which the experimental conditions are selected by solving an optimisation problem. With the rapid development of high-performance computing, such optimisation-based design approaches have become increasingly practical, as computational capability has become less prohibitive in many applications.

2.2.1 Key Methodologies

Design criteria

The design criterion, which serves as the objective function in an OED problem, depends on the purpose of the experiment. In mathematical modelling, experimental design typically aims

either to discriminate between competing model structures or to estimate model parameters with high precision.

Several OED criteria have been proposed for model discrimination, including maximising the Euclidean distance between model outputs (Hunter and Reiner, 1965), maximising the expected change in entropy (or information gain) between prior and posterior model probabilities (Box and Hill, 1967), the T-criterion (Atkinson and Fedorov, 1975 a,b ; Dette et al., 2017; Uciński and Bogacka, 2005), the KL-criterion (López-Fidalgo et al., 2007 b ; Skanda and Lebiedz, 2010), and the Akaike information criterion (Kenneth P. Burnham, 2002). Since model discrimination is outside the scope of this thesis, interested readers are referred to López-Fidalgo and Tommasi (2018) for a comprehensive review.

For parameter estimation problems, a design is considered more informative if the covariance matrix of the estimated parameters obtained from the experimental data is smaller. Consequently, several approaches have been developed to approximate the covariance matrix of parameter estimates and formulate the OED problem.

FIM-based approach to approximating the covariance matrix

The most widely used design criterion for evaluating the information content of experimental data is the FIM, whose inverse provides a lower bound on the covariance matrix of any unbiased estimator of unknown parameters. Since the FIM is a matrix, it must be reduced to a scalar quantity to serve as an optimisation objective. This dimensionality reduction inevitably leads to some information loss, and the choice of scalar function should therefore be made carefully to ensure that it represents a meaningful measure of information content. Theoretical properties required for such scalar functions are discussed in (Franceschini and Macchietto, 2008; Huan et al., 2024; Pukelsheim, 2006).

Among the classical alphabetic optimality criteria, D-optimality is based on the determinant of the FIM, A-optimality on the trace of its inverse, and E-optimality on the minimum eigenvalue of the FIM (Franceschini and Macchietto, 2008; Silvey, 1980). Geometrically, these criteria correspond to different properties of the parameter confidence ellipsoid. D-optimality minimises its volume, A-optimality minimises the dimensions of

the hyperrectangular box enclosing the ellipsoid, and E-optimality minimises its longest principal axis. Among these criteria, D-optimality is the most widely used because it is invariant to parameter rescaling (Fedorov, 1972; Franceschini and Macchietto, 2008; Huan et al., 2024). E-optimality can improve worst-direction identifiability, but it introduces computational challenges because the criterion is non-smooth and is therefore difficult to solve using gradient-based optimisation methods (Telen et al., 2015). A-optimality minimises the average variance of the parameter estimates, but it may still yield poor precision for individual parameters and should therefore be applied with caution. Other optimality criteria, such as G-, L-, and C-optimality, have also been proposed, although they are less commonly used in practice. A detailed overview can be found in Pukelsheim (2006).

According to the General Equivalence Theorem (Fedorov, 1972; Kiefer, 1974), criterion-specific necessary and sufficient conditions can be established for optimal experimental designs in linear models. Different alphabetic optimality criteria correspond to different scalar measures of parameter estimation precision and may therefore lead to different optimal designs. For nonlinear models, however, the FIM generally depends on the unknown parameter values. Classical optimal-design criteria are therefore commonly applied locally by evaluating the FIM at a nominal or initial parameter estimate (Fedorov and Leonov, 2013). The resulting locally optimal design can be sensitive to the assumed parameter values, particularly when parameter uncertainty is large. This dependence motivates the development of RED methods discussed in Section 2.3.

Another important challenge in OED lies in the numerical solution of the optimisation problem. For example, E-optimal design leads to a non-differentiable objective function, and eigenvalues of matrices larger than 4×4 generally lack closed-form expressions. To address this difficulty, Telen et al. (2015) reformulated the OED problem using the Sylvester criterion, enabling the use of gradient-based optimisation solvers.

In general, OED problems are nonlinear and non-convex (Schöneberger et al., 2010). As a result, the obtained design is often a local optimum that depends on the initial guess and the optimisation algorithm used, such as gradient descent, quasi-Newton methods, or

conjugate gradient methods (Banga and Balsa-Canto, 2008). Different initial conditions may converge to the same local optimum, while different solvers may converge to different solutions (Vanaret et al., 2021). To mitigate this issue, Vanaret et al. (2021) proposed a two-phase approach that first approximates the non-convex problem using pattern-based or discretisation methods to obtain a good initial design, which is then refined using gradient-based optimisation.

For large-scale models, numerical difficulties may arise due to poorly conditioned or non-invertible FIM matrices. To address this problem, Shahmohammadi and McAuley (2019*a,b*) proposed reduced-dimension sensitivity approaches that remove poorly identifiable parameters or use pseudoinverse techniques to improve numerical stability. More generally, experimental design can be used to improve the practical identifiability of nonlinear dynamic models by selecting experimental conditions that reduce parameter uncertainty and parameter correlation. However, optimal experimental design cannot in general resolve structural non-identifiability associated with a fixed model and observation structure; in such cases, model reformulation, additional measured outputs, or alternative experimental inputs may be required. Practical identifiability, by contrast, depends on the amount and quality of available data and can often be improved through appropriately designed experiments (Balsa-Canto et al., 2010; Shahmohammadi and McAuley, 2019*a,b*).

In practical applications, FIM-based OED may produce experimental designs that concentrate measurements near operational limits, which can lead to implementation difficulties and inefficient use of experimental resources. To address such issues, Guillén et al. (2024) proposed incorporating penalty terms into the design criterion to balance information content and experimental feasibility. Other practical constraints, such as minimum spacing between sampling times, have also been discussed in (Garre et al., 2018).

FIM-based criteria are also frequently used in multi-objective experimental design problems. For example, Wang et al. (2024) proposed a convex mixed-integer (non)linear programming framework that integrates measurement budgets into the OED formulation. To address the effects of model nonlinearity, Manesso et al. (2017) proposed a multi-objective

optimisation approach that simultaneously maximises the D-optimality criterion and minimises model curvature. Other studies have incorporated parameter correlation measures into the optimisation framework to reduce estimation bias and improve numerical stability (Maheshwari et al., 2013). Similarly, Wang et al. (2018) proposed combining the A-optimality criterion with a modified E-optimality criterion to improve parameter decorrelation.

Other approaches to computing the covariance matrix

Alternative approaches have been proposed to estimate the covariance matrix of parameter estimates. For example, bootstrap methods (Efron, 1994) can be used to approximate the covariance matrix by repeatedly solving the parameter estimation problem using resampled output data. However, for complex dynamic systems, a very large number of samples may be required to obtain accurate results, resulting in significant computational cost (Schenkendorf et al., 2009). To reduce the required sample size, Schenkendorf et al. (2009) introduced a sigma-point method to estimate parameter covariance. This method significantly reduces the number of required samples and avoids the need for sensitivity calculations. However, the scaling parameters used in the sigma-point method must be carefully selected to ensure accurate covariance estimation.

Other approaches include derivative-free methods for evaluating the information content of planned experiments. For example, Heine et al. (2008) proposed a Bayesian maximum *a posteriori* approach for assessing experimental informativeness. Similarly, Telen et al. (2013) proposed estimating the covariance matrix through a Riccati equation formulation, which reduces the number of sensitivity equations that must be solved. Nevertheless, this approach remains a local method and may be sensitive to model mismatch.

More recently, experimental design criteria have also been adapted to incorporate machine learning techniques. For example, Sangoi et al. (2024) proposed an objective function based on ANN prediction accuracy to generate informative *in-silico* data for training neural-network classifiers. Similarly, Treloar et al. (2022) employed reinforcement learning to directly perform optimal input design. Machine learning techniques are generally integrated with classical OED in two main ways. First, they can reduce the computational burden

associated with solving complex OED problems, such as searching for the optimum of highly nonconvex design problems Treloar et al. (2022) or repeatedly evaluating high-dimensional kinetic models to obtain model outputs. Second, OED can guide the selection of experimental settings to generate informative datasets that improve the efficiency of constructing machine learning surrogate models Sangoi et al. (2024). Although these approaches can significantly reduce the computational burden of OED, particularly in online settings, they typically require extensive training and often rely on accurate mechanistic models during the learning process.

2.2.2 Limitations and Research Gap

Although MBDoE has proven effective for mathematical modelling, it still faces several challenges, mainly in the following aspects:

- **Sensitivity to uncertainties in nonlinear systems.** Uncertainty in models is inevitable; otherwise, modelling itself would not be necessary. In addition, practical uncertainties arising during laboratory implementation are also unavoidable. Ignoring these uncertainties may not only lead to uninformative experiments and inefficient use of time and resources, but may also result in designs that approach impractical or unsafe operating conditions (Asprey and Macchietto, 2002; Telen et al., 2014).
- **Lack of guidance on experimental data requirements.** Classical OED methods primarily identify the most informative regions in the design space under predefined experimental requirements, such as the number of measurements to be collected in an experiment. However, they do not provide guidance on how many measurements or experiments are required to achieve a desired precision of parameter estimates, e.g., a minimum covariance matrix (Guillén et al., 2024; Vanaret et al., 2021).
- **Difficulty in adapting OED to specific systems.** In practice, experimental design must often be customised to accommodate system-specific model structures, design objectives, operational constraints, and practical limitations. Even with powerful

open-source toolboxes such as AMIGO2 (Balsa-Canto et al., 2016), adapting OED methods to particular applications remains non-trivial due to the diverse backgrounds of experimenters and the complexity of modelling frameworks.

Model-based design of experiments (MBDoE) has developed into a powerful framework for designing informative experiments in complex dynamical systems. Numerous methodologies have been proposed to maximise the information content of experimental data and improve parameter estimation accuracy. However, most existing approaches rely on local sensitivity measures and assume reliable prior knowledge of model parameters. These limitations motivate the development of RED methods that explicitly account for uncertainty, which will be discussed in the following section.

2.3 Robust Experimental Design (RED)

Although MBDoE has achieved considerable success in improving parameter estimation accuracy, many classical OED methods rely on local sensitivity analysis and accurate prior parameter estimates. In practical applications, however, model parameters and operating conditions are often subject to significant uncertainties. These uncertainties may lead to suboptimal or even infeasible experimental designs. To address these challenges, RED methods have been developed to ensure satisfactory experimental performance across a range of possible parameter values or uncertainty scenarios.

2.3.1 Methodology

Several methodological approaches have been proposed to address parametric uncertainty in MBDoE. These approaches can be broadly categorised into three groups: methods that robustify classical local design criteria under uncertainty, methods that adopt alternative information-, sensitivity-, or decision-theoretic formulations for nonlinear systems, and

adaptive design strategies that update experiments as new information becomes available. The main representative methodologies are briefly reviewed below.

Maximin design and pseudo-Bayesian design

Locally OED for nonlinear systems (Fedorov and Leonov, 2013) performs satisfactorily when parameter uncertainty is small or when the model is approximately linear with respect to the parameters. However, when substantial parameter uncertainty is present, RED methods such as the maximin design and the pseudo-Bayesian design are commonly employed (Asprey and Macchietto, 2002).

The maximin design addresses parameter uncertainty by optimising the worst-case parameter scenario within a predefined uncertainty region (Körkel et al., 2004; Pronzato and Walter, 1988; Rojas et al., 2007). However, it requires a deterministic and bounded uncertainty set and can lead to overly conservative designs when the worst-case parameter values lie in low-probability regions of the uncertainty space. In addition, maximin design is sensitive to the chosen uncertainty bounds, since the worst-case parameters often lie on the boundary of the uncertainty region (Kusumo et al., 2022). From a computational perspective, the FIM may become ill-conditioned or even singular for worst-case parameter values, as the information content of such scenarios can be extremely small.

The pseudo-Bayesian design determines the design vector by averaging classical design criteria over the prior distribution of the parameters, thereby accounting for parameter uncertainty. Since it does not explicitly apply Bayes' rule to update posterior distributions during the design process, this approach is often referred to as pseudo-Bayesian design to distinguish it from fully Bayesian experimental design (Ryan et al., 2016). However, pseudo-Bayesian design requires prior knowledge of parameter distributions, which is often difficult to obtain in practice. To alleviate the difficulty of specifying parametric priors, posterior samples obtained from Bayesian analysis of historical data can also be reused as the prior uncertainty description in pseudo-Bayesian design, as demonstrated by Strouwen et al. (2022). Another limitation of pseudo-Bayesian design is that it may produce designs that

are overly optimistic: while the average information content may be satisfactory, the design can still be uninformative for certain parameter scenarios (Kusumo et al., 2022).

To address these limitations, López-Fidalgo et al. (2007a) proposed quantile- and probability-level design criteria that ensure a low probability that the information content across the parameter uncertainty space falls below a specified threshold. However, these criteria often lead to non-convex optimisation problems. Alternatively, Valenzuela et al. (2015) introduced conditional value-at-risk (CVaR) into the OED framework to handle parameter uncertainty by maximising the mean information content among the worst-performing parameter scenarios below a specified percentile $1 - \beta$. When $\beta = 0$, the CVaR-based design reduces to pseudo-Bayesian design, whereas when $\beta \rightarrow 1$, it approaches the maximin design. One advantage of the CVaR-based approach is that the resulting optimisation problem can be concave when the FIM is concave with respect to the design variables. Furthermore, Kusumo et al. (2022) proposed a bi-objective design criterion combining pseudo-Bayesian and CVaR-based approaches to balance average information content and robustness.

Curvature-based design

Instead of relying on the FIM, which is based on first-order sensitivity approximations, curvature-based design approaches incorporate second-order sensitivity information through the Hessian matrix (Bates and Watts, 1980). A Q-optimality criterion based on a quadratic approximation of the parameter confidence region was proposed for nonlinear regression models (Hamilton and Watts, 1985). Later, Benabbas et al. (2005) introduced curvature-based design criteria for nonlinear models that explicitly account for second-order parameter sensitivities.

GSA-based design

Global Sensitivity Analysis (GSA) has also been explored as an alternative framework for experimental design. Chu and Hahn (2013) proposed a necessary condition, known as the Consistency Condition, to determine whether a global sensitivity analysis (GSA) metric can be applied within alphabetic optimality-based experimental design. Subsequent studies (Lei et al., 2023; Schenkendorf et al., 2018) demonstrated that GSA-based approaches can

improve robustness to parameter uncertainty and model nonlinearity. However, systematic guidelines for determining when global sensitivity measures outperform local sensitivity methods remain limited.

Sequential design

Sequential experimental design represents another typical strategy for addressing parameter uncertainty in nonlinear systems. In sequential design, multiple experiments are conducted in sequence, with the results of previous experiments informing the design of subsequent experiments (Bubel et al., 2024). Parameter estimates are iteratively refined by alternating between experimentation, parameter estimation, and experimental redesign (Fedorov and Leonov, 2013; Franceschini and Macchietto, 2008; Silvey, 1980). Sequential design approaches have been widely studied using local information measures (Barz et al., 2010; Bubel et al., 2024; Duarte et al., 2021; Franceschini and Macchietto, 2008; Goujot et al., 2012; Shahmohammadi and McAuley, 2019*a,b*), and can naturally be integrated with Bayesian frameworks (Rainforth et al., 2024; Sürer et al., 2024). However, sequential design also poses practical challenges, as repeated posterior updating and redesign must be performed throughout the experimental campaign, while future experiments may be affected by changes in environmental conditions, feasibility constraints, or timing (Huan et al., 2024).

Online design

Online experimental design can be viewed as a within-experiment adaptive strategy, in which the experimental policy is updated during the execution of an experiment by dividing the experimental horizon into several time segments or sub-experiments (Galvanin et al., 2009). Information obtained from earlier measurements is used progressively to update parameter estimates, which are then used as prior information for the design of subsequent sub-experiments. This concept was initially proposed for linear systems (Gerencser and Hjalmarsson, 2005; Mehra, 1974) and later extended to nonlinear systems (Stigter et al., 2006). For nonlinear models, additional challenges such as ill-conditioning must be addressed. Several improvements have been proposed, including disturbance estimation (Galvanin et al., 2012), parameter subset selection to ensure well-conditioned optimisation problems

(Barz et al., 2013), and sliding-window experimental redesign for parallel experiments (Cruz Bournazou et al., 2017). Related online redesign approaches have also exploited currently available information directly during the experiment (De-Luca et al., 2016), while dual-control and feedback formulations have incorporated information acquisition into control or measurement-time optimisation (Heirung et al., 2015; Jost et al., 2017). More recently, Friso and Galvanin (2024) proposed a FIM-driven online sequential design strategy to improve computational efficiency, while Mikesell et al. (2025) applied reinforcement learning agents to dynamically generate input signals that maximise parameter identifiability during online experiments.

Fully Bayesian design

Bayesian experimental design adopts a decision-theoretic framework in which the design variables are selected to maximise an expected utility function (Overstall, 2022). In contrast to pseudo-Bayesian design, which averages a classical design criterion over the prior parameter distribution, fully Bayesian design evaluates the expected utility of a design while explicitly accounting for posterior updating induced by future observations. Common utility functions include the expected information gain (EIG) (Lindley, 1956) and the negative squared error loss (NSEL) (Chaloner and Verdinelli, 1995; Overstall, 2022). Fully Bayesian experimental design has also been developed for nonlinear dynamic and ODE-based models, including applications in biological systems (Overstall et al., 2020) and chance-constrained formulations for nonlinear dynamic systems (Paulson et al., 2019).

A major challenge of Bayesian experimental design lies in its computational cost. Since EIG and NSEL often lack closed-form expressions, approximation methods are typically required. For example, Walker (2016) proposed a Fisher information gain approximation, which was subsequently applied in Bayesian OED by Overstall (2022). Nested Monte Carlo methods have also been used to approximate EIG (Strutz and Curtis, 2024). To address the high computational cost associated with large-scale models governed by partial differential equations (PDE)s, Wu et al. (2023) proposed a scalable computational framework that

exploits low-rank Hessian structures, dominant data subspaces, and Laplace approximations of the posterior distribution.

Integrating machine learning techniques

Recent studies have also explored integrating machine learning techniques into RED. For example, Treloar et al. (2022) showed that reinforcement learning agents trained over a parameter distribution can learn input strategies that are robust to parametric uncertainty. However, the study considered only a uniform parameter distribution and a D-optimal design objective. Extending such approaches to more general uncertainty distributions and alternative design criteria remains an open research direction.

To summarise, RED methodologies can be broadly classified into three categories. First, classical local design criteria can be robustified under parametric uncertainty through worst-case, expectation-based, or risk-aware formulations, including maximin, pseudo-Bayesian, and CVaR-based approaches. Second, alternative information or sensitivity measures, such as curvature-based and global-sensitivity-based criteria, have been proposed to address limitations of first-order local approximations in nonlinear systems. Third, adaptive design strategies, including sequential and online approaches, seek to reduce uncertainty progressively by updating experimental designs as new data become available. Despite these developments, most RED methods primarily address parametric uncertainty and often require strong assumptions about uncertainty structures or significant computational effort. These limitations motivate further research on robust experimental design methods capable of addressing practical uncertainties and improving computational efficiency.

2.3.2 Applications

RED methods have been increasingly applied in complex systems where nonlinearity and parametric uncertainty limit the effectiveness of nominal or locally optimal design strategies.

In engineering applications, particularly cyber-physical testing of marine and offshore structures, (Abbiati and Sauder, 2021) applied Bayesian experimental design to optimise

control variables for calibrating hydrodynamic loading models based on quadratic transfer functions. This approach demonstrated potential for reducing experimental costs while improving model calibration quality. In a related cyber-physical setting, (Stamenov et al., 2024) proposed a computationally efficient Fisher-information-based design framework with an expectation-based (pseudo-Bayesian) treatment of parameter uncertainty to identify low-frequency hydrodynamic loads on floating structures.

In the biological and biomedical domain, where systems exhibit significant nonlinear dynamics and parametric uncertainty, RED methods have also been explored. (Treloar et al., 2022) developed reinforcement learning-based experimental design strategies for biological systems, in which agents are trained across the full parameter space. The resulting input policies exhibited robustness when applied to simulated biological systems such as bacterial growth parameter inference. In biochemical networks, (Isenberg et al., 2024) employed Bayesian optimal experimental design on large-scale biochemical pathway models to improve prediction accuracy of therapeutic performance metrics. In systems and synthetic biology, adaptive and model-based experimental-design strategies have also been used to improve robustness to parameter uncertainty. For example, Balsa-Canto et al. (2010) developed an iterative identification framework combining identifiability analysis, parameter estimation and OED for biochemical networks. Later studies demonstrated online optimal input design and optimal model discrimination in synthetic biological systems (Bandiera et al., 2020, 2018). These studies illustrate how adaptive experimental design can progressively improve model identification by using new experimental information to update subsequent design decisions.

Similar RED applications have been reported in chemical process modelling and environmental systems. Robust design formulations have been used for model calibration under model discrepancy, robust optimisation, conceptual model discrimination, and groundwater flow modelling (Krishna et al., 2022; Pham and Tsai, 2023; Ushijima et al., 2021; Wang et al., 2022).

These applications demonstrate that RED can enhance experimental efficiency and parameter estimation reliability across diverse domains. However, most implementations remain problem-specific, and broader adoption in real-time or high-dimensional industrial settings remains challenging in practice.

2.3.3 Challenges

Despite the increasing adoption of RED, several challenges remain:

- **Assumptions on uncertainty.** Many RED methods rely on assumptions regarding the uncertainty space. For example, maximin design requires predefined uncertainty bounds, while Bayesian design requires prior parameter distributions. In practice, such prior knowledge is often limited or unavailable, and inaccurate assumptions can lead to biased or suboptimal design results.
- **Robustness evaluation and verification.** There is currently a lack of systematic metrics and standardised procedures for objectively evaluating and comparing the robustness of experimental designs obtained using different RED methods.
- **Computational complexity.** RED problems, such as maximin bilevel optimisation and high-dimensional integration in Bayesian design, are typically significantly more computationally demanding than classical OED problems. This computational burden limits their applicability to large-scale or highly complex models.
- **Trade-offs between robustness and estimation accuracy.** Different RED approaches emphasise different performance criteria. For example, maximin designs may become overly conservative, while pseudo-Bayesian designs may perform poorly in worst-case scenarios. Achieving an appropriate balance between robustness and estimation performance therefore remains an important challenge.

2.4 Decision Variables in MBDoE

Decision variables in experimental design correspond to controllable experimental settings that can be adjusted to improve the information content of collected data. The specific choice of design variables depends on the system under study. In model-based experimental design, controllable settings are typically divided into two main categories: input-related variables, e.g., dynamic stimuli and initial states, and measurement-related variables, e.g., sampling time and measurement set selection.

Dynamic input design refers to designing time-varying input signals for dynamic systems such as chemical processes, mechanical systems, and biological systems (Strouwen et al., 2022). Instead of using static or fixed inputs, the waveform, amplitude, spectrum, and duration of the input signal are optimised to maximise experimental informativeness. For example, Morelli (1993) proposed a dynamic programming approach for input design in which the input signal was restricted to square-wave profiles. Jauberthie et al. (2006) later proposed a two-step optimisation strategy for dynamic input design: an optimal square-wave signal was first determined by maximising the A-optimality criterion of the FIM, and the signal was then refined by smoothing the amplitude and switching time in a second optimisation step.

A well-designed dynamic input signal can excite system dynamics more effectively than simple step or pulse inputs, thereby generating richer information within the same experimental duration. However, dynamic input design is inherently an infinite-dimensional problem because the input signal varies continuously over time. In practice, discretisation methods such as piecewise constant approximation are commonly used to represent the input profile (Lei et al., 2023; Menolascina et al., 2009; Strouwen et al., 2022). Even after discretisation, the number of optimisation variables can remain very large, leading to substantial computational complexity, particularly for high-order dynamic systems. In (Mikesell et al., 2025), reinforcement learning was used to determine the optimal input profile in real time by maximising the FIM at each time step. Nevertheless, complex input signals

may impose demanding requirements on actuators and may be difficult to realise accurately in practical experiments (Hjalmarsson, 2005).

Initial state design Another form of input design is the optimisation of initial states of dynamic systems. In many dynamic systems, initial conditions (e.g., reactant concentrations, controller states, or preparatory states before neural stimulation) can be manipulated through operational settings. Designing the initial state therefore serves as a natural extension of experimental design for dynamic systems (Pronzato, 2008; Skanda and Lebiedz, 2010).

Measurement set selection. Modern complex systems, such as chemical plants, biological networks, and environmental monitoring systems, often contain dozens or even hundreds of potential measurable variables. Many of these variables may exhibit high correlation or redundancy. Due to experimental resource constraints, it is often impractical to measure all available variables for modelling purposes (Yu, 2018). Measurement set selection aims to identify the most informative subset of measurable variables. For example, Brown et al. (2008) applied RED methods to select the measurement set for an I κ B–NF- κ B signalling pathway network, while Jia and Yue (2012) performed measurement selection for a signal transduction pathway model to design informative experiments for parameter estimation.

Sampling time design. Sampling time design determines when system outputs should be measured in order to maximise the information obtained from the experiment. Sampling-time optimisation has been applied extensively to nonlinear biochemical and systems-biology models, where measurements must be placed in dynamically informative regions of the trajectory (Balsa-Canto et al., 2008, 2010; Kutalik et al., 2004). It forms a bridge between continuous-time system dynamics and the discrete-time datasets used for parameter estimation. By determining when measurements are taken, sampling time design directly influences the information density of experimental data. Typically, sampling time design either determines the optimal sampling period for evenly spaced measurements (Fox and Munsky, 2019) or selects optimal sampling time points within a predefined measurement horizon.

Design with multiple experimental variables. In many practical applications, multiple experimental settings may be optimised simultaneously. For example, Friso and Galvanin

(2024) considered multiple design variables jointly within an online experimental design framework, including inputs and initial conditions. In (Pankajakshan et al., 2023), initial conditions and dynamic inputs were optimised simultaneously. Deussen and Galvanin (2022) considered temperature, experiment duration, and initial concentrations as design variables for improving parameter estimation accuracy. Similarly, the design vector in (Waldron et al., 2020) includes initial states, dynamic inputs, and experiment duration. In these studies, the design variables are typically simple signals, such as constant inputs, step signals, or ramp signals.

Other works have explored different combinations of experimental variables. For instance, Sangoi et al. (2024) investigated OED for several combinations of variables, including sampling time and temperature, initial conditions and temperature, and joint optimisation of all variables. In (Luna and Martínez, 2018), the design vector consisted of the feed profile and the sampling schedule. However, uncertainty was not explicitly considered in these studies. In addition, multi-variable design problems are typically more computationally demanding because of the increased dimensionality of the design space and the difficulty of evaluating and optimising design criteria in nonlinear settings (Huan et al., 2024).

Other decision variables. Some studies have explored experimental design by modifying system parameters. For example, Stamenov et al. (2024) utilised cyber–physical testing to optimise mooring stiffness and damping parameters of a hydrodynamic system in order to maximise the information gain for parameter identification. This approach differs from input design, because modifying stiffness and damping parameters alters the intrinsic system dynamics, whereas input design changes only the excitation applied to the system. This type of design treats adjustable physical parameters within a predefined model as decision variables to improve experimental informativeness. This approach effectively shifts experimental design from passive observation toward active intervention. However, it is only applicable to specific systems with adjustable physical parameters and typically requires real-time computational models, such as virtual mooring systems in cyber–physical testing environments.

Among the above design variables, sampling time design is the primary focus of this thesis because it can improve parameter estimation without altering system operation or introducing additional external stimuli.

2.5 Numerical Algorithms for MBDoE

Numerical algorithms for model-based experimental design have evolved from classical approaches developed for linear models to modern optimisation techniques capable of handling nonlinear dynamic systems and robust design formulations. In this section, a brief overview of numerical algorithms used to solve optimal and robust experimental design problems is provided.

2.5.1 Classical methods for nearly linear systems

The Fedorov exchange method (Fedorov, 1972) selects design points from a discrete candidate set and performs a greedy search to identify the most informative experimental points from a large number of possible combinations. This approach was later extended to continuous design spaces as the Fedorov–Wynn method (Atkinson, 2007; Fedorov, 1972; Wynn, 1970), which provides theoretical convergence guarantees. The Fedorov–Wynn method discretises the continuous design space using supporting points with associated weights and iteratively updates these supporting points to obtain the optimal design. Alternatively, the multiplicative algorithm (Silvey et al., 1978) updates the weights of the supporting points directly. These two approaches have been widely applied due to their simplicity, although their performance may degrade for high-dimensional problems and complex nonlinear systems (Esteban-Bravo et al., 2017). Many later methods (Harman and Pronzato, 2007; Torsney and Martín-Martín, 2009; Yang et al., 2013) are essentially extensions or modifications of the Fedorov–Wynn algorithm or the multiplicative algorithm. For example, Yu (2011) proposed an accelerated variant of the multiplicative algorithm known as the cocktail algorithm, while Schmid et al. (2024) provided convergence rate analysis and demonstrated sub-linear and

linear convergence behaviour. These classical algorithms are primarily used for small-scale problems involving linear or approximately linear models and typically operate on discrete candidate sets.

Although classical iterative algorithms such as the Fedorov exchange algorithm and the multiplicative algorithm have largely been surpassed by more powerful nonlinear programming approaches when addressing complex nonlinear systems, their core concepts, such as using variance functions to guide the search and updating designs in continuous measure spaces, continue to influence modern algorithm development. Moreover, in traditional statistical experimental design, these classical algorithms remain widely used due to their simplicity and reliability.

2.5.2 Modern methods for nonlinear systems

OED problems for dynamic systems are typically nonlinear, nonconvex, and high-dimensional. In addition, the evaluation of the FIM requires repeatedly solving the underlying system dynamics, e.g., ordinary differential equation (ODE)s or PDEs, and computing parametric sensitivities during the optimisation process. Consequently, experimental design problems can be computationally demanding. Numerical algorithms for solving MBDoE problems can generally be divided into two categories: gradient-based methods and derivative-free methods.

Gradient-based methods

One common approach is to formulate the OED problem as a nonlinear programming (NLP) problem and solve it using gradient-based optimisation algorithms such as interior-point methods (Lu and Pong, 2013), active-set methods, or sequential quadratic programming (Bauer et al., 2000). The NLP framework has also been applied to RED problems. For example, pseudo-Bayesian design can be formulated as a classical OED problem when the

expected design criterion is approximated using sample-average approximation (Yu et al., 2018b).

The advantage of the NLP framework is that it naturally accommodates constraints and often exhibits super linear convergence. However, gradient-based methods generally converge only to local optima and are sensitive to the initial starting point (Banga and Balsa-Canto, 2008). Multi-start optimisation is therefore commonly used to improve the likelihood of finding a near-global solution (Wang and Yue, 2021). Nevertheless, global optimality cannot be guaranteed and the obtained solution is often considered the best solution found within the explored region.

Hybrid optimisation strategies have also been proposed to address this issue. For example, global optimisation algorithms such as particle swarm optimisation (PSO) or genetic algorithms (GA) can first identify promising regions of the design space, after which local NLP solvers refine the solution (Egea et al., 2009). In some cases, OED problems can be relaxed into convex optimisation problems and solved using well-established techniques (Boyd, 2004). Due to structural properties of the FIM, certain OED formulations can be relaxed into semi-definite programming (SDP) problems (Telen et al., 2014; Yu et al., 2015, 2018a). Other approaches to addressing nonconvexity include the two-phase method proposed by Vanaret et al. (2021), in which pattern-based strategies such as factorial design were used to generate informative initial solutions for subsequent nonlinear optimisation.

An important aspect of gradient-based optimisation is the calculation of derivatives of the design criterion, which is typically a scalar function of the FIM. However, some criteria are not continuously differentiable, for example, E-optimality and modified E-optimality. Reformulations based on the Sylvester criterion have been proposed to address this difficulty (Telen et al., 2015). Despite these developments, gradient-based methods remain challenging to apply to systems with discontinuous or non-smooth dynamics.

Computational complexity is another important issue. For large-scale problems involving PDE-constrained models or long time horizons, discretisation can generate extremely high-dimensional optimisation problems, leading to the so-called curse of dimensionality

(Alexanderian et al., 2016). Additional issues, such as singularity of the FIM, have also been mentioned in OED development (Shahmohammadi and McAuley, 2019^{a,b}).

Derivative-free methods

Derivative-free optimisation methods provide an alternative approach when gradient information is unavailable or expensive to compute. These methods rely solely on comparisons of objective function values and can generally be divided into two categories.

Metaheuristic algorithms. Metaheuristic optimisation algorithms incorporate stochastic components to avoid local optima, although they cannot guarantee global optimality (García-Ródenas et al., 2020). Many nature-inspired metaheuristic algorithms have been applied to OED problems, including genetic algorithms (Latif and Brunner, 2016; Menolascina et al., 2009) and particle swarm optimisation (Qiu et al., 2014; Shi et al., 2019; Yu et al., 2018^a). These approaches explore the design space globally using population-based search strategies. Reviews of metaheuristic approaches for OED can be found in Chen et al. (2022); García-Ródenas et al. (2020).

Classical derivative-free methods. Powell's conjugate-direction method is a classical derivative-free optimisation method originally developed for continuous optimisation (Powell, 1964). Extensions of this approach, including Powell's quadratically convergent method, were subsequently developed (Powell, 1970, 1977). The underlying Powell search strategy has also been adapted to discrete sampling-time optimisation. For example, Kutalik et al. (2004) applied a Powell-based search strategy to sampling-time selection, and related implementations have subsequently been used in chemical and biological experimental-design studies (Franceschini and Macchietto, 2008; Yu et al., 2015).

Surrogate-based methods. Surrogate-based optimisation methods construct computationally inexpensive surrogate models to approximate expensive system simulations and perform optimisation using a surrogate model. Common surrogate models used in OED

include Gaussian process models (Petsagkourakis and Galvanin, 2021) and polynomial chaos expansions (Nimmegeers et al., 2020).

2.5.3 Numerical methods for robust experimental design

The numerical solution of RED problems is typically more challenging than classical OED. Several key difficulties arise:

- **Maximin optimisation.** Maximin experimental design problems are often formulated as bilevel optimisation problems. A common strategy is to convert them into single-level optimisation problems. For example, iterative optimisation algorithms progressively add worst-case parameter scenarios to the constraint set, converting an infinite-dimensional problem into a finite-dimensional one (Asprey and Macchietto, 2002; Rojas et al., 2007). Although reliable, this approach can be computationally expensive because each iteration requires solving a potentially nonconvex optimisation problem.
- **Worst-case search strategies.** Direct search strategies first compute an optimal design under nominal parameter values, then identify the worst-case parameter scenario for that design, and finally redesign the experiment accordingly (Asprey and Macchietto, 2002; Wang and Yue, 2020). This approach is computationally faster but does not guarantee convergence.
- **Robust convex reformulations.** In some cases, parameter uncertainty can be propagated to the FIM using first-order Taylor approximations, allowing maximin E-optimal design problems to be reformulated as robust SDP problems under norm-bounded uncertainty (He et al., 2010; Telen et al., 2014). Although this formulation can yield globally optimal solutions, it is typically applicable only to small uncertainties and requires higher-order sensitivity information.
- **Expectation-based and fully Bayesian design computation.** A central challenge in Bayesian experimental design is the evaluation of multidimensional expectations.

Monte Carlo sampling is the most general method for approximating these expectations, allowing the resulting optimisation problem to be solved similarly to classical OED (Huan et al., 2024). For low-dimensional parameter spaces, numerical integration methods such as Gaussian quadrature may also be used, although their computational cost grows rapidly with dimensionality. Alternatively, lower-cost approximations based on the mean FIM have been considered (Jung and Lee, 2021). However, applying the scalarisation function to the expected FIM is generally not equivalent to taking the expectation of the scalarised criterion, and may therefore underestimate the effect of parameter uncertainty.

Numerous numerical algorithms have been developed to address experimental design problems. Classical algorithms remain effective for linear or nearly linear models, while modern nonlinear programming methods allow the treatment of complex nonlinear dynamic systems with constraints. Derivative-free and metaheuristic optimisation techniques offer additional flexibility when gradient information is unavailable or computationally expensive to obtain. Nevertheless, RED problems remain particularly challenging due to their high computational cost and the presence of parameter uncertainty. These challenges highlight the need for efficient and robust experimental design strategies, especially for sampling time design in nonlinear dynamic systems, which forms the main focus of this thesis.

2.6 Summary

This chapter has reviewed the current literature on model-based OED and RED for parameter estimation. The chapter began with a brief historical overview, which established the rationale for model-based experimental design by highlighting its advantages and its central role in modern statistical experimentation. The review then focused on design criteria used in MBDoE. It showed that FIM-based criteria remain the dominant approach, with most recent developments aimed at adapting these criteria to address specific system characteristics, numerical limitations, practical constraints, and multi-objective design requirements.

A major limitation frequently identified in the literature is that classical OED methods are highly sensitive to uncertainties. Consequently, this chapter reviewed the evolution of RED methods. Existing RED approaches typically extend the local FIM-based framework by introducing robust criteria, such as maximin and expectation-based formulations, higher-order sensitivity approximations, or global sensitivity measures. Alternatively, robustness can be improved through adaptive experimental strategies, including sequential and online experimental designs.

This chapter also reviewed the main decision variables used in experimental design, which correspond to controllable experimental settings. These include dynamic input signals, initial conditions, measurement set selection, and sampling time design. In addition, the numerical algorithms developed to solve OED and RED problems were discussed, covering both classical algorithms developed for linear systems and modern optimisation techniques designed for nonlinear and computationally demanding problems.

Despite the substantial progress achieved in this field, several important challenges remain. In particular, many RED methods rely on strong assumptions regarding parameter uncertainty, suffer from high computational cost, and lack standardised metrics for evaluating robustness. Moreover, a fundamental trade-off often exists between robustness and estimation performance. These challenges, especially the need to address large parametric uncertainties without relying on precise prior knowledge, and the need to develop reliable design criteria under input uncertainty, form the primary motivation for the research presented in this thesis. The subsequent chapters therefore focus on developing robust sampling time design strategies that address these challenges. To support the development of the proposed RED framework, the theoretical foundations and mathematical preliminaries are introduced in the next chapter.

Chapter 3

Optimal Experimental Design Fundamentals and Preliminaries

Mathematical modelling plays a crucial role in almost all areas of science and engineering. By constructing a reliable model for a complex dynamic system, researchers can better understand system behaviour and make predictions beyond the reach of practical experiments. Furthermore, a model is essential for the simulation, control, and optimisation of dynamic systems (Friso and Galvanin, 2024). Optimal experimental design (OED), particularly model-based OED, is an efficient technique in data-based modelling. Carefully designed experiments can significantly improve both the efficiency and accuracy of developing a credible model.

This chapter first introduces the data-based modelling procedure, explaining how a mathematical model can be established systematically and highlighting the pivotal role of OED in this process. It then presents the most relevant techniques used in OED, including identifiability analysis, sensitivity analysis (SA), and parameter estimation (PE). Identifiability analysis distinguishes structural non-identifiability, which cannot be resolved simply by collecting more data under the same model and observation structure, from practical non-identifiability, which may be improved by collecting additional or more informative experimental data. Sensitivity analysis reduces the dimensionality of the OED problem by identifying the most

influential parameters, while PE provides the basis for formulating the objective function in OED. These concepts are introduced as essential preliminaries before developing OED methods for different design objectives. Finally, the classical formulation of PE problems is presented, which provides the theoretical basis for the core contributions of this thesis. In particular, the mathematical formulation of optimal sampling time design is introduced, which will support the development of robust experimental design (RED) methods in the subsequent chapters.

3.1 Data-Based Modelling Procedure

Establishing a mathematical model from experimental data requires a systematic procedure. Such iterative model-development procedures commonly combine identifiability analysis, parameter estimation, sensitivity analysis, and optimal experimental design (Balsa-Canto et al., 2010; Franceschini and Macchietto, 2008). The general steps of this modelling process are summarised below.

Step 0: Initial setting. Based on an initial understanding of the underlying physical laws, multiple mathematical models can be proposed at the early stage. Initial parameter values may be obtained from previous studies or the literature, or estimated from an initial experimental dataset when available.

Step 1: Identifiability analysis. Identifiability analysis aims to ensure that the model parameters can be estimated from the available data. Structural identifiability analysis is first performed on the initially proposed models to determine whether unidentifiable models should be modified or eliminated (Villaverde, 2019). Subsequently, practical identifiability analysis is carried out for the structurally identifiable models. If a model is found to be practically non-identifiable, it indicates that the available data may be insufficient, and additional experiments may be required before performing parameter estimation. After structurally non-identifiable models have been modified or excluded, the remaining structurally identifiable

models are retained as candidate models for subsequent analysis. Detailed discussions on identifiability analysis are provided in Section 3.4.

Step 2: Preliminary parameter estimation (PE). This step provides initial estimates of model parameters before proceeding to experimental design and further estimation. Some parameter values can be obtained directly from previous experimental studies or from the literature, while others may be estimated from preliminary experimental data. Initial experiments are therefore conducted to collect input–output data, and the unknown model parameters can be estimated using PE methods. Several commonly used PE methods are introduced in Section 3.5.

Step 3: Parametric sensitivity analysis (SA). Sensitivity analysis is performed to identify the most influential parameters that should be included in the parameter estimation problem. Parameters with relatively low sensitivity are typically fixed at their nominal values during PE. The sensitivity of each parameter is evaluated according to its influence on the selected model outputs. This parameter screening process helps reduce the dimensionality of the problem in both model discrimination and parameter estimation. Details of the sensitivity analysis methods are presented in Section 3.3. Following sensitivity analysis, the Fisher Information Matrix (FIM) can be constructed from the local sensitivity matrices, providing a classical measure of the information content of the data. The FIM is widely used in identifiability analysis and optimal experimental design.

Step 4: Optimal experimental design (OED). Before conducting experiments, OED is used to determine experimental conditions that maximise the information content of the collected data for the intended modelling objective. In data-based modelling, OED is mainly applied for two purposes. The first is model discrimination, where informative experiments are designed to enhance the differences between competing candidate models. The second is parameter estimation, where informative experiments are designed to reduce the uncertainty of the estimated parameters. The latter is the main focus of this thesis. The mathematical formulation of several OED problems is presented in Section 3.7.

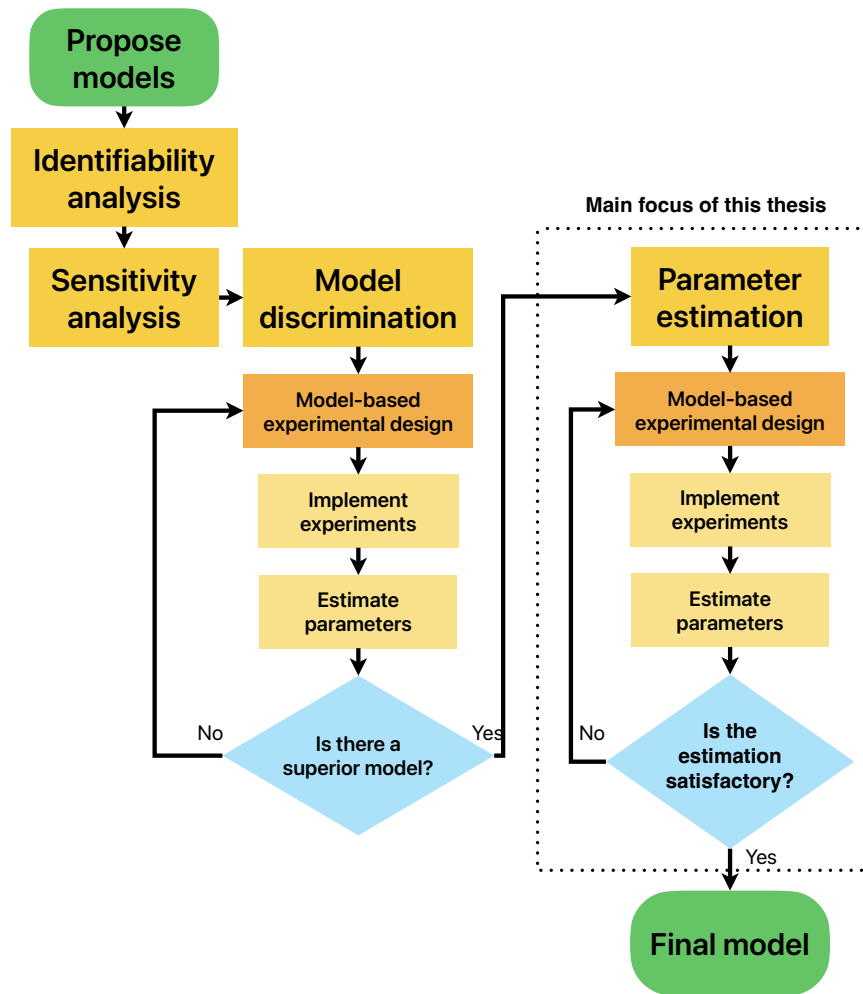


Fig. 3.1 Overall workflow of data-based model development, with the main focus of this thesis indicated by the dashed box.

Step 5: Parameter estimation. Model parameters are estimated using the input–output data collected from the optimally designed experiments. If the resulting parameter estimates are not sufficiently satisfactory, further experimental design and data collection may be required.

The modelling procedure is generally iterative. If no candidate model can be satisfactorily discriminated, additional model-discrimination experiments may be required. Similarly, if the parameter estimates remain insufficiently precise, further experimental design and data collection can be performed.

The overall model-building procedure is illustrated in Fig. 3.1. The workflow highlights the roles of identifiability analysis, sensitivity analysis, model discrimination, parameter estimation, and model-based experimental design. The dashed box indicates the main focus of this thesis, namely model-based experimental design for improving parameter estimation under uncertainty.

3.2 Dynamic System Models

State differential equation models are commonly used mathematical representations of dynamic systems. The states are time-dependent variables that characterise the evolution of system dynamics. For many scientific and engineering systems, differential equation models can be derived from fundamental physical laws, such as Newton's second law of motion, the law of radioactive decay, and the law of mass action in chemical systems. Although mathematical models cannot capture every detail of real-world systems, they provide valuable insight into system behaviour and enable prediction and analysis of system dynamics.

3.2.1 State dynamics

Consider a general dynamic model in the form of ordinary differential equation (ODE):

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{u}(t), \mathbf{x}(t); \boldsymbol{\theta}), \mathbf{x}(0) = \mathbf{x}_0, \quad (3.1)$$

$$\mathbf{y}(t) = \mathbf{h}(\mathbf{x}(t)) + \boldsymbol{\xi}(t), \quad (3.2)$$

where $\mathbf{x} = [x_1, x_2, \dots, x_{N_x}]^\top \in \mathbb{R}^{N_x}$ is the vector of state variables, $\mathbf{u} = [u_1, \dots, u_{N_u}]^\top \in \mathbb{R}^{N_u}$ is the input vector, and $\boldsymbol{\theta} = [\theta_1, \dots, \theta_{N_p}]^\top \in \mathbb{R}^{N_p}$ is the parameter vector. The vector $\mathbf{x}_0 \in \mathbb{R}^{N_x}$ denotes the initial condition of the state variables.

The function $\mathbf{f}(\cdot)$ represents the set of dynamic functions governing the system behaviour and is assumed to be continuous and differentiable with respect to the states and parameters. The linearity of the system depends on the form of $\mathbf{f}(\cdot)$; a system is considered linear if $\mathbf{f}(\cdot)$

is linear with respect to the state variables and their derivatives, and nonlinear otherwise. In this work, time-invariant nonlinear dynamic models are considered, meaning that the parameters θ remain constant over time. Although analytical solutions to (3.1) are rarely available, numerical solutions can be obtained efficiently using various simulation tools.

The function $\mathbf{h}(\cdot)$ represents the observation function that maps the system states to measurable outputs. In many cases, $\mathbf{h}(\cdot)$ acts as a selection matrix that extracts the measurable state variables to form the model output $\mathbf{y} = [y_1, y_2, \dots, y_{N_y}]^T \in \mathbb{R}^{N_y}$. The vector $\boldsymbol{\xi}(t) = [\xi_1, \dots, \xi_{N_y}]^T$ represents measurement errors.

3.2.2 Input variables

In the dynamic model described by (3.1), the input variables $\mathbf{u}$ can be manipulated to influence the system dynamics. Two types of inputs are commonly considered:

- **External stimuli:** These inputs may be constant or time-dependent signals applied to the system.
- **Controllable initial states:** In some systems, the initial conditions of certain state variables can be manipulated and treated as experimental inputs. In this case, $\mathbf{u} = \tilde{\mathbf{x}}_0$, where $\tilde{\mathbf{x}}_0$ is a subset (or the full set) of $\mathbf{x}_0$.

In (3.1), the input variables are represented as continuous functions of time. However, in real-world experiments, input signals are typically recorded at discrete time points. Constructing a continuous input function from discrete measurements therefore requires careful treatment.

Linear interpolation of the measurement data has been widely used (Quach et al., 2007; Swameye et al., 2003) because of its simplicity. More accurate approaches, such as cubic interpolation splines or cubic smoothing splines, have also been applied (Maiwald and Timmer, 2008; Raue et al., 2009). These methods capture more detailed input dynamics but increase modelling complexity. Schelker et al. (2012) observed that when input functions are estimated separately before parameter estimation, deviations between the interpolated input

and the true input dynamics can negatively affect PE. They therefore proposed estimating the model parameters and input signals simultaneously using a modified objective function. In batch processes, adjustable initial state values are often used as control inputs.

In this thesis, input experimental design focuses on selecting appropriate initial state values to support efficient PE.

3.2.3 Observations (outputs) and measurement errors

System observations refer to measurable quantities that are directly or indirectly related to the state variables. The observation, also referred to as the system output, is described by (3.2). The observation function $\mathbf{h}(\cdot)$ can be a selection matrix that extracts measurable state variables. In the following derivations, when $\mathbf{h}(\cdot)$ is a simple selection operation, it is omitted for notational convenience. In some cases, $\mathbf{h}(\cdot)$ may also consist of nonlinear functions of the state variables due to experimental limitations, for example when scaling or transformation is applied to measurement signals (Loos et al., 2018).

The additive term $\xi(t)$ in (3.2) represents measurement errors. Measurement noise is often assumed to follow an independent Gaussian distribution characterised by the probability density function (pdf)

$$\xi \sim N(0, \Sigma),$$

where Σ is a diagonal covariance matrix whose i -th diagonal element is σ_i^2 , σ_i^2 represents the variance of ξ_i and may either be fixed based on prior analysis of experimental data or estimated together with the model parameters. Estimating σ_i^2 jointly with the parameters allows reasonable variance estimates even when repeated measurements are limited, although this increases the dimensionality of the PE problem (Raue et al., 2013).

The Gaussian noise assumption may not be suitable for some applications. For example, Maier et al. (2016) considered heavy-tailed noise distributions when performing PE on data corrupted by outliers in order to improve the robustness of parameter estimates.

3.2.4 Parameters

The parameters θ in biochemical system models mainly represent dynamic parameters that govern the system dynamics, such as reaction rates. In biological and biochemical systems, prior knowledge of parameter values is often limited. As a result, parameter bounds in benchmark models frequently span several orders of magnitude. Accurate parameter estimation is therefore a crucial problem in these systems.

3.3 Parametric Sensitivity Analysis

The purpose of SA is to investigate how variations in model factors (parameters in this research) influence the model outputs (Pianosi et al., 2016). Parametric SA plays a crucial role in the modelling procedure. In preliminary modelling studies, SA can be applied to detect technical errors in the model, identify critical regions in the input space, and establish priorities for PE (Saltelli, 2008).

For a specified modelling objective and experimental setting, sensitivity analysis can be used to identify parameters whose variations have relatively little influence on the selected model outputs. Such parameters may be fixed at nominal or independently determined values to reduce the dimensionality of the parameter-estimation problem. However, this simplification should be used with caution, since low sensitivity under a particular setting does not imply that a parameter is physically unimportant, and misspecified fixed values may affect model predictions or bias the estimates of the remaining parameters. In model-based experimental design, parametric sensitivities are used to construct the FIM, which forms the basis of the optimisation design.

SA methods can be classified into different types depending on the objectives of the analysis. For screening purposes, which aim to identify parameters with negligible influence on model outputs, SA methods can be categorised into quantitative and qualitative approaches.

To investigate the effects of individual or combined factors on output variability, the methods can also be divided into One-At-A-Time and All-At-A-Time approaches.

For parameter ranking, which is the focus of experimental design in this thesis, SA methods are typically classified into local sensitivity analysis (LSA) and global sensitivity analysis (GSA). LSA examines the changes in model response caused by varying parameters individually around their nominal values. In contrast, GSA evaluates model responses across the entire parameter space while also considering parameter interactions and correlations (Gan et al., 2014).

3.3.1 Local sensitivity analysis

For a continuous-time system, a common approach to LSA is the derivative-based method, which evaluates parametric sensitivity by computing the first-order partial derivatives of the system output with respect to model parameters at their nominal values. Parameters with larger derivative magnitudes are considered more sensitive than those with smaller values (Nodet and Vidard, 2017).

Let $\mathbf{S} \in \mathbb{R}^{N_x \times N_p}$ denote the parametric sensitivity matrix for model (3.1):

$$\mathbf{S} = \frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}} = \begin{pmatrix} \frac{\partial x_1}{\partial \theta_1} & \cdots & \frac{\partial x_1}{\partial \theta_{N_p}} \\ \vdots & \ddots & \vdots \\ \frac{\partial x_{N_x}}{\partial \theta_1} & \cdots & \frac{\partial x_{N_x}}{\partial \theta_{N_p}} \end{pmatrix}. \quad (3.3)$$

Denoting $s_{i,j}$ as the (i, j) -th element of $\mathbf{S}$, the local sensitivity of the i -th state x_i with respect to the j -th parameter θ_j is defined as

$$s_{i,j} = \frac{\partial x_i}{\partial \theta_j} = \lim_{\Delta \theta_j \rightarrow 0} \frac{x_i(\theta_j + \Delta \theta_j) - x_i(\theta_j)}{\Delta \theta_j}, \quad (3.4)$$

where $\Delta \theta_j$ represents a small perturbation around the nominal parameter value θ_j .

Two commonly used methods for computing the sensitivity matrix are described below.

Finite Difference Method

For problems with relatively small dimensionality, the finite difference method can be used to approximate the first-order partial derivatives:

$$s_{i,j} \approx \frac{x_i(\theta_j + \Delta\theta_j) - x_i(\theta_j)}{\Delta\theta_j}. \quad (3.5)$$

A smaller $\Delta\theta_j$ gives a more accurate approximation. In practice, $\Delta\theta_j$ is chosen such that further reductions or increases in its magnitude do not significantly change the computed sensitivities. The finite difference method is straightforward to implement but becomes computationally expensive for high-dimensional systems and may suffer from numerical rounding errors.

Direct Differential Method (DDM)

The direct differential method (DDM) computes sensitivities by solving differential equations for the sensitivity coefficients (Dickinson and Gelinas, 1976; Rabitz et al., 1983). The dynamics of the sensitivity equations is written as

$$\dot{\mathbf{S}} = \frac{d\mathbf{S}}{dt} = \frac{d}{dt} \frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}} = \frac{\partial \mathbf{f}}{\partial \mathbf{x}} \frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}} + \frac{\partial \mathbf{f}}{\partial \boldsymbol{\theta}} = \mathbf{J}\mathbf{S} + \mathbf{F}, \quad \mathbf{S}(0) = \mathbf{S}_0, \quad (3.6)$$

where $\mathbf{J} = \frac{\partial \mathbf{f}}{\partial \mathbf{x}} \in \mathbb{R}^{N_x \times N_x}$ is the Jacobian matrix of the system, and $\mathbf{F} = \frac{\partial \mathbf{f}}{\partial \boldsymbol{\theta}} \in \mathbb{R}^{N_x \times N_p}$ is the parametric Jacobian matrix. The initial condition $\mathbf{S}_0$ is usually zero unless the sensitivity depends on the initial states. By solving the sensitivity equations (3.6) together with the system dynamics (3.1), the time profile of sensitivities $\mathbf{S}(t)$ can be obtained simultaneously with the state trajectory $\mathbf{x}(t)$.

The advantage of DDM is that it avoids the need to select perturbation sizes $\Delta\theta_j$, and all entries of $\mathbf{S}$ are obtained simultaneously. However, for large-scale systems the computational cost increases because two sets of differential equations must be solved together (Zi, 2011).

Other approaches are also available for computing local sensitivities. For example, the adjoint method constructs a kernel function for the model and uses its adjoint system

to compute sensitivities. This method can be computationally more efficient than DDM when the number of parameters exceeds the number of states (Rabitz et al., 1983), although it may become difficult to apply to highly nonlinear models (Thuburn and Haine, 2001). Monte Carlo methods can also approximate parametric sensitivities through repeated model evaluations. These methods are simple to implement but must be used with care because they rely on several approximations (Nodet and Vidard, 2017).

In this thesis, the DDM is used for the numerical computation of sensitivities. Since model parameters and state variables may vary over wide ranges, sensitivity effects must be evaluated on a comparable scale. For this reason, the relative sensitivity is introduced (Yu, 2018; Zi, 2011):

$$\bar{s}_{i,j}(t) = \frac{\partial x_i(t)}{\partial \theta_j} \frac{\theta_j}{x_i(t)} = \frac{\partial \ln x_i(t)}{\partial \ln \theta_j}. \quad (3.7)$$

When applying this scaling, care must be taken if x_i becomes zero during numerical simulation. In such cases, a small positive constant can be added to avoid numerical instability.

For dynamic systems, sensitivities vary with time. Therefore, the overall sensitivity effect should consider the sensitivity coefficients over the entire observation horizon. Suppose the system is sampled at time points $\mathbf{t}_{sp} = [t_1, \dots, t_{N_{st}}]^\top$. The overall influence of parameter θ_j on state x_i can be quantified using the root-sum-square measure (Yu, 2018):

$$RS_{i,j} = \frac{1}{N_{st}} \sqrt{\sum_{l=1}^{N_{st}} \bar{s}_{i,j}^2(t_l)}. \quad (3.8)$$

3.3.2 Global sensitivity analysis

LSA examines the impact of small variations of parameters around their nominal values on model outputs. However, in many practical situations, reliable nominal parameter values are unavailable or subject to considerable uncertainty, which makes LSA less reliable. In such cases, GSA, which explores the entire parameter space and varies all parameters simultaneously, should be employed (Saltelli, 2008; Zi, 2011). Several representative methods for GSA calculations are briefed in the following.

Variance-Based Methods

Variance-based methods evaluate the importance of a parameter by estimating the expected reduction in the variance of the model output when that parameter is known with certainty (Borgonovo and Plischke, 2016). Based on the functional analysis of variance (ANOVA) decomposition, the contributions of different groups of parameters to the total variance of the model output can be represented separately. The sensitivity index of a parameter is defined as the fraction of output variance attributed to that parameter relative to the total variance.

Sobol's indices (Sobol', 1990) are widely used to quantify the variance contribution of parameters. Homma and Saltelli (1996) further introduced the total-effect index, which extends Sobol's method by including all interaction effects associated with a parameter. One common technique for estimating sensitivity indices is the Monte Carlo method. With modern computational resources, these indices can be evaluated numerically using Monte Carlo integration (Ghanem et al., 2017).

Another approach for estimating global sensitivity indices is the spectral method. The most commonly used spectral approach is the Fourier amplitude sensitivity test (Cukier et al., 1973, 1975; Schaibly and Shuler, 1973). In this method, the variance of the output is approximated and decomposed through Fourier analysis according to Parseval's theorem (Saltelli and Bolado, 1998).

Variance-based GSA is popular because it does not rely on linearity assumptions and accounts for all parameter interactions (Saltelli, 2008). However, these methods can be computationally demanding for large-scale systems, as they require a large number of model evaluations (Zi, 2011).

Derivative-Based Methods

Since variance-based approaches can be computationally expensive and sometimes impractical for high-dimensional models, derivative-based GSA methods provide an alternative with significantly lower computational cost (Kucherenko and Iooss, 2017).

One straightforward approach is the weighted average of local sensitivities (Bentele et al., 2004). In this method, multiple parameter samples are drawn from the parameter space to compute local sensitivities, and the global sensitivity is obtained by averaging these local measures. The Morris screening method (Morris, 1991) is another widely used technique for GSA. It is based on the concept of elementary effects, which approximate parametric derivatives using finite differences between sampled points generated through a predefined random sampling strategy.

Derivative-based global sensitivity measures can be viewed as a generalisation of the Morris method (Kucherenko et al., 2009), obtained by averaging local derivatives evaluated at randomly or quasi-randomly sampled points across the parameter space. These methods generally provide more accurate results than the Morris method because the derivatives are computed directly at multiple points within the uncertainty space rather than approximated using large perturbations.

Other approaches, such as regression-based sensitivity analysis, are also available for GSA calculation. A comprehensive review of GSA methods can be found in Borgonovo and Plischke (2016); Gan et al. (2014). Despite their usefulness for model analysis, GSA is not the primary tool used in the experimental design framework considered in this thesis, where local sensitivities are mainly employed for constructing the FIM.

3.4 Identifiability Analysis

Identifiability analysis examines whether model parameters can be uniquely determined from the available observations. It is an essential prerequisite for parameter estimation and experimental design in dynamic modelling. When a mathematical model is proposed for a dynamic system, estimating its parameters from observation data is usually required. However, identifiability analysis should be performed before parameter estimation, particularly in chemical and biological systems modelling where experimental limitations are common

(Villaverde, 2019). Non-identifiable parameters may lead to inaccurate parameter estimates with mechanistic interpretations, which in turn result in unreliable model predictions.

There are two main types of identifiability: structural identifiability and practical identifiability. Structural identifiability is a theoretical property of the model structure, whereas practical identifiability depends on the quality and quantity of experimental data. Structural non-identifiability can be addressed by modifying the model structure, while practical non-identifiability can often be improved by collecting additional or more informative data (Balsa-Canto et al., 2010; Chis et al., 2011b; Wieland et al., 2021). This section briefly introduces these two types of identifiability analysis, which form an important part of the preliminary analysis in dynamic systems modelling.

3.4.1 Structural identifiability

According to Walter and Pronzato (1997), a parameter θ_i is said to be globally identifiable if

$$\hat{\boldsymbol{\theta}} \in \boldsymbol{\Theta}, \mathbf{y}(\boldsymbol{\theta}) = \mathbf{y}(\hat{\boldsymbol{\theta}}) \implies \theta_i = \hat{\theta}_i. \quad (3.9)$$

Here $\hat{\boldsymbol{\theta}}$ stands for an alternative parameter vector of $\boldsymbol{\theta}$, $\boldsymbol{\Theta}$ is the PE domain. A parameter θ_i is locally identifiable if there exists a neighbourhood $\mathbf{v}(\boldsymbol{\theta}) \subset \boldsymbol{\Theta}$ of $\boldsymbol{\theta}$ such that

$$\hat{\boldsymbol{\theta}} \in \mathbf{v}(\boldsymbol{\theta}), \mathbf{y}(\boldsymbol{\theta}) = \mathbf{y}(\hat{\boldsymbol{\theta}}) \implies \theta_i = \hat{\theta}_i. \quad (3.10)$$

A model is (globally or locally) structurally identifiable if all parameters in the parameter vector $\boldsymbol{\theta}$ are (globally or locally) structurally identifiable. Otherwise, the model is structurally non-identifiable. A non-identifiable parameter θ_i means that variations in this parameter do not influence the model outputs because its effect may be compensated by changes in one or more other parameters.

Two main approaches are used to analyse structural identifiability: *a priori* and *a posteriori* methods. *A priori* analysis relies solely on the mathematical model structure and can

therefore be performed before conducting experiments. In contrast, *a posteriori* analysis utilises experimental data to detect non-identifiable parameters (Wieland et al., 2021). It should be noted that in some literature, *a priori* and *a posteriori* analyses are used as synonyms for structural and practical identifiability analysis, respectively (Anstett-Collin et al., 2020; Lam et al., 2022).

Various techniques have been developed for *a priori* structural identifiability analysis. For example, Lie group theory can be used to analyse non-identifiability caused by Lie symmetries in ODE models (Merkt et al., 2015). Other approaches include methods based on power series expansion. Reviews of these techniques can be found in Chis et al. (2011b); Villaverde (2019). Many of these methods are limited to relatively low-dimensional models because they involve symbolic computations that are computationally intensive.

In contrast, *a posteriori* analysis investigates identifiability from the perspective of fitting the model to experimental data. In theory, structural identifiability can be detected if infinite noise-free data are available. Based on this idea, Hengl et al. (2007) suggested performing numerous data fittings to analyse structural identifiability in low-dimensional models. In addition, the profile likelihood approach (Murphy and Van Der Vaart, 2000) has been successfully applied to detect non-identifiable parameters using experimental data. Bayesian Markov chain Monte Carlo sampling methods can also be used for this purpose, provided that sufficient prior information is available to ensure convergence of the Markov chains (Gupta et al., 2020; Raue et al., 2013).

With the rapid development of computational methods, structural identifiability analysis for nonlinear dynamic systems is no longer a major bottleneck. Several software toolboxes are available to perform such analyses, including DAISY (Bellu et al., 2007), GenSSI (Chis et al., 2011a), COMBOS (Meshkat et al., 2014), SIAN (Hong et al., 2019), and STRIKE-GOLDD (Díaz-Seoane et al., 2023; Villaverde et al., 2016). A recent review of structural identifiability analysis toolboxes is provided in Rey Barreiro and Villaverde (2023).

3.4.2 Practical identifiability

Structural identifiability implies that a model should theoretically be able to identify unknown parameters if infinite noise-free data were available (Wieland et al., 2021). However, practical experimental limitations often lead to non-identifiable parameters even when the model is structurally identifiable. Practical identifiability analysis therefore examines whether the uncertainty of estimated parameters, obtained from a given dataset or set of datasets, lies within acceptable bounds.

Practical non-identifiability is mainly caused by the following factors (Yu, 2018):

- The experimental data used for model fitting are sparse and noisy, resulting in limited information for PE.
- The system outputs under certain experimental conditions are insensitive to particular parameters.

Several approaches have been proposed for practical identifiability analysis, including sensitivity-based methods, Monte Carlo simulations, profile likelihood methods, and Bayesian methods. In this section, we focus on the sensitivity-based approach, which is closely related to experimental design.

Practical identifiability analysis often uses a matrix similar to the FIM, namely $\bar{\mathbf{S}}^\top \bar{\mathbf{S}}$, where $\bar{\mathbf{S}}$ is the scaled sensitivity matrix defined using the relative sensitivity coefficient in (3.7), that is,

$$\bar{\mathbf{S}} = \begin{pmatrix} \bar{s}_{1,1} & \cdots & \bar{s}_{1,N_p} \\ \vdots & \ddots & \vdots \\ \bar{s}_{N_x,1} & \cdots & \bar{s}_{N_x,N_p} \end{pmatrix} = \begin{pmatrix} \frac{\theta_1}{x_1} \frac{\partial x_1}{\partial \theta_1} & \cdots & \frac{\theta_{N_p}}{x_1} \frac{\partial x_1}{\partial \theta_{N_p}} \\ \vdots & \ddots & \vdots \\ \frac{\theta_1}{x_{N_x}} \frac{\partial x_{N_x}}{\partial \theta_1} & \cdots & \frac{\theta_{N_p}}{x_{N_x}} \frac{\partial x_{N_x}}{\partial \theta_{N_p}} \end{pmatrix} \in \mathbb{R}^{N_x \times N_p}. \quad (3.11)$$

If $\bar{\mathbf{S}}^\top \bar{\mathbf{S}}$ is ill-conditioned, the model may suffer from practical identifiability issues (Lam et al., 2022).

The collinearity index method can be used to quantify the practical identifiability of dynamic models. First, the scaled sensitivities of the i -th output with respect to the j -th parameter are normalised along the time axis as

$$\tilde{s}_{i,j}(t_l) = \frac{\bar{s}_{i,j}(t_l)}{\sqrt{\sum_{l=1}^{N_{st}} \bar{s}_{i,j}^2(t_l)}}. \quad (3.12)$$

Using $\tilde{s}_{i,j}$ to construct a matrix $\tilde{\mathbf{S}}$ similar to (3.11), the parameter collinearity index PCI is defined as

$$PCI = \frac{1}{\sqrt{\lambda_{\min}(\tilde{\mathbf{S}}^\top \tilde{\mathbf{S}})}}, \quad (3.13)$$

where $\lambda_{\min}(\tilde{\mathbf{S}}^\top \tilde{\mathbf{S}})$ denotes the smallest eigenvalue of $\tilde{\mathbf{S}}^\top \tilde{\mathbf{S}}$. Larger values of PCI indicate poorer practical identifiability. A threshold value of 20 is suggested to ensure practical identifiability (Brun et al., 2001).

3.5 Parameter Estimation

The PE problem aims to determine the parameter values that best fit the experimental measurements. In many studies, it is also referred to as an inverse problem. Parameter estimation is generally challenging for several reasons. From the modelling perspective, deviations between model outputs and measurements arise because the model is only an approximation of the real system and may contain structural inaccuracies due to incomplete knowledge of the underlying mechanisms. From the experimental perspective, measurement data are inevitably affected by noise, measurement errors, and limitations in experimental resources. In addition, from a numerical standpoint, solving the PE problem can be difficult due to model nonlinearity and high dimensionality.

The following subsections introduce the basic principles for formulating the PE problem mathematically. Existing methods generally approach parameter estimation from two perspectives. One approach minimises the deviations (residuals) between model simulation

outputs and experimental measurements. The other formulates the problem statistically using maximum likelihood estimation. Statistical techniques used to evaluate the quality of parameter estimates are then discussed. Finally, the identifiability issue is revisited, as it is one of the most common challenges encountered in parameter estimation and provides useful insights for experimental design.

3.5.1 Estimators

An estimator is a function of the observed data $\mathbf{D}$, denoted as $\hat{\boldsymbol{\theta}}(\mathbf{D})$. Once experimental data are obtained, parameter estimates can be computed through the estimator function.

According to Lehmann and Casella (1998), no uniformly best estimator exists except in trivial cases where the estimator is constant. Therefore, estimators satisfying certain desirable properties are generally preferred. One such property is *consistency*:

$$\lim_{N \rightarrow \infty} P \left\{ \left| \hat{\boldsymbol{\theta}} - \boldsymbol{\theta} \right| < \varepsilon \right\} = 1, \quad \forall \varepsilon \in \mathbb{R}_{++}, \quad (3.14)$$

where $P\{\cdot\}$ denotes probability and N is the number of observations. Consistency implies that parameter estimates obtained from datasets converge to the true parameter values.

Another desirable property is *unbiasedness*:

$$\mathbb{E} \left\{ \hat{\boldsymbol{\theta}}(\mathbf{D}) \right\} = \boldsymbol{\theta}. \quad (3.15)$$

where $\mathbb{E}$ is the expectation function. An unbiased estimator means that over repeated experiments, the overestimation and underestimation of parameters cancel out on average.

A further property of interest is *efficiency*. Suppose two unbiased estimators $\hat{\boldsymbol{\theta}}_1$ and $\hat{\boldsymbol{\theta}}_2$ are available. The estimator $\hat{\boldsymbol{\theta}}_1$ is considered more efficient than $\hat{\boldsymbol{\theta}}_2$ if

$$\mathbb{V} \left\{ \hat{\boldsymbol{\theta}}_1 \right\} < \mathbb{V} \left\{ \hat{\boldsymbol{\theta}}_2 \right\}. \quad (3.16)$$

where $\mathbb{V}$ is the variance function. Ideally, the best estimator is an unbiased estimator with minimum variance, known as the minimum variance unbiased (MVU) estimator.

3.5.2 Residual-Based methods

Norm Approximation

A natural way to evaluate model fitting quality is to measure the residuals between experimental data $\mathbf{D} = [d_1, \dots, d_{N_y}]^\top \in \mathbb{R}^{N_y}$ and the model outputs. The residual function can be written as

$$R(\boldsymbol{\theta}) = \|\mathbf{D} - \mathbf{x}(\boldsymbol{\theta})\|. \quad (3.17)$$

where $\|\cdot\|$ is a norm function. The PE problem can therefore be formulated as

$$\hat{\boldsymbol{\theta}} = \arg \min_{\boldsymbol{\theta} \in \Theta} R(\boldsymbol{\theta}). \quad (3.18)$$

A widely used PE method is the least square estimation (LSE), which minimises the squared 2-norm of residuals. The weighted LSE, shown in (3.19), is more commonly applied because it accounts for heteroscedastic measurement noise and ensures better statistical quality of estimates.

$$\begin{aligned} \hat{\boldsymbol{\theta}} &= \arg \min_{\boldsymbol{\theta} \in \Theta} \left\| \boldsymbol{\Sigma}^{-\frac{1}{2}} (\mathbf{D} - \mathbf{x}(\boldsymbol{\theta})) \right\|_2^2 \\ &= \arg \min_{\boldsymbol{\theta} \in \Theta} (\mathbf{D} - \mathbf{x}(\boldsymbol{\theta}))^\top \boldsymbol{\Sigma}^{-1} (\mathbf{D} - \mathbf{x}(\boldsymbol{\theta})). \end{aligned} \quad (3.19)$$

For dynamic systems with measurements sampled at time points $\mathbf{t}_{sp} = [t_1, \dots, t_{N_{st}}]^\top$, the LSE problem should be formed by including all residuals at $\mathbf{t}_{sp}$, that is,

$$\hat{\boldsymbol{\theta}} = \arg \min_{\boldsymbol{\theta} \in \Theta} \sum_{l=1}^{N_{st}} (\mathbf{D}(t_l) - \mathbf{x}(\boldsymbol{\theta}, t_l))^\top \boldsymbol{\Sigma}^{-1} (\mathbf{D}(t_l) - \mathbf{x}(\boldsymbol{\theta}, t_l)). \quad (3.20)$$

For models that are linear to parameters $\boldsymbol{\theta}$, this optimisation problem (3.20) is convex and yields a global optimum. However, for models that are nonlinear in the parameter $\boldsymbol{\theta}$, the

convexity of optimisation problem (3.20) depends on the characteristics of $\mathbf{x}(t, \boldsymbol{\theta})$ and the choice of norms. In such cases, Taylor expansion is often used to linearise the residual function locally, resulting in a local and approximate solution. In both cases, the estimation of $\boldsymbol{\theta}$ can be represented by

$$\hat{\boldsymbol{\theta}} \approx \boldsymbol{\theta}_0 + \left(\frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}_0}^\top \boldsymbol{\Sigma}^{-1} \frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}_0} \right)^{-1} \left(\frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}_0}^\top \boldsymbol{\Sigma}^{-1} (\mathbf{D} - \mathbf{x}(\boldsymbol{\theta}_0)) \right). \quad (3.21)$$

Besides the 2-norm approximation, other norms such as the 1-norm and ∞ -norm (Chebyshev norm) can also be used for PE. The objective function of the p -norm approximation ($1 \leq p < \infty$) is written as

$$\left(\sum_{l=1}^{N_{st}} \sum_{i=1}^{N_y} |d_i(t_l) - y_i(t_l, \boldsymbol{\theta})|^p \right)^{1/p}, \quad (3.22)$$

where d_i is the data of the i -th output.

As discussed in Boyd (2004), different norm choices produce different residual distributions. The 1-norm is more robust to outliers (Aster, 2019) but leads to non-differentiable optimisation problems. It is expected that the 1-norm approximation can be transformed into a linear programming problem when the model output $\mathbf{x}(t, \boldsymbol{\theta})$ is linear to parameter $\boldsymbol{\theta}$. The 2-norm objective function will be largely affected if an outlier exists, however, it finds the model that best fits data on the whole, when the quality and quantity of data can be ensured.

Penalty Approximation

Another approach introduces penalty functions to handle residuals:

$$\hat{\boldsymbol{\theta}} = \arg \min_{\boldsymbol{\theta} \in \Theta} \sum_{l=1}^{N_{st}} \sum_{i=1}^{N_y} v(d_i(t_l) - x_i(t_l, \boldsymbol{\theta})). \quad (3.23)$$

For penalty function $v(x) = |x|^p$ where $1 \leq p < \infty$, the penalty approximation problem is equivalent to the p -norm approximation. Common penalty functions include the deadzone-

linear penalty, log-barrier penalty, and the Huber penalty (robust least squares) that combines properties of both 1-norm and 2-norm residuals.

3.5.3 Maximum likelihood estimation

Another approach to solving the PE problem is maximum likelihood (ML) estimation. Suppose N_D datasets $\{\mathbf{D}^{(1)}, \dots, \mathbf{D}^{(N_D)}\}$ are available. Assume that the deviation between the observed data and the model output, $(\mathbf{D}^{(k)} - \mathbf{x})$, follows a probability distribution $p(\cdot)$. The likelihood function evaluates the probability of observing the datasets given a parameter vector $\boldsymbol{\theta} \in \Theta$. It is defined as

$$L(\boldsymbol{\theta}) = \prod_{k=1}^{N_D} p(\mathbf{D}^{(k)} - \mathbf{x}(\boldsymbol{\theta}) \mid \boldsymbol{\theta}). \quad (3.24)$$

The parameter estimate obtained by ML estimation is the parameter value that maximises the likelihood function. In practice, numerical optimisation algorithms typically require computing first-order derivatives of the objective function. Since the likelihood function in (3.24) is a product of many terms, its derivatives are inconvenient to compute directly. Therefore, the logarithm of the likelihood function is usually employed. Maximising the likelihood is equivalent to minimising the negative log-likelihood:

$$\hat{\boldsymbol{\theta}} = \arg \min_{\boldsymbol{\theta} \in \Theta} (-\ln L(\boldsymbol{\theta})) = \arg \min_{\boldsymbol{\theta} \in \Theta} \left(-\sum_{k=1}^{N_D} \ln p(\mathbf{D}^{(k)} - \mathbf{x}(\boldsymbol{\theta}) \mid \boldsymbol{\theta}) \right). \quad (3.25)$$

Assuming that the measurement errors are independently Gaussian distributed, $\boldsymbol{\xi} \sim N(0, \boldsymbol{\Sigma})$, the deviation between the data and the model output $(\mathbf{D} - \mathbf{x})$ also follows a Gaussian distribution

$$p(\mathbf{D} - \mathbf{x} \mid \boldsymbol{\theta}) \propto \exp \left(-\frac{1}{2} (\mathbf{D} - \mathbf{x}(\boldsymbol{\theta}))^\top \boldsymbol{\Sigma}^{-1} (\mathbf{D} - \mathbf{x}(\boldsymbol{\theta})) \right). \quad (3.26)$$

For dynamic systems whose measurements are sampled at time points $\mathbf{t}_{sp} = [t_1, \dots, t_{N_{st}}]^\top$, and assuming a single dataset ($N_D = 1$), the ML estimation problem in (3.25) becomes

$$\hat{\boldsymbol{\theta}} = \arg \min_{\boldsymbol{\theta} \in \Theta} \left(\frac{1}{2} \sum_{l=1}^{N_{st}} (\mathbf{D}(t_l) - \mathbf{x}(\boldsymbol{\theta}, t_l))^\top \boldsymbol{\Sigma}^{-1} (\mathbf{D}(t_l) - \mathbf{x}(\boldsymbol{\theta}, t_l)) \right). \quad (3.27)$$

This formulation is equivalent to the weighted LSE problem in (3.20).

The assumed distribution of observations directly affects the likelihood function in (3.24). Therefore, ML estimation can provide more reliable parameter estimates when the distribution of measurement errors is known. However, the estimation results may become misleading if the assumed distribution deviates from the true data distribution. Such deviations may arise from modelling errors, parameter uncertainties, experimental conditions, or incorrect assumptions regarding measurement noise.

3.6 Fisher Information Matrix and Cramér–Rao Bound

To quantify the information about unknown parameters contained in random observations, the FIM is one of the most widely used tools. It is derived from the likelihood function under the ML framework. The FIM has several important properties, including non-negativity and additivity, which make it particularly suitable for experimental design. Under standard regularity conditions, the inverse of the FIM approximates the covariance of the asymptotic maximum likelihood estimator. Another important concept is the Cramér–Rao bound (CRB), which provides a lower bound on the covariance of any unbiased estimator. For unbiased estimators, the CRB is given by the inverse of the FIM, indicating the best achievable estimation accuracy under the given statistical model.

3.6.1 Fisher information matrix (FIM)

Suppose the following regularity conditions are satisfied:

- The parameter space Θ is an open set.
- The distribution p has common support which is independent of θ .
- The first and second derivative ($\frac{\partial p}{\partial \theta}$ and $\frac{\partial^2 p}{\partial \theta \partial \theta^\top}$) exists and is finite for any $\theta \in \Theta$.
- The order of integration and differentiation can be exchanged: $\int \frac{\partial p}{\partial \theta} dy = \frac{\partial}{\partial \theta} \int p dy$.

Consider the maximum likelihood estimation (MLE) problem in (3.25). The optimal parameter estimate satisfies

$$\frac{\partial \ln L}{\partial \theta} = 0. \quad (3.28)$$

A score function is defined to evaluate parameter estimation quality:

$$\boldsymbol{\eta} = \frac{\partial \ln L}{\partial \theta}. \quad (3.29)$$

An important property of the score function is that its expectation is zero, i.e.,

$$\mathbb{E}\{\boldsymbol{\eta}\} = \mathbb{E}\left\{\frac{\partial \ln p(\mathbf{D} | \theta)}{\partial \theta}\right\} = 0. \quad (3.30)$$

The covariance of the score function gives the FIM:

$$\mathbb{V}\{\boldsymbol{\eta}\} = \mathbb{E}\{\boldsymbol{\eta}^\top \boldsymbol{\eta}\} = \mathbb{E}\left\{\frac{\partial \ln L}{\partial \theta}^\top \cdot \frac{\partial \ln L}{\partial \theta}\right\} \triangleq \mathbf{FIM}. \quad (3.31)$$

Under regularity conditions, the Fisher information matrix can be expressed as

$$\mathbf{FIM} = -\mathbb{E}\left\{\frac{\partial^2 \ln p}{\partial \theta^2}\right\} = -\mathbb{E}\{\mathbf{H}\}. \quad (3.32)$$

Here $\mathbf{H}$ is the Hessian matrix of the log-likelihood function. This indicates that the FIM is closely related to the curvature of log-likelihood at the true parameter values. The FIM describes the potential of finding precise parameter estimations under the current likelihood function. The log-likelihood function with a sharp peak means the observation contains more information about the unknown parameters.

Under the additional assumption that measurement errors are Gaussian distributed, the likelihood function takes a quadratic form, and the Fisher information matrix in (3.32) simplifies to

$$\mathbf{FIM} = \mathbf{S}^\top \mathbf{\Sigma}^{-1} \mathbf{S}. \quad (3.33)$$

Due to the additive characteristics of the expectation operator, the FIM is additive for multiple independent outputs (Aster, 2019). For dynamic systems with measurements at sampling times $\mathbf{t}_{sp} = [t_1, \dots, t_{N_{st}}]^\top$, the Fisher information matrix is

$$\mathbf{FIM} = \sum_{l=1}^{N_{st}} \mathbf{S}^\top(t_l) \mathbf{\Sigma}^{-1}(t_l) \mathbf{S}(t_l). \quad (3.34)$$

3.6.2 Cramér–Rao bound

The CRB provides a lower bound on the covariance of unbiased estimators:

$$\mathbb{V}(\hat{\boldsymbol{\theta}}) \succeq \mathbf{FIM}^{-1}. \quad (3.35)$$

This bound indicates that no unbiased estimator can achieve a covariance smaller than the inverse of FIM. When an estimator attains this bound, it is called an efficient estimator.

The CRB can be derived using the covariance inequality based on the Cauchy–Schwarz inequality. By defining the estimation error $\boldsymbol{\zeta} = \hat{\boldsymbol{\theta}} - \mathbb{E}\{\hat{\boldsymbol{\theta}}\}$ and the score function $\boldsymbol{\eta} = \frac{\partial \ln p}{\partial \boldsymbol{\theta}}$, one obtains

$$\mathbb{V}\{\hat{\boldsymbol{\theta}}\} \succeq \mathbb{E}\{\boldsymbol{\zeta} \boldsymbol{\eta}^\top\} \mathbf{FIM}^{-1} \mathbb{E}\{\boldsymbol{\eta} \boldsymbol{\zeta}^\top\}. \quad (3.36)$$

For unbiased estimators, this simplifies to the classical CRB.

3.7 Optimal Experimental Design Formulation

As illustrated in Fig. 3.2, OED aims to determine the optimal experimental strategy such that the resulting data are maximally informative for a given modelling objective. The

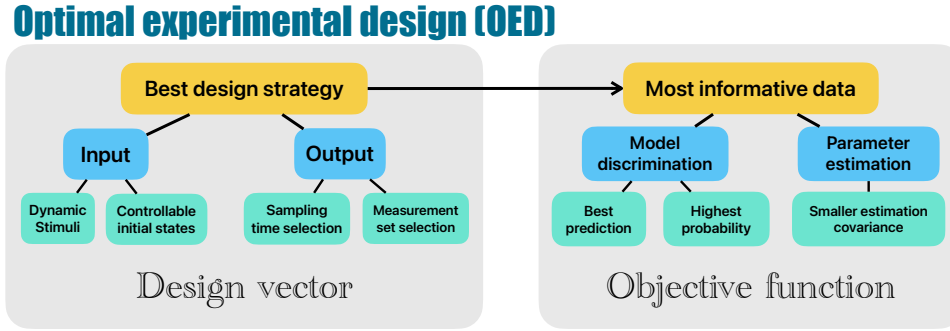


Fig. 3.2 Optimal experimental design

experimental strategy typically includes controllable inputs (e.g., time-varying stimuli and initial states) and measurement configurations (e.g., sampling times and measurement sets). Mathematically, these elements are collected into a design vector, which serves as the decision variable in the OED problem.

The objective function in OED quantifies the information content of the data and depends on the specific modelling objective. For model discrimination, the objective function may be defined based on the discrepancy between competing model predictions or the likelihood of candidate models given the data. For parameter estimation, which is the focus of this thesis, the objective is typically related to the covariance (or its lower bound) of the parameter estimates.

Based on the results in Section 3.6, the information content of data can be quantified through the Fisher information matrix or, equivalently, through its inverse, which represents the lower bound on the covariance of unbiased parameter estimators. Accordingly, the OED problem can be formulated as

$$\boldsymbol{\varphi} = \arg \min_{\boldsymbol{\varphi}} \phi \left(\mathbf{I}^{-1}(\boldsymbol{\theta}, \boldsymbol{\varphi}) \right), \quad (3.37)$$

where $\boldsymbol{\varphi}$ denotes the design variables, $\mathbf{I}(\boldsymbol{\theta}, \boldsymbol{\varphi})$ is the information matrix, and $\phi(\cdot)$ is a scalarisation function that maps the matrix $\mathbf{I}^{-1}$ to a scalar objective for optimisation.

A general class of scalarisation functions can be used to unify several classical optimality criteria (Kiefer, 1974). For a model with N_p parameters, such a class may be written as

$$\phi_{\kappa}(\mathbf{I}^{-1}(\boldsymbol{\theta}, \boldsymbol{\varphi})) = \left(\frac{1}{N_p} \sum_{i=1}^{N_p} \lambda_i^{\kappa} \right)^{\frac{1}{\kappa}}, \quad \kappa > 0, \quad (3.38)$$

where λ_i are the eigenvalues of $\mathbf{I}^{-1}$. Within this family, the classical A-, D-, and E-optimality criteria can be recovered as special cases, up to scaling or monotonic transformation.

Different optimal design criteria are obtained for different values of κ :

- $\kappa = 1$: **A-optimality**. This criterion is based on $\text{tr}(\mathbf{I}^{-1})$ and minimises the average variance of the parameter estimates. However, it is scale-dependent for nonlinear models and may perform poorly when parameters are highly correlated (Franceschini and Macchietto, 2008; Stallings and Morgan, 2015). Weighted A-optimality can be used to mitigate scaling effects (García-Ródenas et al., 2020; Stallings and Morgan, 2015).
- $\kappa \rightarrow 0$: **D-optimality**. In this limit, the scalarisation approaches the geometric mean of the eigenvalues of $\mathbf{I}^{-1}$ and is therefore equivalent to a determinant-based criterion. D-optimality is commonly written in terms of $|\mathbf{I}^{-1}|$ and minimises the volume of the confidence ellipsoid of the parameter estimates. It is invariant under non-degenerate parameter transformations (e.g., scaling) and is widely used in practice. However, it may place excessive emphasis on the most sensitive parameter directions, potentially neglecting less sensitive parameters (Franceschini and Macchietto, 2008).
- $\kappa \rightarrow \infty$: **E-optimality**. In this limit, the scalarisation approaches $\lambda_{\max}(\mathbf{I}^{-1})$. E-optimality therefore minimises the worst-case variance direction among the parameter estimates, or equivalently maximises the smallest eigenvalue of the information matrix. Although it can often be formulated as a convex optimisation problem (e.g., via semi-definite programming (SDP)), it may overly focus on the worst-estimated direction and ignore overall estimation performance.

More detailed discussions on scalarisation criteria can be found in Franceschini and Macchietto (2008).

3.7.1 Classical optimal experimental designs for parameter estimation

The classical model-based design of experiments (MBDoE) for parameter estimation is developed under the assumption that the measurement error ξ is independently and normally distributed. Under this assumption, the LSE and ML formulations lead to the same optimisation problem, as shown in (3.20) and (3.27).

For linear systems, or nonlinear systems locally approximated around nominal parameter values, an (approximately) unbiased estimator $\hat{\theta}$ can be obtained as in (3.21). Therefore, the classical OED can be formulated using either the FIM in (3.33) or the corresponding estimation covariance:

$$\boldsymbol{\varphi} = \arg \min_{\boldsymbol{\varphi}} \phi(\mathbf{FIM}^{-1}) = \arg \min_{\boldsymbol{\varphi}} \phi \left(\left[\mathbf{S}^\top(\boldsymbol{\theta}_0) \boldsymbol{\Sigma}^{-1} \mathbf{S}(\boldsymbol{\theta}_0) \right]^{-1} \right), \quad (3.39)$$

where $\boldsymbol{\theta}_0$ denotes the nominal parameter values.

The formulation in Eq. (3.39) assumes that the FIM is nonsingular. If the FIM is singular, its determinant and minimum eigenvalue are zero and its inverse is undefined, indicating insufficient independent local information for at least one parameter direction. Consequently, the log-D criterion tends to $-\infty$, the E-criterion becomes zero, and inverse-FIM-based criteria such as A-optimality cannot be evaluated in their usual form.

In the numerical implementation, the FIM is first symmetrised as

$$\mathbf{FIM}_s = \frac{1}{2} (\mathbf{FIM} + \mathbf{FIM}^\top).$$

Its eigenvalues are then evaluated, and eigenvalues smaller than the numerical threshold $\epsilon_\lambda = 10^{-12}$ are replaced by ϵ_λ ,

$$\tilde{\lambda}_j = \max(\lambda_j, \epsilon_\lambda).$$

The resulting regularised spectrum is used only to avoid numerical failure when evaluating nearly singular trial designs. This treatment is a numerical safeguard and does not imply that a singular or nearly singular FIM becomes informative.

For linear systems, under the standard assumptions, the covariance of an efficient estimator can attain the CRB, i.e., the inverse of the FIM. For nonlinear systems, the FIM-based covariance approximation is generally local because it is evaluated at nominal parameter values. Its accuracy therefore depends on how well the nominal parameters represent the true system. Nevertheless, the CRB remains a useful approximation of estimation quality when the nominal parameter values are sufficiently close to the true values.

For dynamic systems, exploiting the additivity of the FIM and assuming measurements are taken at sampling times $\mathbf{t}_{sp}$, the classical OED problem becomes

$$\boldsymbol{\varphi} = \arg \min_{\boldsymbol{\varphi}} \phi \left(\left[\sum_{l=1}^{N_{st}} \mathbf{S}^\top(\boldsymbol{\theta}_0, t_l) \boldsymbol{\Sigma}^{-1}(t_l) \mathbf{S}(\boldsymbol{\theta}_0, t_l) \right]^{-1} \right). \quad (3.40)$$

3.7.2 Input design

As discussed previously, input design determines the time-varying stimuli or the controllable initial states. For batch or fed-batch experiments, designing controllable initial states is commonly considered, i.e., $\boldsymbol{\varphi} = \mathbf{x}_0$.

Since analytical expressions of model outputs are generally unavailable for complex nonlinear dynamic systems, the OED problem in (3.40) becomes a nonconvex constrained optimisation problem, which is difficult to solve analytically:

$$\begin{aligned} \boldsymbol{\varphi} = \arg \min_{\mathbf{x}_0} \quad & \phi \left(\left[\sum_{l=1}^{N_{st}} \mathbf{S}^\top(\mathbf{x}_0, \boldsymbol{\theta}_0, t_l) \boldsymbol{\Sigma}^{-1}(t_l) \mathbf{S}(\mathbf{x}_0, \boldsymbol{\theta}_0, t_l) \right]^{-1} \right) \\ \text{s.t.} \quad & \mathbf{x}_0^L \preceq \mathbf{x}_0 \preceq \mathbf{x}_0^U. \end{aligned} \quad (3.41)$$

Here, $\mathbf{x}_0^L$ and $\mathbf{x}_0^U$ denote the lower and upper bounds of the initial states.

Typical numerical solvers, such as *fmincon* in MATLAB, can only guarantee locally optimal solutions. A common strategy to improve solution quality is to employ multi-start initialisation. However, this approach becomes computationally expensive for high-dimensional systems, as each evaluation requires solving the underlying ODE model.

3.7.3 Sampling time design

To perform sampling time design, the experimental time horizon is discretised into N_T candidate time points. A binary weighting vector $\mathbf{w}$ is introduced to indicate whether a sampling time is selected:

$$\begin{Bmatrix} t_1 & t_2 & \cdots & t_{N_T} \\ w_1 & w_2 & \cdots & w_{N_T} \end{Bmatrix}, \quad (3.42)$$

where $w_l = 1$ indicates that measurements are taken at time t_l , and $w_l = 0$ otherwise.

The sampling time design problem can then be formulated as

$$\begin{aligned} \mathbf{w}^* = \arg \min_{\mathbf{w}} \quad & \phi \left(\left[\sum_{l=1}^{N_T} w_l \mathbf{S}^\top(t_l) \boldsymbol{\Sigma}^{-1} \mathbf{S}(t_l) \right]^{-1} \right) \\ \text{s.t.} \quad & \sum_{l=1}^{N_T} w_l = N_{st}, \\ & w_l \in \{0, 1\}, \quad l = 1, \dots, N_T, \end{aligned} \quad (3.43)$$

where N_{st} is the prescribed number of sampling points. This formulation leads to a combinatorial (integer) optimisation problem, which is generally difficult to solve. To improve solvability, the binary variables w_l can be relaxed to continuous values in $[0, 1]$, making a continuous optimisation problem. After relaxation, the binary selection variables are replaced

by normalised design weights, so that $\sum_l w_l = 1$.

$$\begin{aligned} \mathbf{w}^* = \arg \min_{\mathbf{w} \in [0,1]} & \quad \phi \left(\left[\sum_{l=1}^{N_T} w_l \mathbf{S}^\top(t_l) \boldsymbol{\Sigma}^{-1} \mathbf{S}(t_l) \right]^{-1} \right) \\ \text{s.t.} & \quad \sum_{l=1}^{N_T} w_l = 1. \end{aligned} \quad (3.44)$$

Since each $\mathbf{FIM}(t_l) = \mathbf{S}^\top(t_l) \boldsymbol{\Sigma}^{-1} \mathbf{S}(t_l)$ is positive semidefinite, their weighted sum is also positive semidefinite for any $\mathbf{w} \succeq 0$. This property enables the E-optimal sampling time design problem to be reformulated as an SDP after relaxation (Boyd, 2004):

$$\begin{aligned} \mathbf{w}^* = & \quad \arg \min_{\mathbf{w}, r} -r \\ \text{s.t.} & \quad \sum_{l=1}^{N_T} w_l \mathbf{FIM}(t_l) \succeq r \mathbf{I}_{N_p}, \\ & \quad \sum_{l=1}^{N_T} w_l = 1, \\ & \quad \mathbf{w} \succeq 0, \quad r \geq 0. \end{aligned} \quad (3.45)$$

Here $\mathbf{I}_{N_p}$ is the N_p -dimensional identity matrix. This convex formulation can be efficiently solved using solvers such as SeDuMi, MOSEK, or toolboxes like YALMIP in MATLAB. However, due to the relaxation, the obtained solution is approximate to (3.43) and may not correspond to a feasible discrete sampling schedule.

A more accurate approach for solving the discrete sampling time design problem is a modified Powell-type method. The pseudo-code is shown in Algorithm 1. This algorithm differs from the classical Powell method in that the search directions are not updated during iterations. This modification ensures that all candidate solutions remain within the discrete feasible set $\mathbf{t}_m$. Instead of updating directions, the method performs iterative exchange operations within a fixed candidate set.

To compensate for the lack of direction updates, an inner iteration loop is introduced to enhance exploration of the search space. The method retains the derivative-free, coordinate-

wise improvement philosophy of Powell's method and is therefore referred to as a Powell-type method in this thesis.

Algorithm 1: Powell-type method for sampling time design

Data: $\mathbf{t}_m \in \mathbb{R}^{N_T}$, N_{st}

```

1  $i = 1$ ;
2 while  $i \leq N_{outer}$  do
3    $\mathbf{t}_{sp}^0 = [t_1^0, \dots, t_{N_{st}}^0]$ , randomly selected from  $\mathbf{t}_m$ ;
4    $\mathbf{FIM}(\mathbf{t}_{sp}^0) = \sum_l \mathbf{FIM}(t_l^0)$ ;
5    $j = 1$ ;
6   while  $j \leq N_{inner}$  do
7     for  $k = 1 : N_{st}$  do
8        $\mathbf{t}_{sp}^- = \mathbf{t}_{sp}^0 \setminus \{t_k^0\}$  (delete the k-th element);
9        $\mathbf{FIM}(\mathbf{t}_{sp}^-) = \mathbf{FIM}(\mathbf{t}_{sp}^0) - \mathbf{FIM}(t_k^0)$ ;
10       $t^* = \arg \min_{t \in (\mathbf{t}_m \setminus \mathbf{t}_{sp}^-)} \phi \left( [\mathbf{FIM}(\mathbf{t}_{sp}^-) + \mathbf{FIM}(t)]^{-1} \right)$ ;
11       $\mathbf{t}_{sp} = \mathbf{t}_{sp}^- \cup \{t^*\}$ ;
12    end
13    Record  $\mathbf{t}_{sp}$  and  $\mathbf{FIM}(\mathbf{t}_{sp})$ ;
14     $\mathbf{t}_{sp}^0 = \mathbf{t}_{sp}$ ;  $j = j + 1$ ;
15  end
16  Select the  $\mathbf{t}_{sp}$  with minimum  $\phi \left( \mathbf{FIM}^{-1}(\mathbf{t}_{sp}) \right)$  from inner iterations;  $i = i + 1$ ;
17 end
Result:  $\mathbf{t}_{sp}^*$  with the best objective value.
  
```

This Powell-type method does not require relaxation or derivative information and directly searches within the discrete design space. However, it does not guarantee convergence to a global optimum. Moreover, the nested iteration structure (outer loop, inner loop, and point-wise updates) leads to significant computational cost, particularly for large candidate sets. The discretisation of the continuous time domain also affects the design quality. A finer discretisation provides more accurate design solutions but increases computational burden. In practice, discretisation should also account for limitations of measurement devices and experimental feasibility.

3.7.4 Measurement set selection

Similar to sampling time design, a binary weighting vector $\mathbf{w}$ is introduced to represent the selection of measurable states:

$$\begin{Bmatrix} x_1 & x_2 & \cdots & x_{N_x} \\ w_1 & w_2 & \cdots & w_{N_x} \end{Bmatrix}, \quad (3.46)$$

where $w_i = 1$ indicates that the i -th state is selected for measurement, and $w_i = 0$ otherwise. Suppose N_m states are to be measured. The OED problem for measurement selection can be formulated as

$$\begin{aligned} \mathbf{w}^* = \arg \min_{\mathbf{w}} \quad & \phi \left(\left[\sum_{i=1}^{N_x} w_i \mathbf{FIM}_i \right]^{-1} \right) \\ \text{s.t.} \quad & \sum_{i=1}^{N_x} w_i = N_m, \\ & w_i \in \{0, 1\}, \quad i = 1, \dots, N_x, \end{aligned} \quad (3.47)$$

where $\mathbf{FIM}_i \in \mathbb{S}_+$ denotes the information matrix for the i -th state, given by

$$\mathbf{FIM}_i = \sum_{l=1}^{N_T} \frac{1}{\sigma_i^2(t_l)} \frac{\partial x_i(t_l)}{\partial \boldsymbol{\theta}} \frac{\partial x_i(t_l)}{\partial \boldsymbol{\theta}}^\top. \quad (3.48)$$

This formulation is again a combinatorial optimisation problem. To improve solvability, the binary variables w_i can be relaxed to continuous values in $[0, 1]$. Under the E-optimality criterion, the relaxed problem can be reformulated as a SDP problem:

$$\begin{aligned} \mathbf{w}^* = \quad & \arg \min_{\mathbf{w}, r} -r \\ \text{s.t.} \quad & \sum_{i=1}^{N_x} w_i \mathbf{FIM}_i \succeq r \mathbf{I}_{N_p}, \\ & \sum_{i=1}^{N_x} w_i = 1, \\ & \mathbf{w} \succeq 0, \quad r \geq 0. \end{aligned} \quad (3.49)$$

Unlike sampling time design, measurement selection does not involve time discretisation, and the candidate set is typically fixed and finite.

In practice, measurement selection is often performed after sampling time design, assuming that all selected variables are measured at the same sampling instants. An alternative strategy is to jointly optimise sampling times and measurement selection by introducing binary variables for each state–time pair. Although this joint design can potentially improve the information content of the data, it significantly increases experimental complexity. In particular, measurements may need to be taken at different times for different variables, which imposes additional operational and human resource constraints.

3.7.5 Experimental design evaluation

After obtaining an experimental design from the OED problem, the statistical properties of the resulting parameter estimates should be assessed in order to compare different design strategies.

A straightforward approach is to apply statistical hypothesis tests such as the χ^2 -test or the F-test to evaluate model fit. However, these tests are primarily designed to detect significant discrepancies between model predictions and data. They are therefore more suitable for model validation, i.e., rejection of inadequate models, rather than for comparing the estimation quality under different experimental designs.

The t -test, on the other hand, can be used to assess the significance of individual parameter estimates. The Student's t -value for parameter θ_j is defined as $t_j = \frac{\hat{\theta}_j}{\sqrt{V_{jj}}}$, where V_{jj} is the variance of the j -th parameter, i.e., the j -th diagonal element of the covariance matrix $\mathbf{V}$. A larger t -value generally indicates higher confidence in the corresponding parameter estimate. However, the t -test relies on assumptions such as statistical independence and low correlation among parameters, which may be violated in practice, particularly for nonlinear models with strongly correlated parameters (Franceschini and Macchietto, 2008).

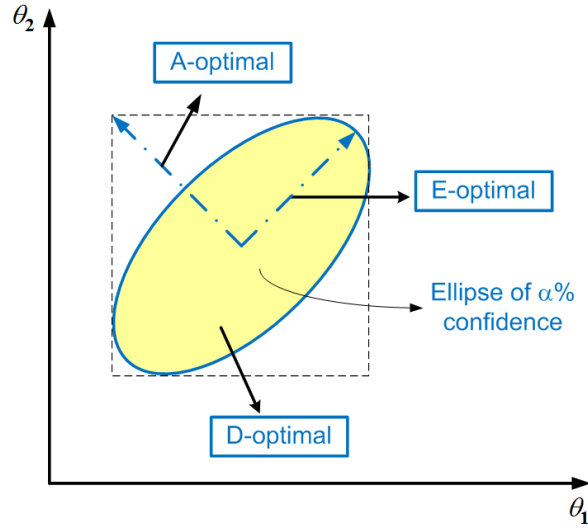


Fig. 3.3 Geometric interpretation of A-, D-, and E-optimal design criteria (Yu, 2018)

Another important tool for design evaluation is the confidence region of parameter estimates. It defines a region in the parameter space that contains the true parameter values with probability $1 - \alpha$:

$$CI = \left\{ \boldsymbol{\theta} : R(\boldsymbol{\theta}) \leq \left(1 + \frac{N_p}{N - N_p} F_{N_p, N - N_p}^{1-\alpha} \right) R(\hat{\boldsymbol{\theta}}) \right\}, \quad (3.50)$$

where α is the significance level (typically $\alpha = 0.05$), F denotes the Fisher distribution, and N is the number of data points. Using a first-order Taylor expansion of $R(\boldsymbol{\theta})$, the confidence region can be approximated as

$$CI = \left\{ \boldsymbol{\theta} : (\boldsymbol{\theta} - \hat{\boldsymbol{\theta}})^\top \left(\frac{2R(\hat{\boldsymbol{\theta}})}{N - N_p} \mathbf{FIM}^{-1} \right)^{-1} (\boldsymbol{\theta} - \hat{\boldsymbol{\theta}}) \leq N_p F_{N_p, N - N_p}^{1-\alpha} \right\}. \quad (3.51)$$

This formulation shows that the FIM provides a geometric interpretation of parameter uncertainty. In particular, the confidence region takes the form of an ellipsoid (or hyper-ellipsoid in higher dimensions), whose size and shape are determined by $\mathbf{FIM}^{-1}$. Accordingly, the A-, D-, and E-optimal design criteria can be interpreted as minimising different geometric properties of this confidence region, such as its average variance (A-optimality), volume (D-optimality), and largest axis (E-optimality), as illustrated in Fig. 3.3.

In addition to variance, parameter correlations play a critical role in both PE and OED. Strong parameter correlations can lead to ill-conditioned estimation problems and poor practical identifiability (López C. et al., 2015). In many nonlinear models, such difficulties are also associated with sloppy parameter combinations, for which the objective function exhibits long, narrow valleys that significantly complicate numerical optimisation (Transtrum et al., 2011). Moreover, these nearly compensating parameter combinations may allow different parameter sets to produce nearly identical model responses, thereby hindering reliable physical or mechanistic interpretations of the estimated parameter values.

Parameter correlations can be quantified using the correlation matrix $\mathbf{C}$, whose elements are computed from the covariance matrix $\mathbf{V}$ as

$$c_{ij} = \frac{V_{ij}}{\sqrt{V_{ii}}\sqrt{V_{jj}}}. \quad (3.52)$$

Therefore, an effective experimental design should aim to achieve: (i) small parameter variances (or a compact confidence region), and (ii) low correlation between parameters. These criteria together provide a comprehensive assessment of estimation quality under different design strategies.

3.8 Summary

This chapter has established the theoretical foundations for model-based optimal experimental design. The first part introduced the key components of data-based modelling for dynamic systems. A systematic modelling procedure was outlined, including model formulation based on physical principles, identifiability analysis, preliminary parameter estimation, and sensitivity analysis. Identifiability analysis distinguishes structural limitations from practical limitations associated with the available data, while sensitivity analysis supports parameter selection and dimensionality reduction. These steps are essential for constructing meaningful and tractable OED problems.

The relationships among identifiability analysis, sensitivity analysis, and PE were further clarified. In particular, parametric sensitivities provide the basis for constructing the FIM, which plays a central role in quantifying the information content of experimental data. The discussion of PE and its lower bounds explains why the FIM (and its inverse) can be used as a proxy for estimation accuracy in experimental design.

The second part of this chapter presented the mathematical formulation of MBDoE. Classical OED relies on the FIM and is particularly effective for linear systems or nonlinear systems when nominal parameter values are close to the true values. Design problems for dynamic systems were formulated in terms of input design, sampling time design, and measurement set selection. Both continuous relaxations (e.g., SDP) and discrete optimisation methods were discussed for solving these problems. In addition, evaluation metrics such as confidence regions and parameter correlations were introduced to assess and compare different design strategies.

Despite its effectiveness, classical OED is inherently sensitive to uncertainty. Its formulation relies on linearisation around nominal parameter values and assumes independent Gaussian measurement noise. In practice, model uncertainty, parameter uncertainty, and input uncertainty may violate these assumptions, leading to degraded design performance. This limitation motivates the development of robust experimental design methods.

The formulations and insights presented in this chapter provide the fundamental framework for the subsequent development of RED approaches. In the following chapters, robust design strategies will be proposed to explicitly account for uncertainties. Classical OED will be used as a benchmark to highlight the advantages of RED under uncertain conditions, while also demonstrating its effectiveness when uncertainty is negligible.

Chapter 4

Robust Sampling Time Design

Development – Methods and Evaluation Framework

As established in Chapter 3, classical optimal experimental design (OED) is formulated based on local sensitivity information evaluated at nominal parameter values. While this approach is effective when the nominal parameters are accurate, its local nature makes the resulting designs sensitive to parametric uncertainty. In nonlinear dynamic systems, the Fisher Information Matrix (FIM) depends strongly on the parameter values at which it is evaluated, and deviations from nominal values may lead to substantial degradation in the information content of the designed experiments. This limitation motivates the need for experimental design strategies that explicitly account for uncertainty.

This chapter focuses on robust sampling time design under parametric uncertainty. The objective is to determine sampling schedules that maintain informative data acquisition in the presence of parameter variations. Two representative robust experimental design (RED) methodologies are considered: the maximin framework, which provides protection against worst-case parameter realisations, and the pseudo-Bayesian framework, which optimises expected performance with respect to a prescribed uncertainty distribution. These two

approaches represent fundamentally different robustness philosophies and form the basis for systematic comparison in this chapter.

Although this chapter focuses on sampling-time selection, the maximin and pseudo-Bayesian frameworks are not restricted to this design variable and can also be extended to initial conditions, input profiles, measurement selection, or combinations of these variables, provided that the corresponding FIM can be evaluated for each candidate design and parameter realisation.

Sampling-time design is considered specifically in this thesis because measurement timing is itself an important source of information in dynamic systems, where parameter sensitivities vary over time and informative sampling regions may shift under parametric uncertainty. A practical advantage is that, when measurements are non-invasive, sampling times can often be optimised without changing the prescribed operating policy or system trajectory. By contrast, input profiles and initial conditions may be constrained by operational or experimental requirements, and changes to these variables may also affect objectives such as production or product quality. Nevertheless, joint optimisation of sampling times with other design variables could potentially yield more informative experiments and is therefore identified as an important direction for future work.

The performance of classical and robust sampling time design strategies is investigated through two case studies with increasing model complexity: an enzyme reaction system and an enzymatic biodiesel production system. The numerical analysis evaluates design performance from multiple perspectives, including nominal efficiency, robustness under increasing uncertainty, sensitivity to the assumed uncertainty distribution, and performance under operating-condition changes. This structured evaluation enables a comprehensive understanding of how different design strategies behave under varying uncertainty scenarios.

A key contribution of this chapter is the development of a distribution-based evaluation framework for robust sampling time design. Rather than relying on a single aggregated performance metric, the information content of a given sampling strategy is assessed over a range of parameter realisations induced by parametric uncertainty. This enables robust-

ness to be characterised from multiple complementary perspectives, including worst-case performance, average performance, and variability across the uncertainty space. Such an evaluation provides a more informative and nuanced basis for comparing classical and robust experimental design strategies, and reveals behaviours that may be obscured by conventional single-value criteria.

This chapter is organised as follows. Section 4.1 introduces the problem formulation. Sections 4.2 and 4.3 present maximin and pseudo-Bayesian methods. Section 4.4 presents the evaluation framework used to assess robustness and design quality. Sections 4.5 and 4.6 provide comparative case studies. Section 4.7 summarises key findings.

4.1 Robust Sampling Time Design

Within the broader experimental-design framework described above, this chapter restricts the design variables to sampling times.

The sampling time design problem considered in this chapter aims to determine the time instants at which measurements are collected, under the assumption that all measured outputs are sampled simultaneously at each selected sampling time. The continuous experimental horizon is discretised into a finite set of candidate sampling points, as introduced in (3.42), and a weighting vector is used to represent the selection of sampling times.

Let the uncertain parameter vector $\boldsymbol{\theta}$ be bounded within known limits, denoted by $\boldsymbol{\theta}^L$ and $\boldsymbol{\theta}^U$. A general RED formulation for sampling time selection can then be expressed as

$$\mathbf{w}^* = \arg \min_{\mathbf{w}} \Phi_{\boldsymbol{\theta} \in \Theta} \{ \phi(\mathbf{FIM}^{-1}(\mathbf{w}, \boldsymbol{\theta})) \} \quad (4.1)$$

where $\mathbf{FIM}^{-1}(\mathbf{w}, \boldsymbol{\theta}) = [\sum_l w_l \mathbf{FIM}(t_l, \boldsymbol{\theta})]^{-1}$ denotes the inverse FIM associated with a given sampling design vector $\mathbf{w}$. The function $\phi(\cdot)$ represents a scalar optimality criterion, e.g., D-, E-, or A-optimality, while $\Phi\{\cdot\}$ denotes a robustness operator, which may correspond to maximin, pseudo-Bayesian, or other formulations.

4.2 Maximin Robust Experimental Design

The maximin RED seeks to optimise the worst-case performance over the admissible parameter uncertainty region (Asprey and Macchietto, 2002), ensuring that the resulting design maintains a guaranteed level of information for all feasible parameter realisations. Using the corresponding information-based optimality criterion, the maximin RED problem can be formulated as

$$\mathbf{w}^* = \arg \max_{\mathbf{w}} \min_{\boldsymbol{\theta} \in \Theta} \phi(\mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta})), \quad (4.2)$$

where Θ denotes the admissible uncertainty domain of the parameter vector $\boldsymbol{\theta}$. This formulation requires only bounded uncertainty and does not rely on any probabilistic description of the parameters.

The maximin problem in (4.2) can be equivalently reformulated as

$$\begin{aligned} \mathbf{w}^* = \arg \max_{\mathbf{w}, v} \quad & v \\ \text{s.t.} \quad & v \leq \phi(\mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta})), \quad \forall \boldsymbol{\theta} \in \Theta. \end{aligned} \quad (4.3)$$

This formulation highlights that the objective is to maximise a lower bound v on the information criterion over the entire uncertainty set.

Solving this problem is challenging, as it constitutes a semi-infinite optimisation problem (Hettich et al., 2025), with a finite number of decision variables but infinitely many constraints due to the continuous parameter space Θ . A common approximation replaces the continuous uncertainty set with a finite set of sampled parameter realisations, thereby converting the problem into a finite (but potentially large-scale) optimisation problem. However, the associated computational burden is substantial: each parameter sample typically requires numerical integration of the system dynamics, evaluation of sensitivity matrices, and computation of the FIM. This computational cost becomes particularly prohibitive for nonlinear dynamic systems with high-dimensional parameter spaces.

To address these challenges, three strategies for maximin sampling time design under parametric uncertainty are considered: fixed worst-case design, alternating worst-case design, and exchange-based maximin design.

4.2.1 Fixed worst-case approach

In this approach, a worst-case parameter realisation is first identified under a baseline sampling scheme (e.g., uniform sampling) and subsequently fixed during the design optimisation. The worst-case parameter is obtained as

$$\boldsymbol{\theta}^{\text{wc}} = \arg \min_{\boldsymbol{\theta} \in \Theta} \phi \left(\mathbf{FIM} \left(\mathbf{w}^{\text{ref}}, \boldsymbol{\theta} \right) \right), \quad (4.4)$$

where $\mathbf{w}^{\text{ref}}$ denotes a uniformly spaced reference sampling design. The parameter $\boldsymbol{\theta}^{\text{wc}}$ is then treated as fixed in the subsequent optimisation of the sampling design.

This approach provides a computationally efficient baseline strategy, as it avoids iterative updates of the worst-case parameter. However, it neglects the dependence of the worst-case parameter on the sampling design. Consequently, the identified parameter may no longer be critical once the sampling scheme is modified, and the resulting design does not guarantee robustness with respect to the full uncertainty set. Therefore, this approach should be regarded as an approximation rather than a true maximin design.

4.2.2 Alternating worst-case approach

The alternating worst-case design iteratively updates the sampling design and the associated worst-case parameter. Starting from an initial sampling design $\mathbf{w}^{(0)}$, the worst-case parameter is first identified, after which the sampling design is re-optimised with respect to this parameter. This procedure can be expressed as

$$\boldsymbol{\theta}^{(k+1)} = \arg \min_{\boldsymbol{\theta} \in \Theta} \phi \left(\mathbf{FIM} \left(\mathbf{w}^{(k)}, \boldsymbol{\theta} \right) \right), \quad \mathbf{w}^{(k+1)} = \arg \max_{\mathbf{w}} \phi \left(\mathbf{FIM} \left(\mathbf{w}, \boldsymbol{\theta}^{(k+1)} \right) \right). \quad (4.5)$$

This alternating procedure allows the design to adapt to changes in the worst-case parameter and partially captures the coupling between the sampling design and parameter uncertainty. However, it does not explicitly retain previously identified critical parameter realisations. As a result, the method provides only a heuristic approximation to the maximin formulation and may exhibit oscillatory behaviour between competing worst-case scenarios in practice.

4.2.3 Exchange-based maximin approach

In this approach, robustness is enforced by maintaining a growing set of worst-case parameter scenarios. At each iteration, the sampling design is obtained by maximising the minimum information criterion over the current scenario set, after which a new worst-case parameter is identified under the updated design. This exchange process continues until no further violating parameter can be found, yielding a design that approximates the true maximin solution over the uncertainty space.

To more rigorously enforce the maximin criterion in (4.2), an exchange-based solution strategy is adopted (Asprey and Macchietto, 2002; Dette et al., 2005; Fiacco and Kortanek, 1983). Unlike the fixed and alternating approaches, this method explicitly retains all previously identified worst-case parameter scenarios during the design optimisation, thereby providing a systematic approximation to the underlying semi-infinite maximin problem.

The procedure is summarised in Algorithm 2. Starting from an initial parameter value $\boldsymbol{\theta}^{[1]}$, the method iteratively refines the sampling design and the associated scenario set. At iteration K , the design problem is formulated as

$$\begin{aligned} [\mathbf{w}^{[K]}, \mathbf{v}^{[K]}] = \arg \max_{\mathbf{w}, \mathbf{v}} \quad & \mathbf{v} \\ \text{s.t.} \quad & \mathbf{v} \leq \phi \left(\mathbf{FIM} \left(\mathbf{w}, \boldsymbol{\theta}^{[i]} \right) \right), \quad i = 1, \dots, K, \end{aligned} \quad (4.6)$$

which involves a finite number of constraints corresponding to the accumulated worst-case scenarios.

Algorithm 2: Exchange-based iterative algorithm for maximin robust sampling time design

Data: Initial parameter value $\boldsymbol{\theta}^{[1]}$, uncertainty set $\boldsymbol{\Theta}$, candidate time grid $\mathbf{T}_m$, number of sampling points N_{st} , criterion $\phi(\cdot)$

Result: Exchange-based maximin sampling time design $\mathbf{w}^{[K]}$

```

1 Set  $K \leftarrow 1$ ;
2 Initialise scenario set  $\mathcal{S}^{[1]} \leftarrow \{\boldsymbol{\theta}^{[1]}\}$ ;
3 repeat                                     // no further violating parameter can be found
    // Solve finite maximin problem over current scenario set
4    $[\mathbf{w}^{[K]}, v^{[K]}] \leftarrow \arg\max_{\mathbf{w}, v} v, \text{ s.t. } v \leq \phi(\mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta})), \forall \boldsymbol{\theta} \in \mathcal{S}^{[K]}$ ;
    // Identify worst-case parameter under current design
5    $\boldsymbol{\theta}^{[K+1]} \leftarrow \arg\min_{\boldsymbol{\theta} \in \boldsymbol{\Theta}} \phi(\mathbf{FIM}(\mathbf{w}^{[K]}, \boldsymbol{\theta}))$ ;
    // Evaluate worst-case performance
6    $\hat{v}^{[K]} \leftarrow \phi(\mathbf{FIM}(\mathbf{w}^{[K]}, \boldsymbol{\theta}^{[K+1]}))$ ;
7   if  $\hat{v}^{[K]} < v^{[K]}$  then
        // Enrich scenario set
8        $\mathcal{S}^{[K+1]} \leftarrow \mathcal{S}^{[K]} \cup \{\boldsymbol{\theta}^{[K+1]}\}$ ;
9        $K \leftarrow K + 1$ .
10  end
11 until  $\hat{v}^{[K]} \geq v^{[K]}$ ;

```

For the resulting design $\mathbf{w}^{[K]}$, a new worst-case parameter $\boldsymbol{\theta}^{[K+1]}$ is identified by minimising the information criterion over the admissible uncertainty set. If this parameter leads to a strictly lower performance value, i.e. $\hat{v}^{[K]} < v^{[K]}$, it is added to the scenario set and the design is re-optimised. The algorithm terminates when no further parameter realisation can be found that degrades the design performance, i.e. when $\hat{v}^{[K]} \geq v^{[K]}$. In this manner, the original semi-infinite maximin problem is transformed into a sequence of finite optimisation problems with progressively enriched constraint sets, enabling a more faithful approximation of the true worst-case design.

This exchange-based formulation provides the most rigorous approximation among the considered maximin strategies, but at the cost of increased computational complexity, as the number of scenarios grows during the iterative process.

The three strategies in this section represent increasing levels of approximation to the true maximin formulation, trading off computational efficiency against robustness guarantees.

4.3 Pseudo-Bayesian Robust Experimental Design

4.3.1 General formulation

Unlike the maximin design, which ensures robustness over the entire parameter uncertainty space by optimising against the worst-case parameter, the pseudo-Bayesian design accounts for parametric uncertainty in an expected-value sense by optimising a statistical performance criterion. Let the parametric uncertainty be described by a probability density function (pdf), i.e., $\boldsymbol{\theta} \sim p(\boldsymbol{\theta})$. The pseudo-Bayesian RED can then be formulated as (Chaloner and Larntz, 1989):

$$\mathbf{w}^* = \arg \min_{\mathbf{w}} \mathbb{E}_{\boldsymbol{\theta}} \left\{ \phi \left(\mathbf{FIM}^{-1}(\mathbf{w}, \boldsymbol{\theta}) \right) \right\}. \quad (4.7)$$

This RED method is commonly referred to as *pseudo-Bayesian design*. Although it incorporates a probabilistic description of parametric uncertainty, the optimisation is performed with respect to an expectation-based utility function rather than a fully Bayesian decision-theoretic framework. In particular, the design criterion typically corresponds to the expected value of a scalar performance measure, rather than the minimisation of a formally defined posterior expected loss. This distinction differentiates pseudo-Bayesian design from fully Bayesian experimental design, where decisions are derived by integrating a loss function over the posterior distribution.

The scalarisation function $\phi(\cdot)$ is usually chosen according to classical optimality criteria, such as D-, A-, or E-optimality, often in their logarithmic forms. However, the formulation in (4.7) requires repeated evaluation of the inverse FIM and its associated scalarisation (e.g., determinant) for each parameter sample, which can be computationally demanding.

To alleviate this burden and provide alternative robustness interpretations, several pseudo-Bayesian formulations have been proposed by altering the order of the expectation, scalarisation, and matrix inversion operators. Common variants include:

- Maximisation of the expected scalarised FIM:

$$\mathbf{w}^* = \arg \max_{\mathbf{w}} \mathbb{E}_{\boldsymbol{\theta}} \{ \phi(\mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta})) \}.$$

- Maximisation of the scalarised expected FIM:

$$\mathbf{w}^* = \arg \max_{\mathbf{w}} \phi(\mathbb{E}_{\boldsymbol{\theta}} \{ \mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta}) \}).$$

These two pseudo-Bayesian design formulations are fundamentally different in both interpretation and robustness properties, as the order of expectation, scalarisation, and matrix inversion directly affects how parameter uncertainty is propagated into the design criterion.

4.3.2 Pseudo-Bayesian design under D-criterion

Under the (logarithmic) D-optimal design, the pseudo-Bayesian design problem in (4.7) can be written as:

$$\mathbf{w}^* = \arg \min_{\mathbf{w}} \mathbb{E}_{\boldsymbol{\theta}} \{ \log \det(\mathbf{FIM}^{-1}(\mathbf{w}, \boldsymbol{\theta})) \}. \quad (4.8)$$

Since $\det(\mathbf{FIM}^{-1}) = \det(\mathbf{FIM})^{-1}$, it follows that

$$\log \det(\mathbf{FIM}^{-1}) = -\log \det(\mathbf{FIM}).$$

Consequently, the inverse operator can be eliminated from (4.8), yielding the equivalent optimisation problem

$$\mathbf{w}^* = \arg \max_{\mathbf{w}} \mathbb{E}_{\boldsymbol{\theta}} \{ \log \det(\mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta})) \}. \quad (4.9)$$

Although this reformulation eliminates the need for explicit matrix inversion, it still requires evaluating the logarithmic determinant of the FIM across all parameter samples. To further reduce computational cost, one might consider moving the expectation operator inside the logarithmic determinant so that the determinant is evaluated only once for the expected FIM. However, this manipulation is not generally valid.

In particular, Jensen's inequality (Boyd, 2004) implies that, since the logarithmic determinant is concave over the cone of positive definite matrices,

$$\mathbb{E}_{\boldsymbol{\theta}} \{\log \det(\mathbf{FIM})\} \leq \log \det(\mathbb{E}_{\boldsymbol{\theta}} \{\mathbf{FIM}\}). \quad (4.10)$$

Equality holds only when the FIM is invariant with respect to $\boldsymbol{\theta}$.

The inequality in (4.10) shows that exchanging the expectation and logarithmic determinant operators fundamentally changes the design objective. The expectation criterion evaluates the average information volume over the parameter uncertainty space, whereas the mean-FIM formulation $\log \det(\mathbb{E}_{\boldsymbol{\theta}} \{\mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta})\})$ corresponds to the information volume of an averaged model. These two criteria are equivalent only when the FIM is invariant with respect to the parameters, which is rarely satisfied in nonlinear dynamical systems.

The mean-FIM formulation implicitly assumes that information contributions obtained at different parameter values can be combined linearly. For nonlinear models, however, sensitivity matrices and their dominant information directions vary across the uncertainty space. As a result, the expected FIM may combine information along directions that do not coexist at any single parameter realisation, leading to an overly optimistic assessment of parameter identifiability.

From a robustness perspective, this averaging effect is problematic. Designs obtained by maximising the determinant of the expected FIM may perform well on average while still producing ill-conditioned or near-singular FIMs for certain admissible parameter values. In such cases, poor identifiability at unfavourable parameter realisations is masked by aggregation, and no protection against worst-case scenarios is provided.

In (4.9), the logarithmic determinant is directly related to the volume of the parameter confidence ellipsoid, and taking its expectation corresponds to maximising the geometric mean of the information volume across the uncertainty space. Compared with arithmetic averaging, geometric averaging penalises parameter values associated with poor identifiability more strongly, thereby reducing the risk that good performance in favourable regions compensates for near-singular behaviour elsewhere. Therefore, this criterion remains sensitive to poorly informative parameter regions while remaining expectation-based, without collapsing to an overly conservative worst-case formulation. The formulation in (4.9) also avoids the need for explicit matrix inversion at each parameter realisation, offering improved computational efficiency compared to the formulation in (4.8).

For these reasons, the expected logarithmic determinant of the FIM, as defined in (4.9), is adopted as the pseudo-Bayesian design criterion in the remainder of this work.

4.3.3 Pseudo-Bayesian design under E- and A-criterion

The preceding discussion highlights that the robustness of pseudo-Bayesian designs depends critically on how parametric uncertainty is aggregated within the design criterion. Similar observations apply to E- and A-optimal criteria.

Under the E-criterion, a natural pseudo-Bayesian formulation is

$$\mathbf{w}^* = \arg \max_{\mathbf{w}} \mathbb{E}_{\boldsymbol{\theta}} \{ \lambda_{\min}(\mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta})) \}, \quad (4.11)$$

which corresponds to an arithmetic averaging of the smallest eigenvalue over the uncertainty space. As a result, poor identifiability at certain parameter values may be compensated by favourable behaviour at other parameter values. Applying the E-criterion to the FIM,

$$\mathbf{w}^* = \arg \max_{\mathbf{w}} \lambda_{\min}(\mathbb{E}_{\boldsymbol{\theta}} \{ \mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta}) \}), \quad (4.12)$$

further weakens robustness by smoothing directional information prior to evaluating the worst-case sensitivity direction.

For the A-criterion, the pseudo-Bayesian formulation is given by

$$\mathbf{w}^* = \arg \min_{\mathbf{w}} \mathbb{E}_{\boldsymbol{\theta}} \left\{ \text{tr}(\mathbf{FIM}^{-1}(\mathbf{w}, \boldsymbol{\theta})) \right\}, \quad (4.13)$$

which averages the total parameter variance across parameters in an arithmetic sense. As with the E-criterion, this formulation does not explicitly penalise near-singular FIMs unless such behaviour occurs over a sufficiently large portion of the uncertainty space.

Compared with the expected log-determinant D-optimal design, pseudo-Bayesian E- and A-optimal criteria rely entirely on arithmetic averaging and therefore provide weaker implicit protection against poorly informative parameter regions under parametric uncertainty. For this reason, they are not adopted as primary design criteria in this work, but are considered only for comparative evaluation.

4.3.4 Numerical solution strategy for pseudo-Bayesian design

The numerical solution of pseudo-Bayesian experimental design problems involves two conceptually distinct components: (i) the evaluation of expectation-based design criteria with respect to parametric uncertainty, and (ii) the optimisation of the resulting objective with respect to the design variables. Accordingly, different numerical methods are required at each stage of the solution process.

Gaussian quadrature approximation The use of expectation-based D-optimal criteria in RED for dynamic systems can be traced back to the work of Asprey and Macchietto (2002), where both expected-value and worst-case formulations of the D-criterion were embedded within a unified optimisation framework. In that context, multidimensional Gaussian-type quadrature rules were employed to evaluate expectations over parametric

uncertainty, providing accurate numerical integration for problems involving a small number of uncertain parameters.

Gaussian quadrature (GQ) provides a deterministic numerical integration technique for approximating weighted integrals of the form

$$\int_{\Theta} \psi(\theta) \rho(\theta) d\theta, \quad (4.14)$$

where $\psi(\theta)$ denotes the integrand and $\rho(\theta)$ is a prescribed weight function. The integral is approximated by a weighted sum

$$\int_{\Theta} \psi(\theta) \rho(\theta) d\theta \approx \sum_{i=1}^m q_i \psi(\theta_i), \quad (4.15)$$

where θ_i and q_i denote the quadrature nodes and weights, respectively. For an m -point GQ rule associated with the prescribed weight function, the approximation is exact for polynomials of degree up to $2m - 1$ (Golub and Welsch, 1969).

For uniformly distributed uncertainty $\theta \sim U[a, b]$, the expectation

$$\mathbb{E}[\psi(\theta)] = \frac{1}{b-a} \int_a^b \psi(\theta) d\theta \quad (4.16)$$

can be approximated using an m -point Gauss–Legendre rule as

$$\mathbb{E}[\psi(\theta)] \approx \frac{1}{2} \sum_{i=1}^m q_i \psi(\theta_i), \quad (4.17)$$

where θ_i denotes the Gauss–Legendre node obtained by mapping the corresponding standard node from $[-1, 1]$ to $[a, b]$, and q_i denotes the associated standard Gauss–Legendre quadrature weight (Golub and Welsch, 1969).

For a vector of independent uniformly distributed uncertain parameters $\boldsymbol{\theta} = (\theta_1, \dots, \theta_p)$, with $\theta_k \sim U[a_k, b_k]$, $k = 1, \dots, p$, the expectation of a multivariate function can be approxi-

mated using a tensor-product Gauss–Legendre rule,

$$\mathbb{E}[\psi(\boldsymbol{\theta})] \approx \frac{1}{2^p} \sum_{i_1=1}^m \cdots \sum_{i_p=1}^m \left(\prod_{k=1}^p q_{i_k} \right) \psi(\theta_{1,i_1}, \dots, \theta_{p,i_p}), \quad (4.18)$$

where each θ_{k,i_k} is obtained by mapping the corresponding standard Gauss–Legendre node to $[a_k, b_k]$. The tensor-product rule therefore requires m^p deterministic parameter scenarios, which grows exponentially with the number of uncertain parameters.

Within the pseudo-Bayesian experimental design framework, the integrand typically takes the form

$$\psi(\boldsymbol{\theta}) = \phi(\mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta})), \quad (4.19)$$

where $\phi(\cdot)$ denotes a scalar design criterion, such as the logarithmic D-optimality criterion $\phi(\mathbf{FIM}) = \log \det(\mathbf{FIM})$. GQ therefore evaluates the expected design objective by computing the FIM at a finite number of selected parameter scenarios.

GQ can also be adapted to other uncertainty distributions by selecting appropriate orthogonal polynomial families. For example, Gauss–Hermite quadrature is commonly used for normally distributed parameters, while Gauss–Laguerre quadrature applies to exponential-type distributions.

Despite their high integration accuracy in low-dimensional settings, GQ rules suffer from an exponential growth in the number of quadrature points with respect to the dimension of the uncertainty space (the so-called curse of dimensionality). This limitation becomes particularly restrictive for nonlinear dynamic models, where each quadrature node requires repeated numerical integration of state and sensitivity equations. These limitations motivate the adoption of sample-based approximation methods, such as sample-average approximation, which avoid the exponential growth in the number of scenarios associated with tensor-product quadrature rules.

Monte Carlo sampling and sample-average approximation The pseudo-Bayesian experimental design problem is formulated as an expectation-based optimisation problem

with respect to parametric uncertainty. To enable numerical solution, a sample-average approximation (SAA) is adopted, in which the expectation in the pseudo-Bayesian design criterion is replaced by an empirical average over a fixed finite set of sampled parameter scenarios (Homem-de Mello and Bayraksan, 2014; Shapiro, 2014). Specifically, a set of N parameter samples $\{\boldsymbol{\theta}_i\}_{i=1}^N$ is drawn from the prescribed uncertainty distribution, and the pseudo-Bayesian objective is approximated by the sample-average function, i.e.,

$$\mathbb{E}_{\boldsymbol{\theta}} \{ \phi(\mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta})) \} \approx \frac{1}{N} \sum_{i=1}^N \phi(\mathbf{FIM}(\mathbf{w}, \boldsymbol{\theta}_i)).$$

The resulting sample-average problem is deterministic. Importantly, the parameter samples are fixed throughout the optimisation process, ensuring reproducible objective evaluations and avoiding the stochastic variability associated with resampling. As the number of scenarios increases, the solution of the sample-average problem converges, under appropriate regularity conditions, to that of the original expectation-based design problem.

In this work, SAA provides a flexible sample-based approximation of the expectation and is considered alongside GQ as a deterministic alternative for low-dimensional uncertainty.

Numerical optimisation of the sample-average objective Once the expectation-based objective has been approximated using SAA, the resulting problem becomes a deterministic finite-scenario sampling-time optimisation problem. Since the sampling times are selected from a finite candidate set, the problem retains the discrete subset-selection structure described previously.

In this work, the SAA objective is optimised using a Powell-type discrete exchange procedure (Yu et al., 2015, 2018a). Starting from an initial subset of N_{st} sampling points, the procedure performs one-for-one exchanges between selected and unselected candidate points. Each selected sampling time is temporarily removed and replaced by the candidate point that gives the largest improvement in the sample-average design criterion. Refinement sweeps are repeated until no further improvement is obtained.

The procedure is a local discrete search method and therefore does not guarantee global optimality. However, it operates directly on the original finite candidate set and avoids introducing a continuous relaxation of the sampling-selection variables.

4.4 Distribution-based Robustness Evaluation Framework

To enable a systematic comparison of sampling time design strategies under parametric uncertainty, a unified robustness evaluation framework is established in this section. The objective of the evaluation is to assess the information content of a given sampling design across the admissible uncertainty space. For each parameter realisation, the information content is quantified using the D-value, defined as the logarithmic determinant of the corresponding Fisher information matrix. This metric reflects the overall volume of the parameter confidence region and is therefore adopted as the primary performance indicator.

Rather than relying on single-point evaluation at nominal parameter values, robustness is assessed through the distribution of D-values obtained over a set of parameter samples. This distribution-based evaluation captures the variability of information content induced by parametric uncertainty and provides a more comprehensive characterisation of design performance.

To summarise the distribution of D-values, four statistical indicators are employed:

- the minimum value, representing worst-case performance;
- the lower 5% quantile (q_{05}), characterising near-worst-case behaviour;
- the median, reflecting typical performance; and
- the interquartile range (IQR), measuring the dispersion and stability of the design.

Parameter samples are generated from the prescribed uncertainty distribution, and the same sample set is used consistently across all compared designs to ensure a fair evaluation.

For each sample, the Fisher information matrix is computed and the corresponding D-value is evaluated.

This framework allows different design strategies to be compared in terms of robustness, typical performance, and stability in a unified manner. In particular, improvements in lower-tail behaviour indicate enhanced protection against poorly informative parameter realisations, while reductions in dispersion reflect increased robustness to uncertainty. The trade-off between worst-case protection and typical performance is therefore explicitly captured through the joint analysis of these statistical indicators.

4.5 Enzyme Reaction System Case Study

4.5.1 Brief system introduction

The enzyme reaction system considered in this section represents a kinetically controlled synthesis process that is widely adopted as a benchmark model in studies of enzyme-catalysed reactions (Yu et al., 2018a). Reaction schemes of this type arise in a variety of industrially relevant processes, including semi-synthetic penicillin production, and therefore provide a meaningful yet well-controlled testbed for methodological investigations in experimental design.

A schematic representation of the reaction network is shown in Figure 4.1. The process involves a donor substrate S , a nucleophile N , and an enzyme catalyst E , which interact to form a desired product Q , a hydrolysis by-product R , and a leaving-group product P . The enzyme participates in the reaction through several intermediate complexes (ES , E^* , EQ , and ER), while water W is treated as constant due to its large excess relative to other species. The kinetics of the reaction network are governed by rate constants k_1 to k_6 .

For the purpose of experimental design, the enzyme reaction system is characterised by:

- a nonlinear dynamic model governed by mass-action kinetics;

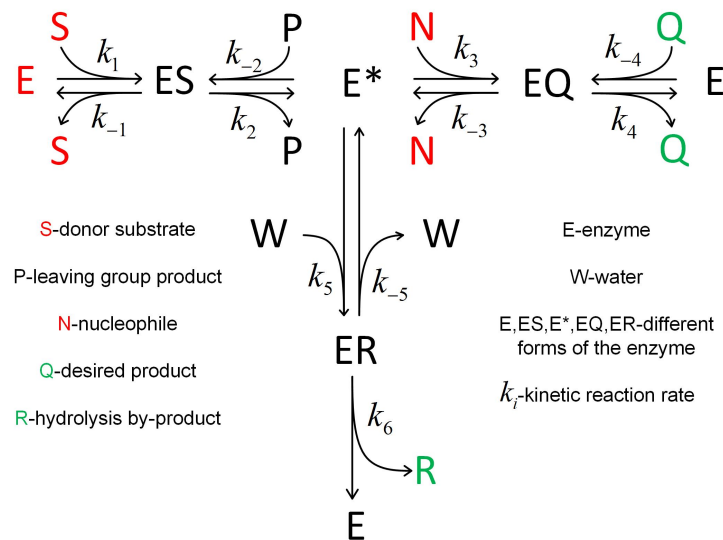


Fig. 4.1 Enzyme reaction system

- fixed experimental conditions throughout the experimental duration;
- a subset of kinetic parameters, namely k_2 , k_{-3} , and k_5W , with nominal values of 100, 200, and 5000, respectively, selected for estimation;
- a measurement vector consisting of the concentrations of S , P , N , Q , and R , since direct measurement of enzyme complexes is impractical due to their low concentrations.

The nominal parameter values, obtained from the literature, are used as the reference values for constructing the parameter uncertainty sets considered in the subsequent experimental design studies.

The complete reaction mechanism, governing ordinary differential equations, full parameter set, and initial conditions are reported in Appendix A for completeness and reproducibility.

Although enzymatic reactions are in practice influenced by environmental factors such as temperature, pH, and enzyme deactivation, these effects are neglected at this stage in order to isolate the impact of parametric uncertainty. A preliminary equilibrium and local sensitivity analysis, provided in Appendix A, was used to define the parameter subset considered in this study. The parameters k_2 , k_{-3} , and k_5W were selected because they provide an identifiable

parameter subset with informative and temporally varying sensitivity profiles under the prescribed measurement configuration and operating conditions. This makes the system suitable for investigating how the allocation of a limited sampling budget affects parameter information.

The exclusion of the remaining parameters does not imply that parameters with lower sensitivities are unimportant or should not be targeted in experimental design. Their inclusion would introduce a broader parameter-identifiability problem that may also depend on other experimental design variables. The present case study instead isolates the effect of sampling-time allocation, while the input profile, measured variables, and other experimental conditions are kept fixed.

This case study serves as a baseline for evaluating sampling time design strategies within the proposed distribution-based evaluation framework. Specifically, classical and robust experimental designs are compared by analysing their performance over a range of parameter realisations within the prescribed uncertainty bounds. This enables the assessment of design quality not only in terms of nominal performance, but also with respect to robustness, variability, and sensitivity to parametric uncertainty.

4.5.2 Classical optimal sampling time design and results analysis

This section focuses on classical OED, in which parameter uncertainty is not explicitly considered, and serves as a baseline for subsequent robustness analysis. The optimal sampling time design for this enzyme reaction system is solved using the discretisation approach described in (3.43), under the following assumptions.

- All five measurable states are sampled simultaneously.
- Assume $N_T = 600$ measurable sampling time points, $\mathbf{t}_m = [10 : 10 : 6000]^\top$ s.
- Suppose the design needs to select $N_{st} = 21$ sampling points from $\mathbf{t}_m$.

- The measurement error is assumed to be independent and normally distributed with standard deviation being linear to model output: $\sigma_i = 0.1x_i + 10^{-4}$.

The optimal sampling-time design is solved under D-, E-, and A-optimality using three numerical approaches: a Powell-type discrete exchange procedure, a continuous relaxation solved using MATLAB `fmincon` with the active-set algorithm, and a semi-definite programming (SDP) formulation for the E-optimal criterion solved using YALMIP/SeDuMi.

For the Powell-type procedure described in Algorithm 1, 100 outer iterations and 4 inner refinement sweeps are used. With $N_{st} = 21$, this corresponds to 8,400 one-for-one exchange operations. Because the FIM is additive with respect to the selected sampling times, the contribution of each candidate point can be precomputed, so each exchange requires only matrix updates rather than repeated model simulation. The procedure operates directly on the discrete candidate set, whereas the `fmincon`- and SDP-based methods solve continuous relaxations. The Powell-type procedure is therefore computationally convenient for the present discrete sampling-time problem, although it remains a local search and does not guarantee global optimality.

To assess sensitivity to the initial sampling subset, the nominal D-optimal sampling-time optimisation was repeated using 10 different random initialisations. All 10 runs converged to the same final sampling schedule and numerically identical D-optimal criterion values, with only machine-level numerical differences. This indicates negligible sensitivity to the tested initialisations under the adopted optimisation settings, although it does not constitute a proof of global optimality.

Sampling strategy results

The sampling strategies obtained under D-, E-, and A-optimality are reported in Table 4.1. Figure 4.2 illustrates the sampling locations together with the absolute parameter sensitivities. The circles represent the sampling time when the states should be measured.

All optimal designs concentrate sampling points in regions where parameter sensitivities are high, confirming that the information content is dominated by specific dynamic phases of the system. Powell's method (blue circles) produces compact and structured sampling clusters, indicating a consistent identification of the most informative time windows. In contrast, *fmincon* results (red circles) exhibit more scattered patterns, reflecting sensitivity to the initial equally spaced design and the effects of relaxation. The SDP-based E-optimal design (yellow circles) aligns closely with the Powell and *fmincon* E-optimal solutions, suggesting that the dominant sensitivity structure is sufficiently captured even under relaxed formulations for this criterion.

The clustered sampling patterns should be interpreted in the context of the discretised in-silico design problem. In the present enzyme case study, the candidate time grid has a resolution of 10 s, which allows multiple measurements to be selected within a relatively narrow time window. Whether such sampling frequencies are practically feasible depends on the measurement technology, sample-processing time, and the extent to which repeated sampling perturbs the system.

In practical applications, these limitations can be incorporated explicitly by imposing additional constraints, such as a minimum interval between consecutive sampling times, a maximum number of measurements within a prescribed time window, or restrictions associated with sample acquisition and processing. The sampling clusters identified here should therefore be interpreted primarily as indicating the most informative temporal regions under the assumed design constraints.

Performance analysis

Tables 4.2 and 4.3 summarise the objective values and computational times obtained using the three numerical approaches. The reported D-, E-, and A-optimal values correspond to the log-determinant of the FIM, the logarithm of its minimum eigenvalue, and the negative logarithm of the trace of its inverse, respectively. Larger values therefore indicate better

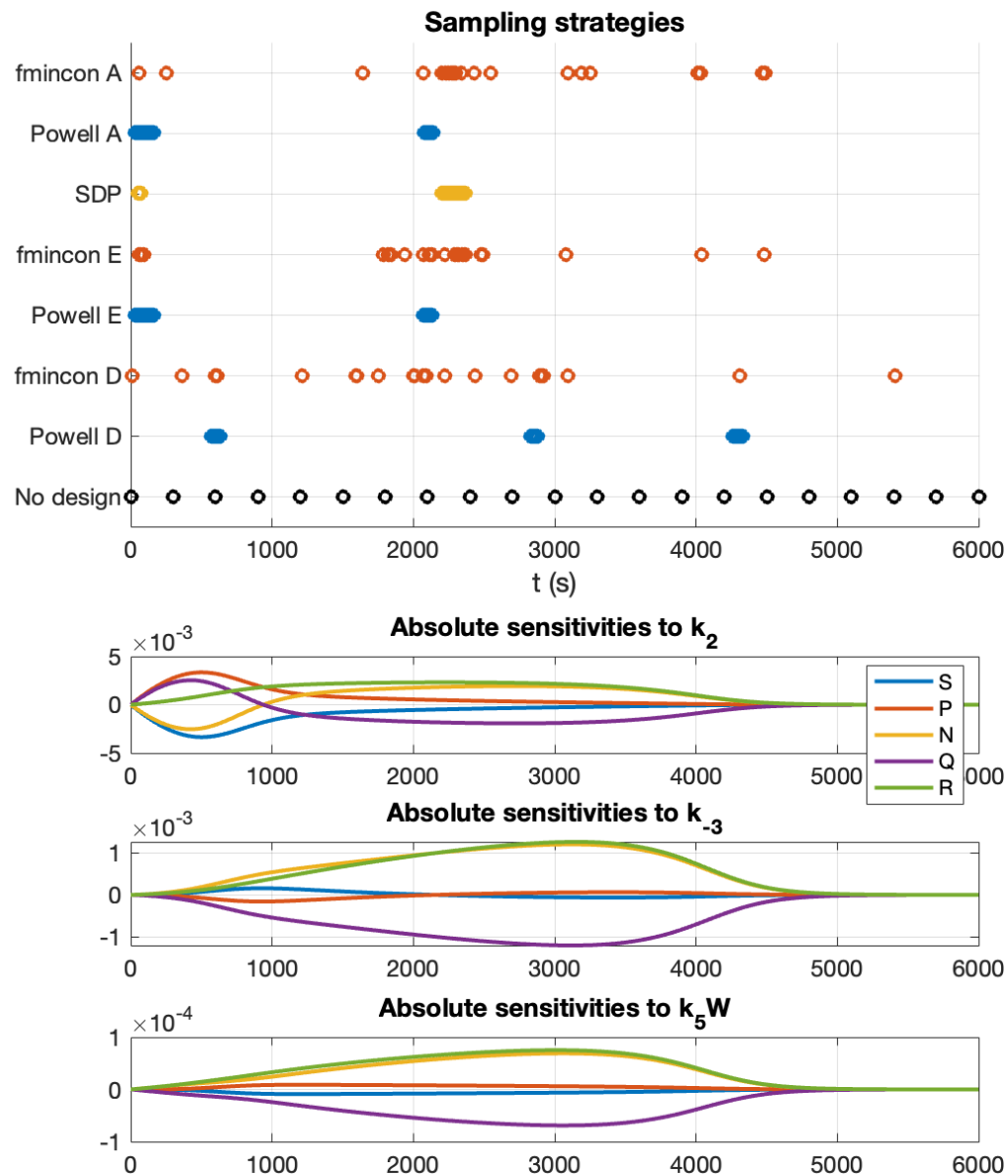


Fig. 4.2 Absolute parameter sensitivities and optimal sampling strategies for the enzyme reaction system under D-, E- and A-optimal criterion (nominal parameters, no uncertainty)

Table 4.1 Optimal sampling time strategies for the enzyme reaction system under D-, E-, and A-optimal criteria (nominal parameters, no uncertainty)

Methods	Results of sampling time points (s)
No design	[0:300:6000]
Powell D	[570:10:630, 2830:10:2880, 4260:10:4330]
fmincon D	[10, 360, 600, 610, 1210, 1590, 1600, 1750, 2000, 2010, 2070, 2090, 2220, 2440, 2690, 2890, 2910, 2920, 3090, 4310, 5410]
Powell E	[30:10:160, 2070:10:2130]
fmincon E	[60, 70, 90, 1790, 1820, 1840, 1940, 2070, 2110, 2130, 2220, 2290, 2310, 2320, 2350, 2370, 2480, 2490, 3080, 4040, 4480]
SDP E	[50, 60, 70, 2200:10:2370]
Powell A	[30:10:160, 2080:10:2140]
fmincon A	[60, 250, 1640, 2070, 2200, 2230, 2250, 2270:10:2300, 2340, 2430, 2550, 3090, 3190, 3250, 4010, 4030, 4470, 4490]

performance under the adopted formulations. All computations were performed in MATLAB R2024b on a Mac mini with Apple silicon M4.

The Powell-type discrete exchange procedure achieves the highest objective value under all three criteria. It is also the fastest method for D-optimality, whereas SDP is the fastest for E-optimality. The fmincon-based continuous relaxation gives lower objective values and, for the D- and A-optimal criteria, performs slightly worse than the equally spaced design after conversion to a discrete sampling schedule. This illustrates that the continuous relaxation may lose design quality when the relaxed solution is mapped back to the discrete candidate set.

Comparison of optimality criteria

Figure 4.3 presents the confidence ellipsoid projections for parameters k_2 , k_{-3} , and k_5W . All optimal designs significantly reduce parameter uncertainty compared to the equally spaced sampling strategy, particularly for k_2 and k_5W . The E- and A-optimal designs produce nearly identical confidence ellipsoids, consistent with their similar sampling strategies. In contrast,

Table 4.2 Optimal objective values (log-scale) of classical sampling time designs (OED) for the enzyme reaction system under D-, E-, and A-optimal criteria

Optimal value	D-optimal	E-optimal	A-optimal
No design	-12.453	-11.4178	-11.4179
Powell	-10.743	-10.238	-10.241
fmincon	-12.535	-11.280	-11.620
SDP	-	-11.309	-

Table 4.3 Computational time of classical sampling time design methods (OED) for the enzyme reaction system

Run time	D-optimal	E-optimal	A-optimal
Powell	1.22s	6.04s	18.24s
fmincon	8.05s	8.25s	9.31s
SDP	-	0.40s	-

the D-optimal design yields the smallest confidence ellipsoids in the comparisons shown, consistent with its objective of maximising the determinant of the FIM and reducing the joint confidence-region volume. Therefore, the Powell-type D-optimal design is selected as the baseline strategy for the subsequent RED analysis.

The above results correspond to classical OED and do not account for parametric uncertainty. Since classical OED relies on local sensitivities evaluated at nominal parameter values, its performance may degrade significantly when the true parameter values deviate from these nominal conditions. This motivates the use of RED strategies.

In the following sections, robust sampling time design methods are investigated using the proposed distribution-based evaluation framework. The analysis focuses on:

- robustness with respect to worst-case parameter realisations,
- average performance across the uncertainty space,

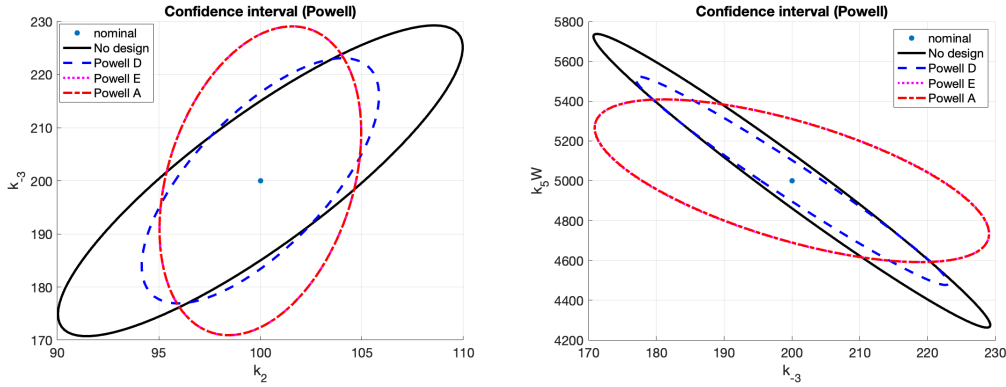


Fig. 4.3 Confidence ellipsoids projections on $k_2 - k_5W$ surface (left) and $k_{-3} - k_5W$ surface (right) for the enzyme reaction system under classical optimal sampling time designs

- variability induced by parameter uncertainty, and
- sensitivity to the assumed uncertainty distribution.

All robust sampling designs are computed using Powell's method under the D-optimal criterion, due to its favourable balance between design quality and computational efficiency observed in the nominal case.

4.5.3 Maximin sampling time design and results analysis

The parametric uncertainty is assumed to follow a uniform distribution over the bounded domain $\boldsymbol{\theta} \in [0.01\boldsymbol{\theta}^*, 10\boldsymbol{\theta}^*]$, where $\boldsymbol{\theta}^* = [100, 200, 5000]$ denotes the nominal values of the kinetic parameters listed in Table A.2. This wide uncertainty range represents severe parametric uncertainty and is intentionally chosen to assess the robustness of sampling time designs beyond the regime where classical OED is expected to perform reliably.

Three maximin-based sampling time design strategies are considered: fixed worst-case design, alternating worst-case design, and exchange-based maximin design. Worst-case parameter identification is performed using both Monte Carlo (MC) sampling and particle swarm optimisation (PSO) to account for the strong nonlinearity of the model and the large uncertainty domain. For the MC-based approach, 10,000 samples are generated, and

Table 4.4 Maximin sampling time strategies for the enzyme reaction system under uniform parametric uncertainty in $[0.01\theta^*, 10\theta^*]$

Algorithm	Results (s)	Run time
Fixed (MC)	[10:10:90, 140:10:250]	119s
Alternating (MC)	[10:10:90, 130:10:240] [10:10:120, 330:10:410]	215s
Exchange (MC)	[20:10:70, 160:10:240, 280, 320, 380, 420, 500, 650]	2067s
Fixed (PSO)	[10:10:90, 130:10:240]	58s
Alternating (PSO)	[10:10:90, 130:10:240] [10:10:120, 320:10:400]	1143s
Exchange (PSO)	[10:10:50, 150:10:230, 250, 290, 310, 370, 470, 560, 590]	956s

independent sample sets are used for each design run to mitigate potential bias induced by specific random realisations. For the PSO-based search, a swarm size of 30 particles and a maximum of 100 iterations are used.

Design results

The resulting sampling time designs and computational runtimes are summarised in Table 4.4. The fixed worst-case strategy yields a single sampling design obtained by optimising with respect to one identified worst-case parameter set. As expected, this approach is computationally efficient but does not adapt to changes in the sampling design, and therefore provides only a limited approximation to the true maximin solution.

For the alternating strategy, two distinct sampling designs are frequently observed, indicating an oscillatory two-cycle behaviour between the sampling design and the associated worst-case parameter. In the present case study, one of these alternating solutions coincides with the fixed worst-case design. To avoid infinite cycling, the number of iterations is capped at 20, and both alternating solutions are reported when this behaviour occurs. This behaviour

highlights the inherent instability of the alternating scheme when multiple competing worst-case parameter realisations exist.

In contrast, the exchange-based maximin design produces sampling strategies with a richer temporal structure, where sampling points are distributed across multiple dynamically informative regions. This reflects its ability to account for multiple worst-case scenarios simultaneously, thereby providing a closer approximation to the true maximin solution over the uncertainty space.

Across all three strategies, both the MC-based and the PSO-based implementations yield highly consistent sampling time designs, indicating that the identified worst-case parameters are relatively insensitive to the choice of global search method. This consistency suggests that the dominant worst-case regions of the parameter space are well-defined despite the large uncertainty range.

In terms of computational efficiency, the fixed worst-case design is the least expensive, while the exchange-based maximin design incurs the highest computational cost due to iterative scenario enrichment and repeated solution of finite maximin subproblems. The computational behaviour of the alternating strategy depends strongly on the worst-case identification method: MC-based implementations benefit from precomputed FIM evaluations, whereas PSO-based implementations require repeated optimisation and therefore exhibit significantly higher computational cost.

Robustness evaluation

Robustness with respect to parametric uncertainty is evaluated using 5,000 independent parameter samples drawn from the uniform uncertainty space $[0.01\theta^*, 10\theta^*]$. For each parameter realisation, the D-value, defined as the logarithmic determinant of the corresponding FIM, is computed for the classical OED and the maximin-based sampling time designs obtained using PSO.

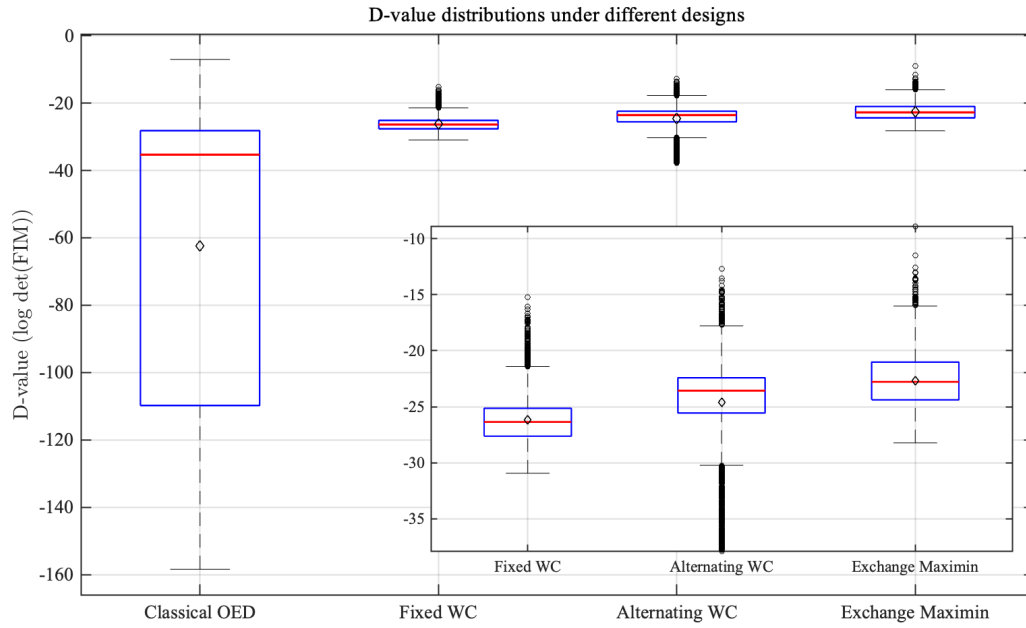


Fig. 4.4 Distribution of D-values for the enzyme reaction system under classical OED and maximin sampling time designs with uniform parametric uncertainty in $[0.01\theta^*, 10\theta^*]$

Figure 4.4 presents the resulting D-value distributions using boxplots. The median is indicated by the central line, the box represents the IQR, whiskers extend to non-outlying values based on the 1.5IQR criterion, and outliers are shown as individual markers. The mean D-value is indicated by a diamond marker. The main panel displays the full distributions for the classical OED and the robust maximin designs, while the inset focuses on the robust designs only to facilitate a detailed comparison.

Table 4.5 summarises the statistical performance metrics, grouped into three categories: robustness, typical performance, and stability. Robustness is characterised by the minimum D-value and the lower quantile q_{05} , capturing worst-case and near-worst-case behaviour. Typical performance is assessed using the mean and median D-values, while stability is quantified by the standard deviation and the IQR, the latter providing a robust measure of dispersion.

Table 4.5 Statistical performance metrics of D-values for the enzyme reaction system under classical OED and maximin sampling time designs with uniform parametric uncertainty in $[0.01\theta^*, 10\theta^*]$

Performance metrics		OED	Fixed WC	Alternating WC	Exchange Maximin
Robustness	minimum	-158.4	-30.93	-37.86	-28.23
	q_{05}	-131.4	-29.53	-35.4	-26.19
Typical performance	mean	-62.34	-26.18	-24.59	-22.68
	median	-35.31	-26.36	-23.57	-22.78
Stability	std.	42.21	2.25	4.11	2.32
	IQR	81.58	2.49	3.14	3.37

The classical OED exhibits extremely poor robustness, as evidenced by its highly negative minimum and lower-quantile values and its very large dispersion. This indicates that designs optimised at nominal parameter values can lead to near-singular FIMs for a substantial portion of the uncertainty space. In other words, classical OED fails to provide reliable parameter identifiability under severe parametric uncertainty.

All three maximin-based designs substantially improve robustness compared with the classical OED, as reflected by the significant increase in the minimum and the q_{05} values and the drastic reduction in variability. This confirms that explicitly accounting for worst-case scenarios effectively mitigates the risk of poor identifiability.

Among the robust strategies, the fixed worst-case design achieves a pronounced improvement in lower-tail performance together with very low variability. However, this performance is tied to a single identified worst-case parameter and therefore does not guarantee protection against other critical regions of the uncertainty space.

The alternating worst-case design yields robustness metrics of a similar order, but exhibits a lower minimum value and larger variability. This behaviour is consistent with its oscillatory nature, which prevents the design from simultaneously accounting for multiple competing worst-case parameter realisations.

The exchange-based maximin design consistently achieves the best robustness performance, with the highest minimum and q_{05} values. This indicates that the design effectively protects against the most adverse parameter scenarios across the uncertainty domain. In addition, it attains the highest mean and median D-values, demonstrating that improved worst-case performance does not come at the expense of typical performance. While the exchange-based design exhibits a slightly larger IQR than the fixed worst-case design, the difference is marginal in absolute terms and remains significantly smaller than that of the classical OED. This indicates that the enhanced robustness is achieved without sacrificing stability. Overall, these results demonstrate that incorporating multiple worst-case scenarios through the exchange mechanism leads to a more balanced and reliable experimental design under severe parametric uncertainty.

Discussion

The above results demonstrate that incorporating worst-case considerations into the design process fundamentally improves robustness under severe parametric uncertainty. In contrast to the classical OED, which exhibits highly degraded worst-case performance and large variability, maximin-based designs effectively stabilise the information content across the uncertainty space.

A key observation is that a significant portion of the robustness improvement can already be achieved by the fixed worst-case design at minimal computational cost. This indicates that, for the present system, the dominant loss of information is driven by a limited set of critical parameter realisations. Targeting a single representative worst-case scenario is therefore sufficient to capture the main source of performance degradation, providing a computationally efficient approximation.

However, the limitations of this approximation become evident when multiple competing worst-case scenarios exist. The alternating worst-case design partially adapts to this situation but exhibits oscillatory behaviour, reflecting the absence of a mechanism to simultaneously

account for multiple critical parameter realisations. This leads to variability in performance and prevents consistent improvement of worst-case behaviour.

The exchange-based maximin design overcomes this limitation by explicitly incorporating all identified worst-case scenarios into the optimisation process. As a result, it provides a more faithful approximation to the underlying semi-infinite maximin problem, yielding consistently improved worst-case and typical performance. This confirms that robustness in nonlinear systems is inherently multi-scenario in nature and cannot, in general, be captured by single-scenario approximations.

Overall, these findings highlight a clear trade-off between computational efficiency and robustness. The fixed worst-case design offers a practical and efficient solution when computational resources are limited or when the uncertainty structure is dominated by a single critical region. In contrast, the exchange-based design is more appropriate when stringent robustness requirements necessitate reliable performance across the entire uncertainty space, and the computational cost is manageable.

4.5.4 Pseudo-Bayesian sampling time design and results analysis

Pseudo-Bayesian sampling time design is investigated under the same parametric uncertainty setting as the maximin case, namely a uniform distribution over $[0.01\theta^*, 10\theta^*]$, enabling a direct and consistent comparison between the two robustness paradigms.

Three pseudo-Bayesian designs are considered: maximisation of the determinant of the expected FIM (FIM-mean), and maximisation of the expected D-value (D-mean), approximated using SAA and GQ, respectively. All designs are obtained using Powell's method under D-optimality.

Design results

The resulting sampling time designs and computational runtimes are reported in Table 4.6. The three criteria lead to markedly different sampling time structures. The FIM-mean design

concentrates most sampling points within a narrow region near the end of the experimental horizon, indicating a strong preference for time intervals where sensitivities are consistently aligned across the uncertainty space. In contrast, both D-mean designs distribute sampling points more broadly over the entire time domain, capturing multiple dynamically informative regions.

This structural difference reflects the fundamental distinction in how uncertainty is aggregated. The FIM-mean criterion averages the information matrix prior to scalarisation, effectively combining sensitivity directions across different parameter realisations. As a result, it favours time points where sensitivities are consistently aligned, while potentially neglecting regions that are informative only under specific parameter values. In contrast, the D-mean criteria evaluate the logarithmic determinant before taking the expectation, thereby preserving parameter-specific information and avoiding the artificial aggregation of incompatible sensitivity directions.

Significant differences in computational cost are also observed. The FIM-mean design is computationally efficient and allows the use of a large number of parameter samples, since it requires only a single determinant evaluation. In contrast, the SAA-based D-mean design is computationally demanding, requiring over 100 minutes despite using only 1500 parameter samples, due to repeated evaluation of the logarithmic determinant across all samples during optimisation. The GQ-based D-mean design achieves a similar sampling structure to the SAA-based approach at a substantially lower computational cost, highlighting the advantage of deterministic quadrature in low-dimensional uncertainty settings.

Robustness evaluation

The statistical performance metrics of the D-values evaluated over uniformly distributed parametric uncertainty in $[0.01\theta^*, 10\theta^*]$ are summarised in Table 4.7.

The FIM-mean design exhibits very poor robustness. Both the minimum and lower-quantile D-values are extremely low, and the large standard deviation and interquartile range indicate strong sensitivity to parameter variations. This behaviour reflects the inherent

Table 4.6 Pseudo-Bayesian sampling time strategies for the enzyme reaction system under uniform parametric uncertainty in $[0.01\theta^*, 10\theta^*]$

Methods	Results of sampling time points	Run time
FIM-mean	[5800:10:6000]	123.83s
D-mean (SAA)	[10:10:110, 280, 400, 560, 660, 1170, 2620, 2870, 3190, 4420, 4910]	6653s
D-mean (GQ)	[10:10:50, 120, 190, 270, 500, 700, 770, 840, 1130, 1150, 2370, 2610, 2740, 3120, 3530, 3640, 4170]	117.18s

limitation of averaging the FIM prior to scalarisation, which can lead to overly optimistic information estimates while obscuring near-singular behaviour at individual parameter realisations.

In contrast, both D-mean designs show markedly improved robustness and typical performance. They achieve substantially higher minimum and q_{05} values, together with the highest mean and median D-values among the pseudo-Bayesian strategies. Their variability is also significantly reduced, indicating more consistent information content across the uncertainty space. Between the two implementations, the SAA-based design yields slightly tighter D-value distributions, while the GQ-based design attains comparable average performance with a modest increase in dispersion. This suggests that GQ provides an efficient approximation of the expectation with acceptable loss in robustness for low-dimensional uncertainty.

Discussion

These results demonstrate that applying the expectation operator after scalarisation (D-mean) leads to substantially improved robustness and stability compared with formulations that average the FIM directly. This behaviour arises from the matrix-valued and nonlinear nature of the FIM. Linear averaging of FIM combines sensitivity directions across different parameter realisations, potentially diluting information that is specific to individual scenarios and leading to misleadingly optimistic designs. In contrast, the D-mean formulation preserves the

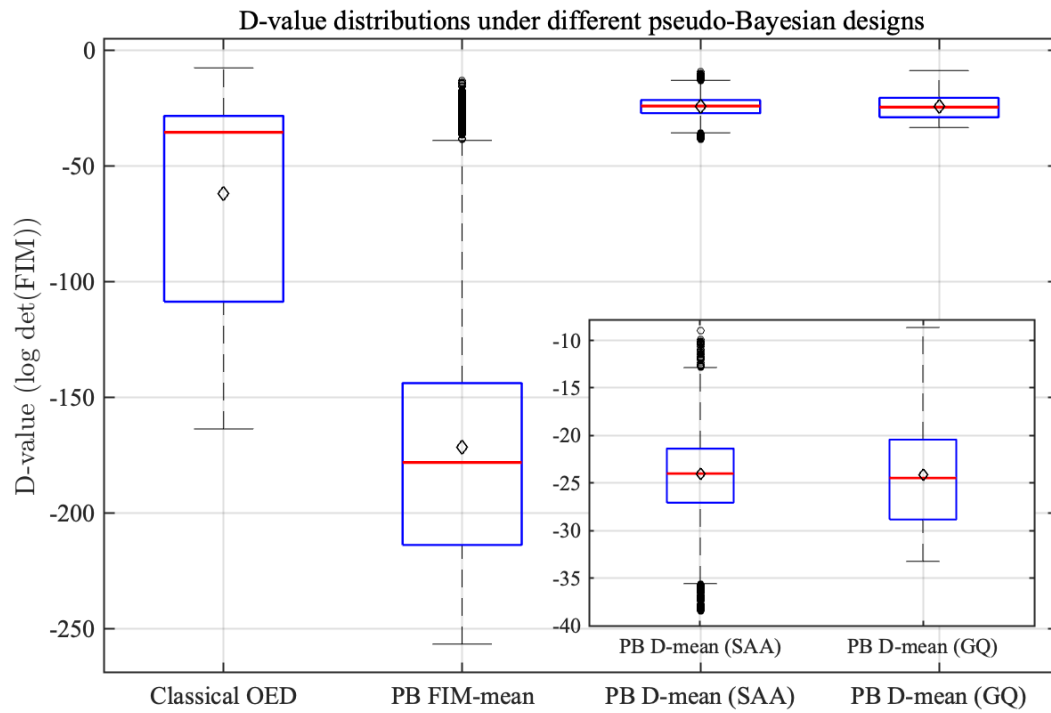


Fig. 4.5 Distribution of D-values for the enzyme reaction system under pseudo-Bayesian sampling time designs with uniform parametric uncertainty in $[0.01\theta^*, 10\theta^*]$

Table 4.7 Statistical performance metrics of D-values for the enzyme reaction system under pseudo-Bayesian sampling time designs with uniform parametric uncertainty in $[0.01\theta^*, 10\theta^*]$

Performance metrics		PB FIM-mean	PB D-mean (SAA)	PB D-mean (GQ)
Robustness	minimum	-256.46	-38.48	-33.23
	q_{05}	-243.27	-30.36	-31.03
Typical performance	mean	-171.33	-23.99	-24.18
	median	-178.03	-24.00	-24.47
Stability	std.	55.38	4.57	4.97
	IQR	69.96	5.69	8.40

information geometry at each parameter realisation prior to aggregation, thereby maintaining sensitivity to poorly informative regions of the uncertainty space.

Overall, pseudo-Bayesian D-mean designs achieve strong average performance and good stability, with GQ providing a computationally efficient implementation. However, as an expectation-based approach, the pseudo-Bayesian framework does not explicitly guarantee protection against worst-case parameter realisations, which may still lead to degraded performance in adverse regions of the uncertainty space.

4.5.5 Parameter-recovery assessment under severe uncertainty

The preceding sections evaluate the sampling strategies primarily using FIM-based criteria and the distributions of D-values. To examine whether the observed differences in information content translate into differences in actual parameter-estimation performance, an additional Monte Carlo parameter-recovery analysis is performed under the severe uniform parametric uncertainty considered above.

A total of 200 independent realisations are generated. For each realisation, the true parameter vector is sampled from the uniform uncertainty region $\theta \in [0.01\theta^*, 10\theta^*]$. The corresponding synthetic measurements are generated using the prescribed measurement-noise model. The parameters k_2 , k_{-3} , and k_5W are then re-estimated using a three-start `fmincon`-based parameter-estimation procedure for all sampling strategies.

Four representative sampling-time designs are compared: nominal OED, fixed worst-case, exchange-based maximin, and GQ-based pseudo-Bayesian D-mean. These designs represent the classical approach, a low-cost maximin approximation, a more systematic maximin formulation, and an expectation-based robust design, respectively. The alternating maximin design is excluded because of its oscillatory behaviour, while the SAA-based pseudo-Bayesian design is not repeated because SAA and GQ approximate the same D-mean objective and showed comparable behaviour; GQ is therefore used as the representative pseudo-Bayesian implementation. For each Monte Carlo realisation, the same true parameter

vector and measurement-noise realisation are used for all designs, with the same nominal parameter vector used to initialise parameter estimation.

Table 4.8 Median and 95th-percentile absolute relative parameter-estimation errors obtained from 200 Monte Carlo realisations under uniform parametric uncertainty in $[0.01\theta^*, 10\theta^*]$. All values are reported as percentages.

Parameter	Metric	Nominal OED	Fixed	Exchange	D-mean (GQ)
k_2	Median	36.21	2.93	3.70	5.25
	95th percentile	226.77	9.29	13.55	15.28
k_{-3}	Median	50.35	29.89	21.72	27.95
	95th percentile	317.30	166.33	101.41	130.13
k_5W	Median	68.53	17.55	13.38	21.86
	95th percentile	475.00	68.64	63.83	86.10

As shown in Table 4.8, all three robust designs substantially improve parameter recovery relative to nominal OED under severe parametric uncertainty. The fixed worst-case design gives the smallest median and 95th-percentile errors for k_2 , whereas the exchange-based maximin design gives the smallest corresponding errors for k_{-3} and k_5W . The pseudo-Bayesian D-mean design also provides clear improvements over nominal OED for all three parameters.

The upper-tail estimation errors provide additional evidence of robustness. The robust designs substantially reduce the 95th-percentile estimation errors relative to nominal OED, indicating a lower risk of severe parameter-recovery failure under adverse parameter realisations. This complements the preceding FIM-based analysis, where robustness was assessed through the lower tail of the D-value distribution. While a low D-value reflects weak joint parameter information, a large estimation error reflects poor realised parameter recovery; the two analyses therefore assess related but distinct aspects of robustness.

The parameter-wise ordering is not identical to the aggregate D-optimality ranking. In particular, the fixed worst-case design performs best for k_2 , whereas the exchange-based maximin design provides better recovery for k_{-3} and k_5W . This is expected because the D-

criterion measures the joint information content across the estimated parameter vector rather than the estimation accuracy of any individual parameter. Overall, the Monte Carlo results show that the robustness improvements identified from the information-based assessment are also reflected in more reliable realised parameter recovery.

4.5.6 Performance assessment across uncertainty levels

To examine how different sampling time design strategies respond to increasing parametric uncertainty, the uncertainty level is varied from 10% to 900% of the nominal parameter values. Here, the uncertainty level denotes a uniform relative deviation around the nominal values (e.g. 10% corresponds to $[0.9, 1.1]\boldsymbol{\theta}^*$). To ensure physical feasibility, all parameters are constrained to be positive by truncating the lower bound at $0.01\boldsymbol{\theta}^*$ for uncertainty levels above 100% (e.g. 900% corresponds to $[0.01, 10]\boldsymbol{\theta}^*$). The designs assessed are the classical OED, fixed worst-case, exchange-based maximin, and pseudo-Bayesian D-mean designs. All designs are evaluated using the same parameter samples at each uncertainty level to ensure consistency.

Performance is assessed using four statistical indicators of the D-values: the minimum, the lower 5% quantile q_{05} , the median, and the IQR, which characterise worst-case robustness, near-worst-case behaviour, typical performance, and stability, respectively. For clarity, the uncertainty range is divided into a *small–moderate* regime (up to 300%) and a *large–severe* regime (above 300%).

Worst-case and near-worst-case behaviour

Figures 4.6 and 4.7 show the evolution of the minimum and lower 5% quantile of the D-values as uncertainty increases. In the small–moderate regime, the classical OED exhibits a progressive deterioration of lower-tail performance. The q_{05} values decrease rapidly, indicating that an increasing fraction of parameter realisations lead to poorly informative

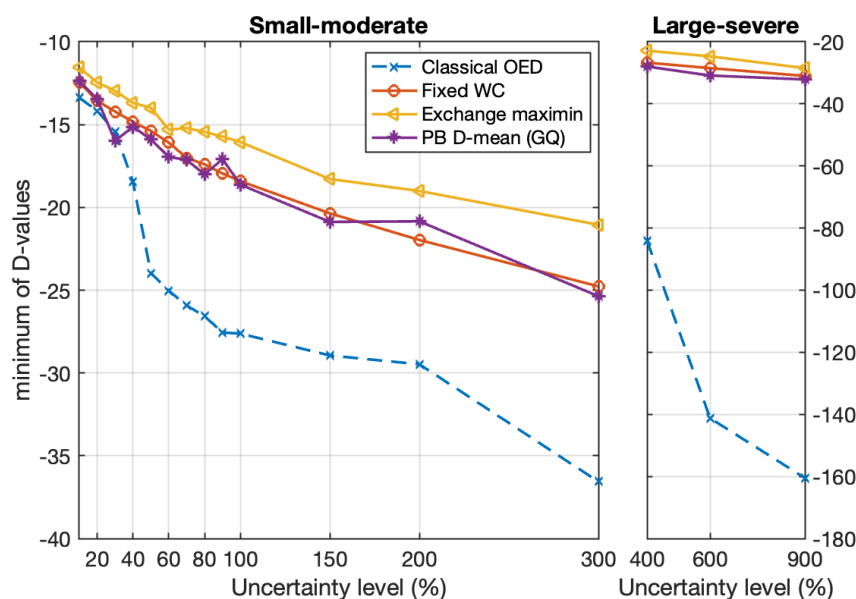


Fig. 4.6 Minimum D-values of the enzyme reaction system under classical OED, fixed worst-case design, exchange-based maximin design and pseudo-Bayesian D-mean design across increasing uncertainty levels

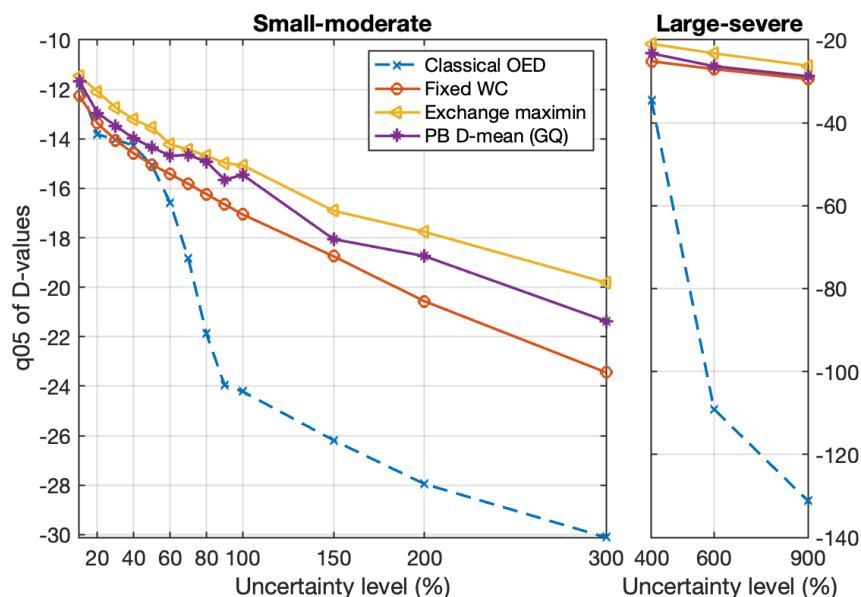


Fig. 4.7 Lowest 5% quantile D-values of the enzyme reaction system under classical OED, fixed worst-case design, exchange-based maximin design and pseudo-Bayesian D-mean design across increasing uncertainty levels

experiments. As uncertainty increases further, the minimum D-values drop sharply, reflecting the emergence of near-singular Fisher information matrices.

In contrast, all robust designs significantly lift the lower tail of the distribution relative to the classical OED, demonstrating their ability to mitigate the risk of poorly informative experiments under uncertainty. Among them, the exchange-based maximin design consistently provides the strongest near-worst-case protection across all uncertainty levels, maintaining the highest minimum and q_{05} values. This indicates that explicitly enforcing robustness over multiple worst-case scenarios remains effective even as the uncertainty region expands.

The pseudo-Bayesian D-mean design also improves lower-tail performance compared with the classical OED, particularly beyond moderate uncertainty levels (above approximately 40%). However, it remains consistently inferior to the exchange-based maximin design, reflecting the inherent limitation of expectation-based criteria in protecting against adverse parameter realisations.

The fixed worst-case design exhibits minimum D-values comparable to those of the pseudo-Bayesian D-mean design, but with more stable behaviour across uncertainty levels. However, its q_{05} performance is consistently lower than that of both the exchange-based and pseudo-Bayesian designs. This indicates that, while targeting a single worst-case parameter improves extreme performance, it does not adequately protect against a broader set of near-worst-case scenarios. As a result, it provides only a partial approximation to the full maximin formulation.

Typical performance

Figure 4.8 reports the median D-values across uncertainty levels. In the low-uncertainty regime (below 100%), the pseudo-Bayesian D-mean design exhibits median performance that is essentially indistinguishable from the classical OED, whereas both maximin-based designs (fixed worst-case and exchange-based maximin) yield lower median values. This behaviour reflects the conservative nature of worst-case-oriented designs, which sacrifice typical performance when uncertainty is mild.

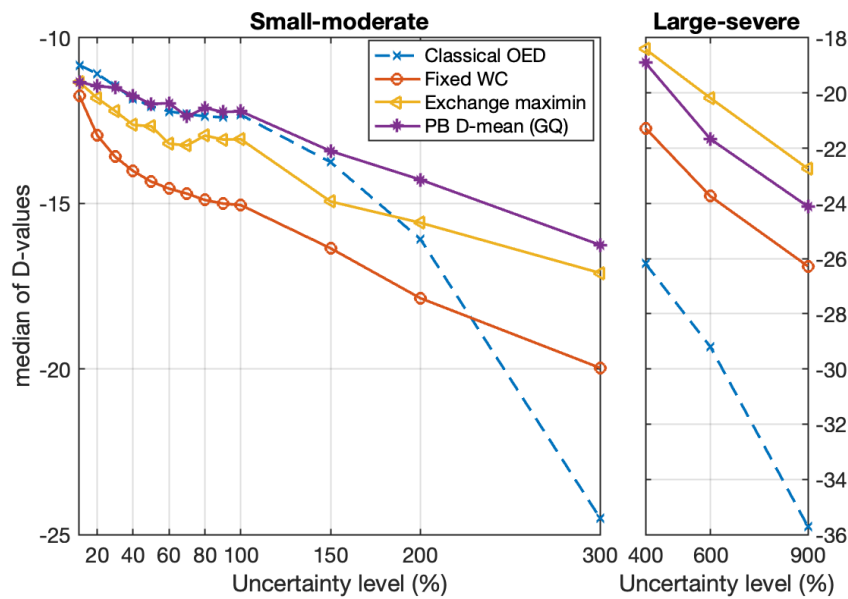


Fig. 4.8 Median D-values of the enzyme reaction system under classical OED, fixed worst-case design, exchange-based maximin design and pseudo-Bayesian D-mean design across increasing uncertainty levels

Beyond 100% uncertainty, the classical OED shows a pronounced deterioration in median performance, while the pseudo-Bayesian design degrades more gradually and consistently outperforms the classical design thereafter. As uncertainty increases further, the relative ordering of the methods changes. The exchange-based maximin design surpasses the classical OED at approximately 200%, while the fixed worst-case design does so at around 300%.

In the large-severe regime (above 300%), the exchange-based maximin design even exceeds the pseudo-Bayesian design in median performance. This indicates that, under sufficiently severe uncertainty, explicit worst-case enforcement not only improves lower-tail robustness but can also enhance typical performance.

Across the entire uncertainty range, the fixed worst-case design remains inferior to both the exchange-based and pseudo-Bayesian designs. This reflects the fact that, although computationally efficient, it provides only a coarse approximation to the full exchange-based maximin solution.

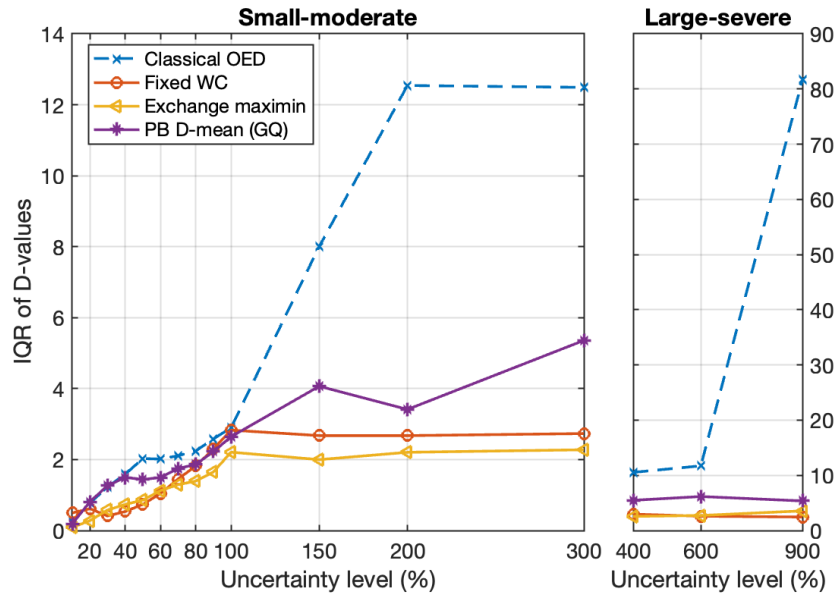


Fig. 4.9 IQR of D-values for the enzyme reaction system under classical OED, fixed worst-case design, exchange-based maximin design and pseudo-Bayesian D-mean design across increasing uncertainty levels

Stability with respect to uncertainty

The IQR trends are shown in Figure 4.9. Within the small–moderate uncertainty regime, the classical OED exhibits a pronounced increase in IQR. After a gradual rise at low uncertainty levels, a sharp expansion occurs once uncertainty exceeds approximately 80%, indicating a rapid loss of stability. The IQR then remains at a high level throughout the large–severe regime.

In contrast, the maximin-based designs exhibit markedly improved stability. Both the fixed worst-case and exchange-based maximin designs maintain low and nearly invariant IQR values across the entire uncertainty range, demonstrating strong robustness to parameter variations. The exchange-based design achieves slightly lower dispersion than the fixed worst-case design in the moderate uncertainty regime, although the difference remains small in absolute terms.

The pseudo-Bayesian design exhibits intermediate behaviour. Its dispersion is consistently larger than that of the maximin designs, but substantially smaller than that of the classical OED at moderate to severe uncertainty levels. At low uncertainty, its IQR is comparable to that of the classical design, while at higher uncertainty levels it provides a clear improvement in stability.

Discussion

The results reveal clearly differentiated robustness–performance trade-offs among the considered design strategies as parametric uncertainty increases. The classical OED performs competitively only in the low-uncertainty regime, but exhibits an early and pronounced degradation in both robustness and stability as uncertainty grows. This behaviour highlights the limitation of local sensitivity analysis (LSA)-based designs when applied outside their nominal validity region.

All robust design strategies significantly improve lower-tail behaviour and reduce dispersion, confirming the importance of explicitly accounting for parametric uncertainty in sampling time design. Among these, the exchange-based maximin design provides the most consistent performance across all uncertainty levels. It achieves the strongest worst-case and near-worst-case protection, maintains low dispersion, and, under large–severe uncertainty, also delivers superior typical performance. This demonstrates that rigorous enforcement of worst-case scenarios can yield benefits beyond robustness alone.

The fixed worst-case design captures a substantial portion of these robustness gains at significantly lower computational cost, but remains inferior to the exchange-based design due to its limited representation of the uncertainty space.

The pseudo-Bayesian D-mean design offers strong typical performance and moderate stability, particularly in the small–to–moderate uncertainty regime. However, as uncertainty increases, its reliance on expectation-based aggregation leads to weaker worst-case protection and higher dispersion compared with maximin-based approaches.

Overall, these results highlight a clear hierarchy: pseudo-Bayesian designs are effective for improving average performance under moderate uncertainty, whereas maximin-based designs, particularly the exchange-based approach, are essential when robust protection against adverse parameter realisations is required.

Design implications The results in this section suggest a practical selection principle for sampling time design under parametric uncertainty. When uncertainty is limited and reliable nominal parameter values are available, classical OED or pseudo-Bayesian designs can provide efficient solutions by prioritising average information content. However, as uncertainty increases, the risk of poorly informative experiments becomes non-negligible, and expectation-based criteria alone are insufficient to guarantee reliable performance. In such settings, maximin-based designs offer a more appropriate framework by explicitly safeguarding against adverse parameter realisations. In particular, the exchange-based maximin approach provides a systematic mechanism for enforcing robustness across the uncertainty space, while the fixed worst-case design offers a computationally efficient approximation when resources are limited.

These observations highlight that the choice of design strategy should be guided by both the level of uncertainty and the required degree of robustness, rather than relying on a single criterion across all regimes.

4.5.7 Influence of uncertainty distribution

In the previous sections, the design strategies were evaluated under uniformly distributed parametric uncertainty, representing a conservative scenario in which extreme parameter realisations are equally likely. In many practical situations, however, prior information or previous experiments suggest that parameter uncertainty is concentrated around nominal values. To investigate the influence of the uncertainty distribution, this section considers a truncated Gaussian description of parametric uncertainty.

Table 4.9 Maximin and pseudo-Bayesian sampling time design results for enzyme reaction system under truncated Gaussian distributed parametric uncertainty

Methods	Results of sampling time points	Run time
Fixed WC	[10:10:90, 130:10:240]	61s
Exchange maximin	[10:10:60, 150:10:230, 260, 300, 350, 410, 470, 520]	1523s
PB D-mean (SAA)	[10:10:110, 280, 400, 560, 660, 1170, 2620, 2870, 3190, 4420, 4910]	6728s
PB D-mean (GQ)	[10:10:110, 200, 240, 430, 710, 1040, 1050, 1520, 2190, 2610, 3260]	120s

The parameters k_2 , k_{-3} , and k_5W are assumed to follow independent Gaussian distributions centred at the nominal values θ^* , with standard deviations equal to 30% of θ^* . The distributions are truncated to $[0.01\theta^*, 10\theta^*]$ to ensure physical plausibility and consistency with previous analyses. Maximin designs are constructed using the fixed worst-case and exchange-based strategies with PSO for worst-case identification, while pseudo-Bayesian D-mean designs are obtained using both SAA with 1,500 samples and a 3-point GQ rule. The resulting sampling time designs and computational costs are reported in Table 4.9.

To assess performance, 5,000 parameter samples are drawn from the truncated Gaussian uncertainty space, and the corresponding D-values are computed for all robust designs and the classical OED. Figure 4.10 shows the resulting D-value distributions.

Compared with the uniformly distributed case, the overall spread of D-values is substantially reduced, reflecting the concentration of probability mass around the nominal parameters (approximately 95% within $[0.4\theta^*, 1.6\theta^*]$). Under this uncertainty model, the classical OED achieves the highest median D-value, indicating strong typical performance. However, a pronounced lower tail persists, indicating that the design remains sensitive to unfavourable parameter realisations.

The pseudo-Bayesian designs provide the strongest lower-tail protection in this setting. Both SAA- and GQ-based implementations significantly improve the minimum and lower-

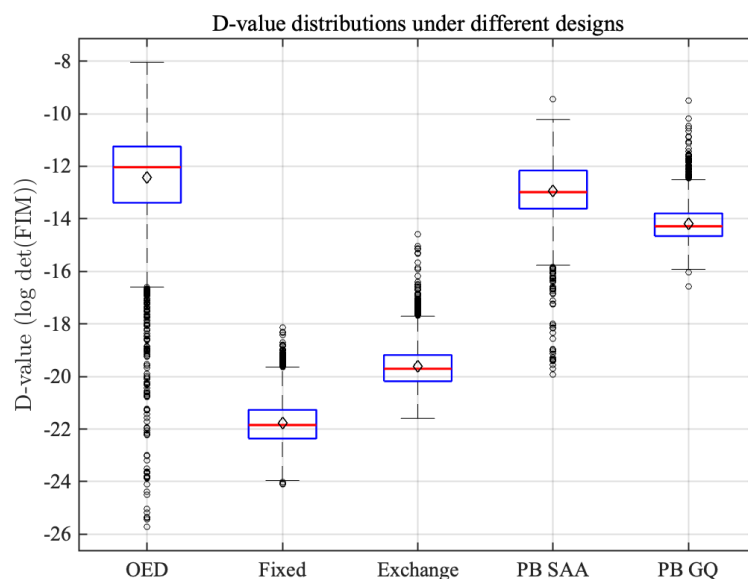


Fig. 4.10 Distribution of D-values for the enzyme reaction system under classical OED and robust sampling time designs with truncated Gaussian parametric uncertainty

quantile D-values relative to the classical and maximin-based designs. Among these, pseudo-Bayesian–GQ yields the smallest IQR, indicating the most concentrated distribution, while pseudo-Bayesian–SAA exhibits slightly higher dispersion but comparable robustness. In terms of median performance, the pseudo-Bayesian designs rank immediately below the classical design, achieving a favourable balance between robustness and typical performance.

The exchange-based maximin design improves the lower tail relative to the fixed worst-case design and exhibits moderate dispersion, but remains inferior to the pseudo-Bayesian designs in both minimum and lower-quantile performance. Its median performance is also lower, reflecting the conservative nature of worst-case-oriented optimisation. The fixed worst-case design is the most conservative among the robust strategies, with the lowest median and comparatively weaker lower-tail improvement.

Overall, the truncated Gaussian uncertainty fundamentally alters the relative performance of the design strategies. When the distribution is concentrated near the nominal parameters, expectation-based approaches such as the pseudo-Bayesian D-mean design become

particularly effective, as they allocate design effort according to the likelihood of parameter realisations. In contrast, maximin-based designs remain driven by extreme scenarios that are now of low probability, leading to conservative sampling strategies.

Importantly, however, the classical OED still exhibits the weakest lower-tail behaviour and the largest dispersion, even under probabilistically structured uncertainty. This indicates that concentration of probability mass alone does not eliminate sensitivity to adverse parameter realisations, and that designs based solely on nominal conditions remain vulnerable.

From a computational perspective, the pseudo-Bayesian design constructed using GQ achieves performance nearly identical to the SAA-based implementation while requiring only a small fraction (2%) of the computational time. This demonstrates that, for probabilistically structured uncertainty, the pseudo-Bayesian D-mean design based on GQ provides an attractive compromise between robustness, typical performance, and computational efficiency.

4.6 Enzymatic Biodiesel Production System Case Study

4.6.1 Brief system introduction

This section introduces an enzymatic biodiesel production process as a second case study for evaluating classical and robust experimental design strategies. Compared with the enzyme reaction system in Section 4.5, this system is higher-dimensional and involves time-varying operating conditions, thereby providing a more challenging and industrially relevant testbed.

Biodiesel is a renewable alternative to fossil-based diesel and can reduce emissions of particulates, sulfur, carbon monoxide, and hydrocarbons (Demirbas, 2007). Among various catalytic routes, enzymatic transesterification is particularly attractive due to its compatibility with variable feedstock quality, lower energy demand, and reduced wastewater generation compared with acid- or base-catalysed processes (Fjerbaek et al., 2009). In this work, a kinetic model for the enzymatic transesterification of rapeseed oil with methanol using a liquid lipase formulation is adopted from the literature (Lv et al., 2010; Price et al., 2014).

The purpose of introducing this system is not to reassess experimental practices reported in the literature, but to examine the behaviour of experimental design strategies when applied to a more complex nonlinear system with time-varying operating conditions. In particular, this case study is used to investigate how sampling time designs respond to condition shifts that are explicitly represented within the model.

For experimental design purposes, the biodiesel production system is characterised by:

- a nonlinear dynamic model describing a biphasic oil–water reaction network with enzyme adsorption at the oil–water interface and competitive methanol inhibition;
- a measurement vector given by mass fractions of key components (TAG, DAG, MAG, FAME, and FFA);
- four kinetic parameters, k_2 , k_6 , k_8 , and k_9 , selected for estimation, with nominal values of 1.69×10^6 , 9.13×10^4 , 2.36×10^4 , and $2.54 \times 10^4 \text{ L} \cdot \text{mol}^{-1} \cdot \text{min}^{-1}$, respectively;
- a time-varying operating condition, namely the methanol feed rate F_a , which may change during the experiment.

The experimental study reported in Lv et al. (2010); Price et al. (2014) comprises 12 experimental configurations, which are summarised in Table B.2 in the appendix.

Experiments 5 and 8 are selected for the present study because they differ only in the prescribed methanol feed profile. Both use an initial methanol dose of 0.2 Eq., a water content of 5 wt.% oil, and an enzyme loading of 0.5 wt.% oil. In Exp. 5, the methanol feed rate is maintained at 0.06 Eq./h throughout the experiment, whereas in Exp. 8 it is 0.185 Eq./h for the first 2 h and 0.06 Eq./h thereafter. This provides a controlled setting for examining whether the performance of the sampling-time design strategies is retained under a prescribed operating-condition change. The variation in F_a is known and explicitly represented in the model, rather than treated as an additional source of uncertainty.

The complete reaction mechanism, governing equations, full parameter set, and the remaining experimental configurations are provided in Appendix B for completeness and reproducibility.

Table 4.10 Classical optimal sampling time strategies for the biodiesel production system under nominal parameters (Exp. 5 and Exp. 8)

	Experiment 5 (min)	Experiment 8 (min)
Real lab-experiments	[15:15:60, 120:60:1500]	
Powell D-optimal	[35:5:110, 775:5:830]	[35:5:115, 615:5:665]
Powell E-optimal	[20:5:155]	[15:5:150]
Powell A-optimal	[20:5:150,940]	[15:5:145, 630]

4.6.2 Classical OED and results analysis

Classical optimal sampling time design is first performed for the biodiesel production system under nominal parameter values and known operating conditions. The objective of this analysis is to characterise how sensitivity-driven sampling strategies respond to changes in operating conditions prior to introducing parametric uncertainty.

Measurement noise is assumed to be Gaussian with constant variance for all five measurable states at all sampling times. The experiment duration is 1,500 minutes, and a candidate grid of sampling times $\mathbf{t}_m = [5 : 5 : 1500]^\top$ min, consisting of $N_T = 300$ potential sampling instants, is considered. To reflect practical laboratory constraints and enable direct comparison with reported experiments, the number of selected sampling points is restricted to $N_{st} = 28$, consistent with the laboratory protocol of measuring every 15 minutes during the first hour, followed by hourly measurements. Based on the sensitivity and identifiability analysis reported in (Yu, 2018), four parameters, k_2 , k_6 , k_8 , and k_9 , are selected for parameter estimation and experimental design. These parameters exhibit informative sensitivity characteristics under the adopted experimental configuration, making them suitable for assessing the effect of sampling-time allocation in the biodiesel system.

The resulting optimal sampling strategies for Experiment 5 and Experiment 8 are obtained using Powell-type discrete exchange procedure and reported in Table 4.10. Figures 4.11–4.13

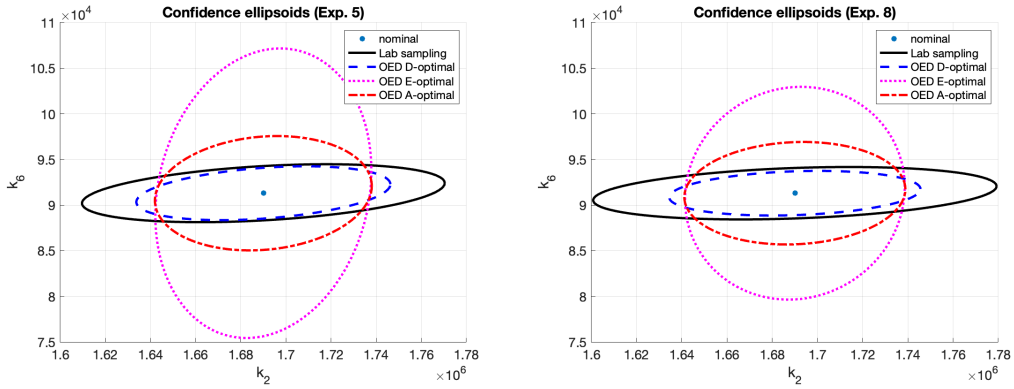


Fig. 4.11 Confidence ellipsoid projections of (k_2, k_6) under classical optimal sampling designs and laboratory sampling (left: Exp. 5; right: Exp. 8)

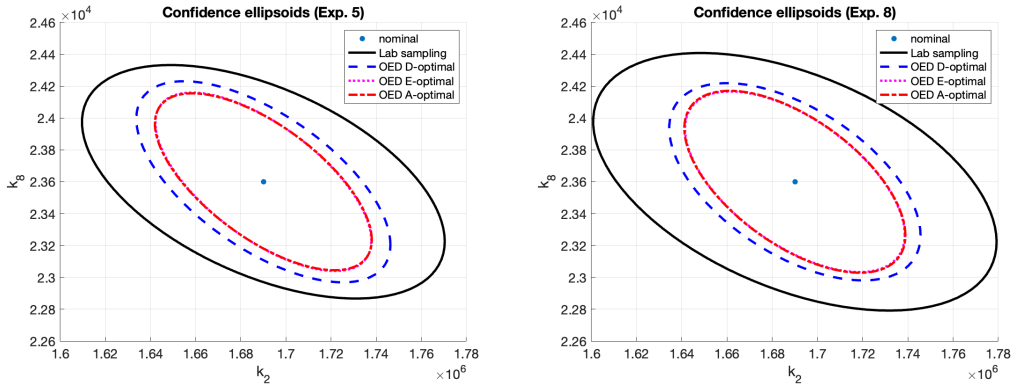


Fig. 4.12 Confidence ellipsoid projections of (k_2, k_8) under classical optimal sampling designs and laboratory sampling (left: Exp. 5; right: Exp. 8)

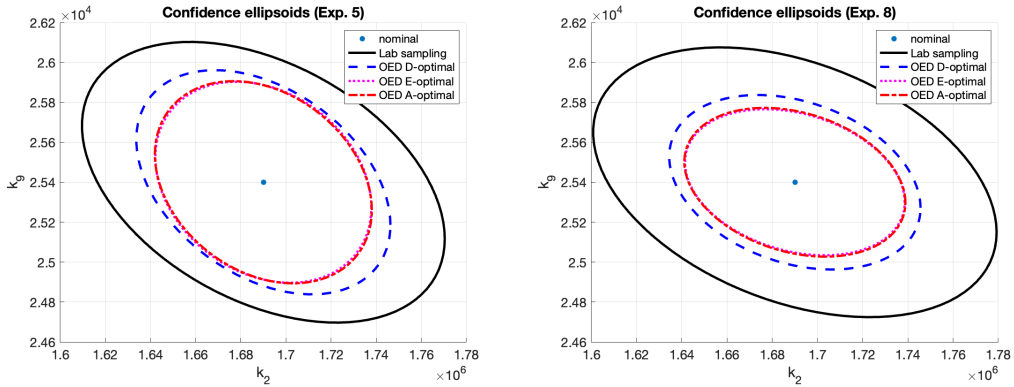


Fig. 4.13 Confidence ellipsoid projections of (k_2, k_9) under classical optimal sampling designs and laboratory sampling (left: Exp. 5; right: Exp. 8)

compare the laboratory sampling strategy with D-, A-, and E-optimal designs for the two experiments, which differ only in the methanol feed strategy.

For all parameter pairs and both experiments, the laboratory sampling strategy consistently yields the largest confidence ellipsoids, indicating limited information content. In contrast, classical OED significantly reduces the confidence regions in both Exp. 5 and Exp. 8, demonstrating that OED remains effective under known operating-condition changes.

Among the considered criteria, the D-optimal design provides the most consistent and balanced improvement. Across all parameter pairs, the D-optimal confidence ellipsoids are substantially smaller than those obtained under laboratory sampling and exhibit similar reductions in the two experimental configurations. This indicates that D-optimal sampling provides substantial information improvement under both prescribed operating conditions.

The A- and E-optimal designs also reduce the FIM-based confidence regions compared with laboratory sampling, but exhibit less consistent behaviour across parameter pairs. In particular, elongated confidence ellipsoids are observed for combinations involving k_6 , indicating uneven reduction of uncertainty across parameter directions. This behaviour reflects the inherent focus of A- and E-optimal criteria on specific aspects of the FIM (trace and minimum eigenvalue, respectively), which may lead to imbalanced improvements in multi-parameter settings.

From a computational perspective, no significant differences in runtime are observed among the A-, D-, and E-optimal designs for Exp. 5 and Exp. 8. This indicates that the change in operating conditions does not materially affect the numerical complexity of classical OED for this system.

Overall, these results confirm that classical OED, and in particular the D-optimal criterion, provides substantial improvements over laboratory sampling and remains effective under known condition shifts. Consequently, the D-optimal design is adopted as the baseline strategy for subsequent RED studies.

4.6.3 Robust sampling time design under parametric uncertainty

Under Exp. 5, the enzymatic biodiesel production system is analysed under parametric uncertainty while maintaining fixed operating conditions. This setting provides a baseline for assessing the behaviour of robust experimental design strategies in a higher-dimensional nonlinear system.

Figures 4.14–4.17 summarise the evolution of the minimum, lower 5% quantile (q_{05}), median, and IQR of the D-values as the uncertainty level increases under uniformly distributed parametric uncertainty. As expected, all designs exhibit a monotonic degradation in information content as uncertainty becomes more severe. However, clear differences emerge in terms of robustness, typical performance, and stability.

In this case study, the fixed worst-case and exchange-based maximin strategies produce identical sampling time designs. During the exchange procedure, the worst-case parameter identified in the first iteration remains active in subsequent iterations, so no additional scenario is introduced and the algorithm terminates without modifying the design. This indicates that a single dominating worst-case parameter realisation defines the active constraint set of the maximin problem under Exp. 5. For brevity, both implementations are hereafter referred to as the maximin design.

The classical OED exhibits a rapid degradation in robustness as uncertainty increases. Both the minimum and q_{05} D-values decrease sharply even at moderate uncertainty levels, indicating that designs based on nominal sensitivities frequently lead to near-singular Fisher information matrices for unfavourable parameter realisations. The increasing IQR further reflects a pronounced loss of stability, with the information content becoming highly sensitive to parameter variations.

In contrast, the maximin design consistently achieves the highest minimum and q_{05} D-values across the entire uncertainty range, demonstrating strong protection against worst-case parameter realisations. It also yields the smallest IQR values, indicating superior stability. The convergence of fixed and exchange-based implementations to the same design further

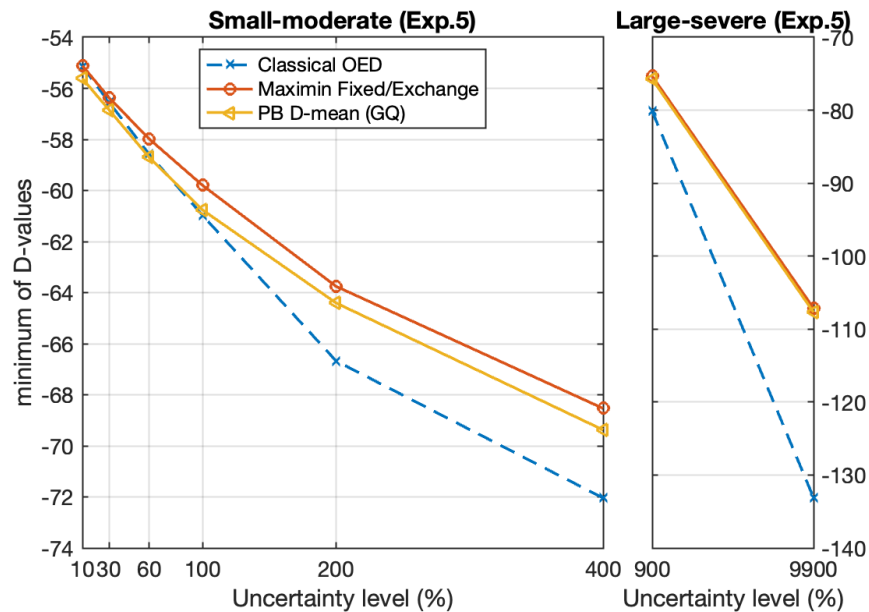


Fig. 4.14 Minimum D-values of the biodiesel production system under classical OED, maximin designs, and pseudo-Bayesian D-mean design across increasing uncertainty levels (Exp. 5)

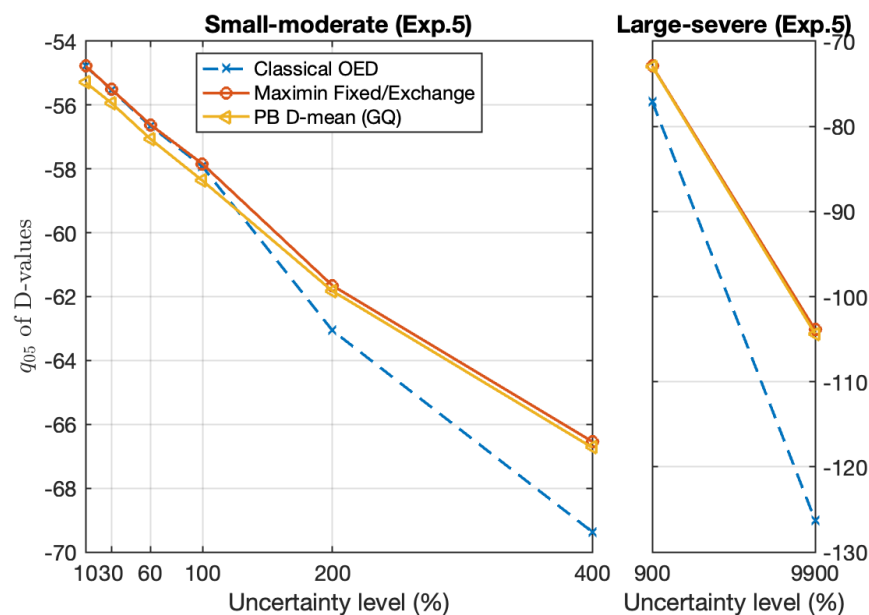


Fig. 4.15 Lower 5% quantile D-values of the biodiesel production system under classical OED, maximin designs, and pseudo-Bayesian D-mean design across increasing uncertainty levels (Exp. 5)

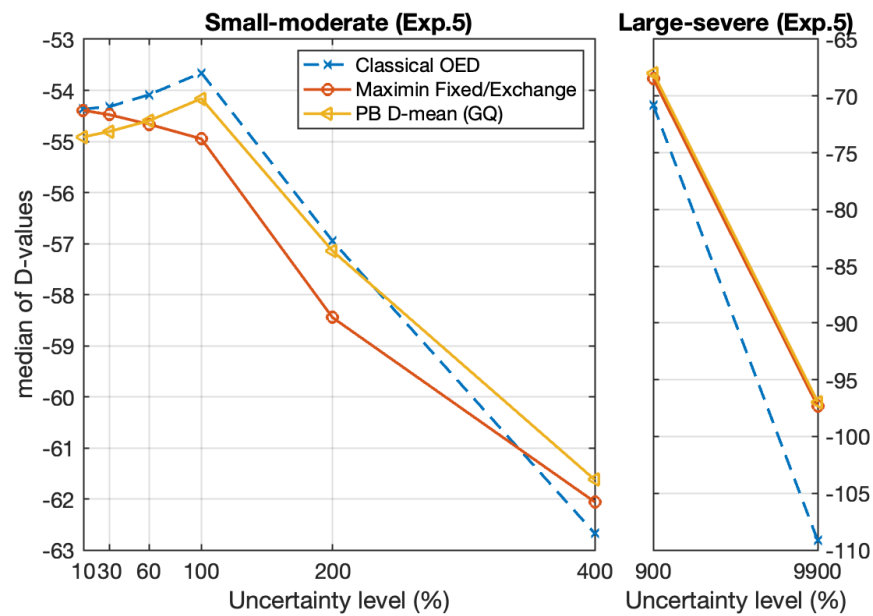


Fig. 4.16 Median D-values of the biodiesel production system under classical OED, maximin designs, and pseudo-Bayesian D-mean design across increasing uncertainty levels (Exp. 5)

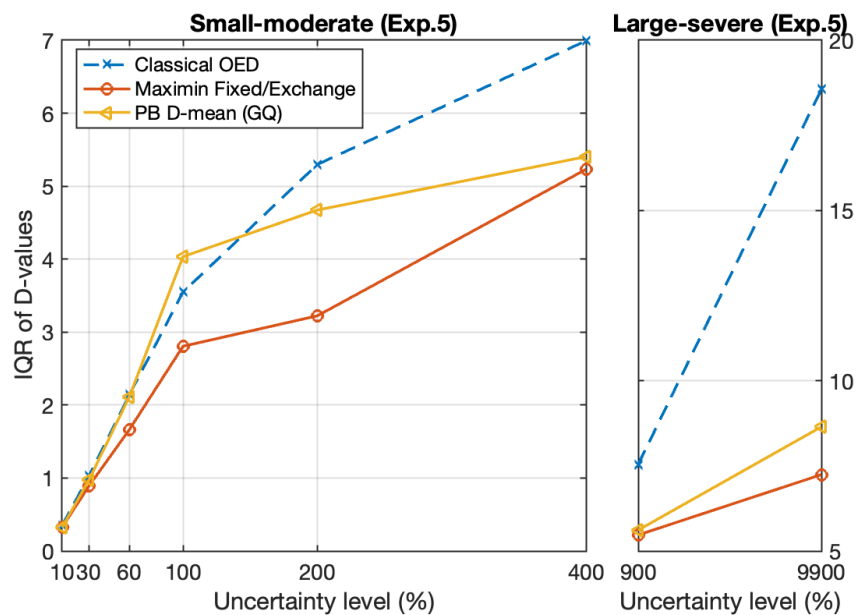


Fig. 4.17 IQR D-values of the biodiesel production system under classical OED, maximin designs, and pseudo-Bayesian D-mean design across increasing uncertainty levels (Exp. 5)

Table 4.11 Computational time of robust sampling time design methods for biodiesel production system under uniform parametric uncertainty (Exp. 5)

Fixed WC	Exchange	PB D-mean
2905s	12339s	245s

suggests that, for this system, robustness is governed by a single critical parameter scenario rather than a distributed set of competing worst cases.

The pseudo-Bayesian D-mean design exhibits a distinct behaviour for the enzymatic biodiesel production system under Exp. 5, particularly in the small-uncertainty regime. At low uncertainty levels, it produces lower minimum, q_{05} , median, and IQR values than both classical OED and the maximin design. This indicates that expectation-based averaging redistributes sampling effort away from the nominally optimal time regions, while the classical design remains well aligned with near-nominal system dynamics. As uncertainty increases, however, the pseudo-Bayesian design gradually improves its robustness relative to classical OED, although it remains inferior to the maximin design in terms of worst-case protection.

Overall, these results suggest that, for the biodiesel system, the scope for improving information content through sampling-time reallocation alone is more limited than in the enzyme reaction system. The relative differences among design strategies are smaller, indicating that the temporal placement of measurements has less flexibility to reshape the information structure in this higher-dimensional and more tightly coupled system. Nevertheless, the substantial degradation observed under classical OED confirms that robust sampling design remains essential to prevent severe loss of information under parameter uncertainty.

From a computational perspective, as reported in Table 4.11, the exchange-based implementation incurs more than four times the computational cost of the fixed worst-case approach despite yielding the same design. The pseudo-Bayesian design based on GQ is the most computationally efficient method among the considered approaches, but it achieves weaker robustness across all uncertainty levels compared with the maximin design.

4.6.4 Robust experimental design under parametric uncertainty and a prescribed operating-condition change

Experiment 8 investigates RED under parametric uncertainty in the presence of a prescribed operating-condition change introduced through a different methanol-feed profile. Although the kinetic model remains unchanged, this prescribed change in the methanol-feed profile alters the temporal distribution of parameter sensitivities, providing a test of whether the relative performance of the design strategies under parametric uncertainty is preserved when the operating condition changes from Exp. 5 to Exp. 8.

The robustness metrics in Figures 4.18–4.21 show that the relative performance of the design strategies observed in Exp. 5 is largely preserved under the condition shift. In particular, the classical OED continues to exhibit a pronounced degradation in lower-tail performance as uncertainty increases, reflected by rapidly decreasing minimum and q_{05} D-values and an increasing IQR. This behaviour indicates that the vulnerability of nominally optimised sampling schedules to parametric uncertainty persists after the prescribed change in the methanol-feed profile from Exp. 5 to Exp. 8.

In contrast, the maximin designs consistently maintain the highest near-worst-case D-values and the smallest IQRs across the entire uncertainty range. This shows that the comparative advantage of the maximin criterion under parametric uncertainty is preserved across the prescribed methanol-feed change between Exp. 5 and Exp. 8.

The pseudo-Bayesian D-mean design exhibits behaviour consistent with that observed in Exp. 5. At small uncertainty levels, its performance remains slightly inferior to that of the classical OED, reflecting the averaging effect of the expectation-based objective. As uncertainty increases, however, it provides clear improvements in robustness relative to the classical design. Since this small-uncertainty behaviour has been analysed in detail in Exp. 5, it is not further discussed here.

Overall, the results of Exp. 8 show that the relative advantages of robust sampling-time designs are retained under the investigated prescribed operating-condition change. These

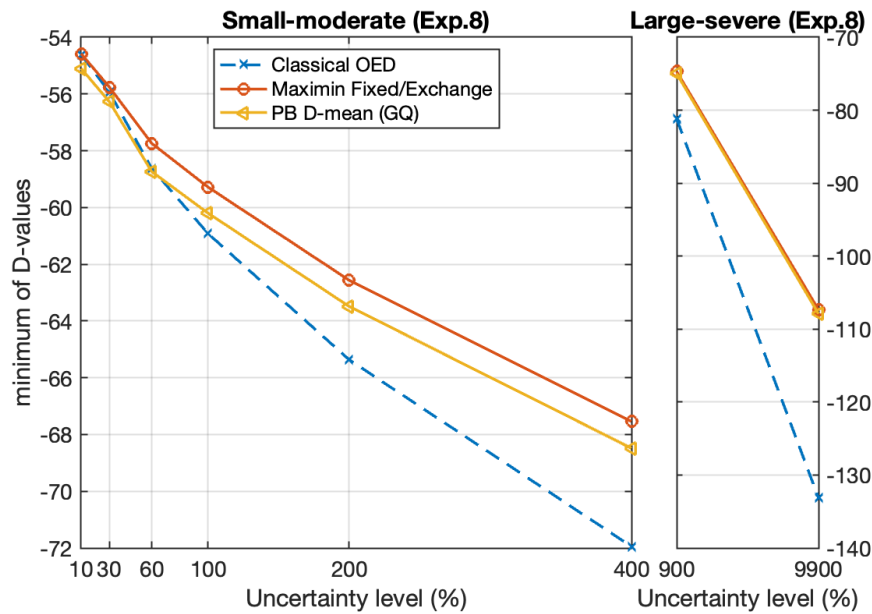


Fig. 4.18 Minimum D-values of the biodiesel production system under classical OED, maximin designs, and pseudo-Bayesian D-mean design across increasing uncertainty levels (Exp. 8)

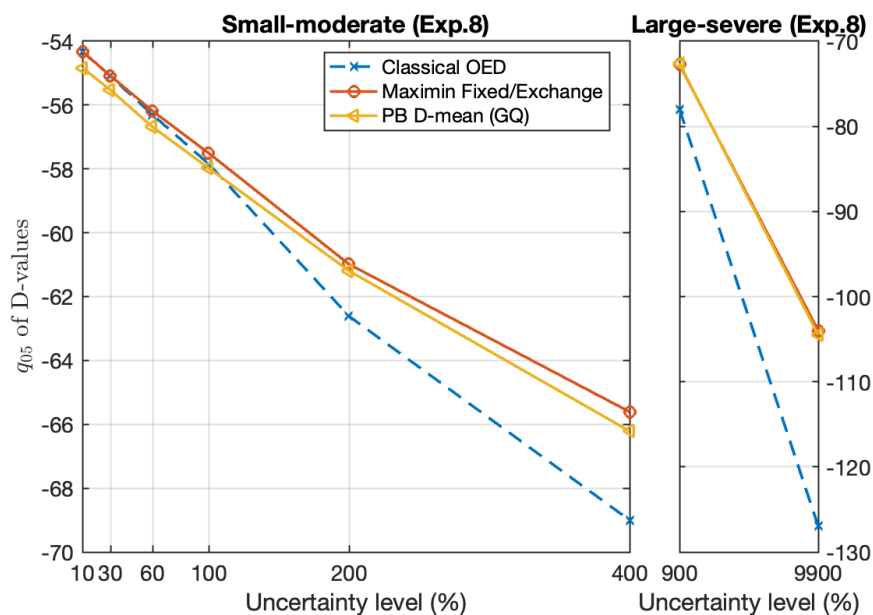


Fig. 4.19 Lower 5% quantile D-values of the biodiesel production system under classical OED, maximin designs, and pseudo-Bayesian D-mean design across increasing uncertainty levels (Exp. 8)

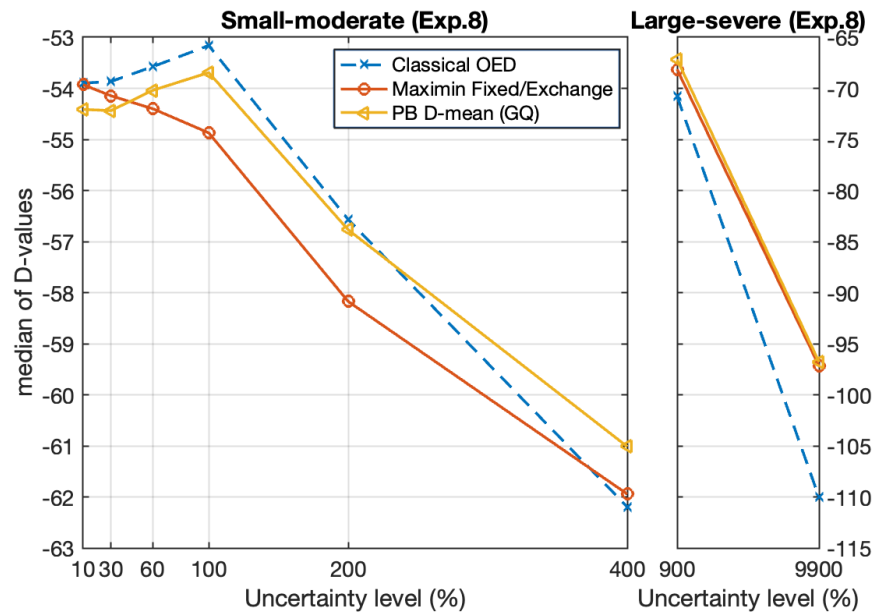


Fig. 4.20 Median D-values of the biodiesel production system under classical OED, maximin designs, and pseudo-Bayesian D-mean design across increasing uncertainty levels (Exp. 8)

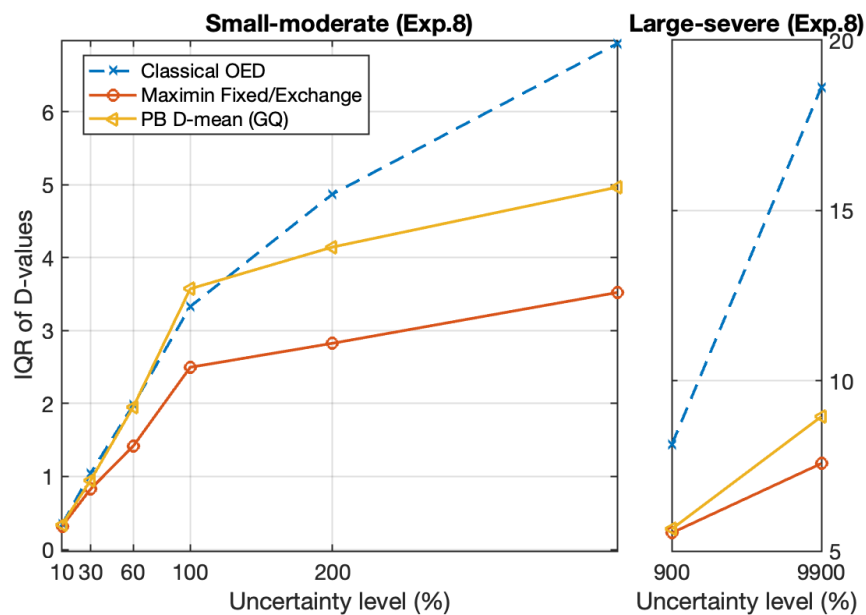


Fig. 4.21 IQR D-values of the biodiesel production system under classical OED, maximin designs, and pseudo-Bayesian D-mean design across increasing uncertainty levels (Exp. 8)

results should be interpreted as validation under the tested methanol-feed variation rather than as a general robustness assessment over arbitrary operating-condition changes.

4.7 Summary

This chapter investigated robust sampling time design for nonlinear dynamic systems under parametric uncertainty, focusing on two principal paradigms: maximin design, which safeguards worst-case performance over a bounded uncertainty set, and pseudo-Bayesian design, which optimises an expectation-based criterion under a prescribed uncertainty distribution.

For maximin design, three solution strategies were examined. The fixed worst-case approach provides a computationally efficient approximation by optimising against a single critical parameter realisation. The alternating strategy updates the worst-case parameter iteratively but remains heuristic and may exhibit oscillatory behaviour. The exchange-based strategy enforces robustness through progressive scenario enrichment and provides the most faithful approximation to the underlying semi-infinite maximin problem.

For pseudo-Bayesian design, the analysis showed that robustness depends critically on how uncertainty is aggregated within the objective function. In particular, exchanging the order of expectation and scalarisation alters the design criterion through Jensen's inequality and may lead to overly optimistic assessments of information content. Accordingly, the expected log-determinant (D-mean) criterion was adopted. Two numerical implementations were considered: SAA and GQ, with GQ offering comparable performance at substantially lower computational cost for low-dimensional uncertainty.

The numerical studies, conducted on two case studies of increasing complexity, demonstrate that classical OED performs well only near nominal parameter values, but deteriorates rapidly in both robustness and stability as uncertainty increases. Maximin designs consistently provide the strongest protection in the lower tail of the information distribution, while pseudo-Bayesian D-mean designs offer improved typical performance but weaker worst-case guarantees under severe uncertainty. The relative performance of these approaches is also

influenced by the uncertainty distribution: probability-weighted designs become more competitive when uncertainty is concentrated around nominal values, whereas maximin designs remain governed by extreme parameter realisations.

The case studies further reveal that the effectiveness of sampling time design is system-dependent. For the enzyme reaction system, sampling-time allocation provides substantial flexibility to reshape the information content, leading to clear distinctions between design strategies. For the biodiesel production system, this flexibility is more limited, and robustness is often governed by a small number of critical parameter scenarios, resulting in reduced performance differences among methods. Importantly, the relative advantages of robust sampling-time designs are also retained under the prescribed methanol-feed change investigated in Exp. 8. This result is specific to the operating-condition variation considered here and should not be interpreted as robustness to arbitrary operating-condition changes.

Several remarks are drawn from a practical perspective:

- Exchange-based maximin design is preferred when strict worst-case protection is required, particularly under severe uncertainty.
- Fixed worst-case design offers an efficient approximation when computational resources are limited and a dominant worst-case scenario exists.
- Pseudo-Bayesian D-mean design is advantageous when a probabilistic uncertainty description is available and balanced typical performance is desired, with GQ providing an efficient implementation in low-dimensional settings.

Overall, this chapter establishes a systematic benchmark of standard robust sampling time design methodologies across systems of varying complexity. It clarifies their robustness characteristics, dependence on uncertainty representation, and computational trade-offs, and provides a reference baseline for the advanced robust experimental design methods developed in the subsequent chapters.

A sequential FIM-based OED strategy would address parameter uncertainty differently from the static robust designs considered here. By repeatedly updating the parameter

estimates and redesigning subsequent experiments, it would tend towards the nominal OED associated with the true parameter values, rather than the maximin or pseudo-Bayesian design defined over an uncertainty set or distribution. Such sequential strategies may also require repeated experimental rounds, which can be impractical for costly, time-consuming, or resource-limited experiments.

These findings reveal a fundamental limitation of static robust designs: while they enhance robustness, they cannot adapt to information gained during experimentation. This limitation motivates the within-run adaptive redesign strategies introduced in Chapter 5.

Chapter 5

Adaptive Midterm Experimental Redesign Framework

Although the maximin and pseudo-Bayesian designs introduced in Chapter 4 improve robustness under parametric uncertainty, they remain fundamentally static. As a result, they may yield inefficient designs in practice. In particular, maximin designs can be overly conservative when the worst-case parameter is unlikely to occur, while pseudo-Bayesian designs may provide insufficient information for parts of the uncertainty space.

A natural approach to address these limitations is iterative experimental design, which alternates between experiment design, data collection, and parameter estimation across multiple experimental runs. However, for systems where experiments are time-consuming or resource-intensive, performing multiple full experimental runs is often impractical.

To overcome this limitation, this chapter develops an adaptive midterm experimental redesign framework that operates within a single experimental run. The experiment is divided into a sequence of sub-experiments, within which parameter estimates are updated and sampling time designs are re-optimised. In this way, the design can adapt progressively as information is acquired, improving both robustness and estimation efficiency without requiring repeated full experiments. This framework bridges the gap between static robust

design and fully iterative redesign, providing a practical compromise between robustness and experimental cost.

The organisation of this chapter is as follows. First, the conceptual foundation and procedural framework of the midterm redesign strategy are introduced. Then, three adjustment strategies are proposed: the equally divided strategy, the auto-updating strategy, and the condition-triggered strategy. Finally, the proposed methods are evaluated using the two case study systems presented in Chapter 4.

5.1 Introduction of Mid-term Adjustment Design

The concept of midterm adjustment design is derived from iterative experimental design methods. Iterative design represents an indirect approach, in which both the robustness and effectiveness of the experimental design depend on the progressive refinement of parameter values (Barz et al., 2013). As illustrated in Figure 5.1, the iterative structure primarily takes three forms: sequential iterative, parallel iterative, and sequential–parallel mixed design (Franceschini and Macchietto, 2008).

The sequential iterative design requires fewer experimental resources; however, since experiments are repeated across multiple cycles, the overall process tends to be time-consuming. In contrast, the parallel iterative design reduces the time demand but requires multiple experimental setups. The sequential–parallel mixed design, often employed in large-scale experimental campaigns, imposes high requirements on both time and equipment.

A key advantage of these iterative designs is that parameter estimates can be updated in each cycle, enabling increasingly accurate parameter values to be used for optimal experimental design (OED) in subsequent iterations. Nevertheless, this improvement is achieved at the cost of increased experimental time and resource consumption.

Similar to the robust experimental design (RED) methods introduced in Chapter 4, these iterative approaches are essentially offline in nature. More recently, online experimental redesign strategies have been proposed, in which the information content is updated during

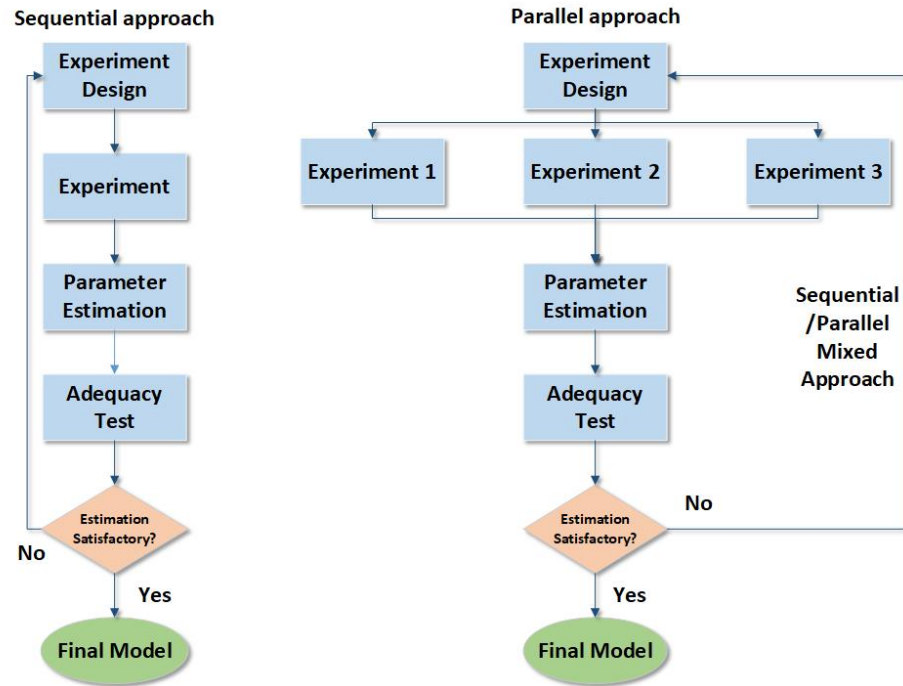


Fig. 5.1 Iterative experimental design methods

the experiment (Galvanin et al., 2012). This allows the information contained in the data to be progressively incorporated as the experiment proceeds. Online experimental redesign can therefore be viewed as a continuous extension of iterative design, and is also referred to as receding-horizon experimental design in the literature (Jayasankar et al., 2010).

Building on the concept of online experimental redesign, the proposed midterm adjustment design partitions a single experimental run into multiple design stages, referred to as sub-experiments. Prior to each sub-experiment, a new experimental design is generated based on the current nominal parameter values, which are updated using all data collected from previous sub-experiments. The overall procedure is illustrated in Figure 5.2.

Although conceptually straightforward, this approach presents several practical challenges in implementation. In the context of sampling time design, these include:

- How to define an effective midterm redesign strategy under limited prior knowledge, including the number of sub-experiments, their durations, and the allocation of sampling points;

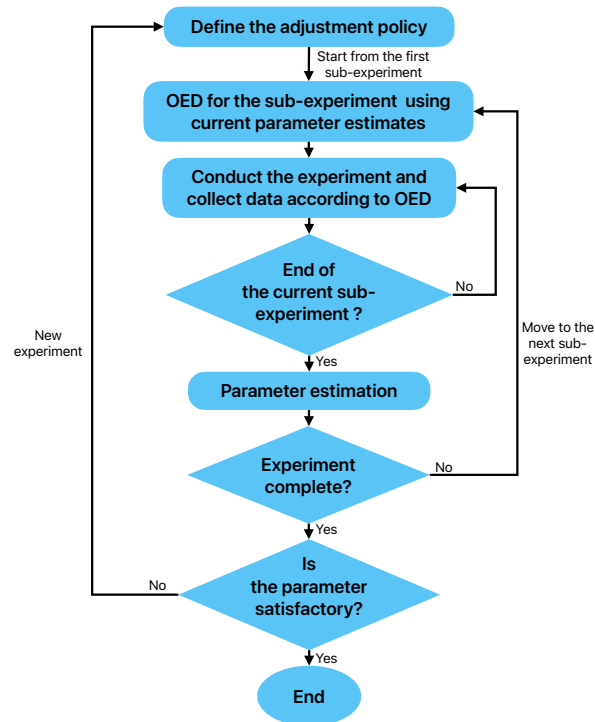


Fig. 5.2 Midterm adjustment experimental design procedure

- The OED for the first sub-experiment may be unreliable due to significant parametric uncertainty;
- Ensuring practical identifiability of unknown parameters in the early stages of the experiment;
- Adapting the design to evolving operating conditions during the experiment.

Consequently, a key challenge lies in developing a partitioning strategy that balances the need for sufficient information to enable reliable parameter estimation with the requirement to minimise disruption to the ongoing experiment. To address these challenges, this work proposes a robust sampling time design framework based on midterm adjustment. This single-run framework provides a practical alternative to multi-run iterative design, enabling adaptive updates of the experimental design without requiring repeated experiments.

Three redesign strategies are introduced: (i) an equally divided strategy, which partitions the total duration into uniform intervals; (ii) an auto-updating strategy, where division points are determined based on practical identifiability analysis; and (iii) a condition-triggered strategy, in which redesign is activated by changes in operating conditions.

To ensure robustness under parametric uncertainty, the first sub-experiment is designed using a maximin RED criterion. This provides a conservative but reliable initial design, safeguarding information content under worst-case parameter realisations.

5.2 Equally Divided Redesign Strategy

The equally divided redesign provides a simple and interpretable framework, particularly when the appropriate timing of redesign or the accuracy of initial parameter estimates is uncertain. This strategy partitions the total experimental duration into equal intervals, each assigned an identical number of sampling points. After each sub-experiment, all accumulated data are used to update the parameter estimates, which then serve as nominal values for the OED of the subsequent sub-experiment.

The detailed procedure for the midterm adjustment sampling time design using the equally divided strategy is outlined below:

1. Initialisation:

- (a) Divide the experimental duration into N_{exp} sub-experiments of equal length.
- (b) Initialise the parameter uncertainty space $\Theta = \left\{ \theta \mid \theta^L \preceq \theta \preceq \theta^U \right\}$.

2. First Sub-Experiment:

- (a) *Experimental design*: Maximin sampling time design.
- (b) *Data acquisition*: Conduct the experiment over the first sub-experiment and collect data according to the designed sampling strategy.
- (c) *Parameter estimation*: Estimate the model parameters.

3. Iterative adaptive loop:

For $K = 2$ to N_{exp} , repeat:

- (a) *OED*: Compute the optimal sampling strategy for the K -th sub-experiment using the updated parameter estimates.
- (b) *Data acquisition*: Execute the experiment over the K -th sub-experiment and collect additional data.
- (c) *Parameter estimation*: Re-estimate the parameters using all accumulated data.

4. **Termination**: The final sampling strategy is obtained by concatenating the designs from all sub-experiments.

Numerically, the experimental time horizon is discretised into N_T candidate sampling points with binary weighting variables, as defined in (3.42). Suppose the time horizon is equally divided into N_{exp} sub-experiment intervals. Each sub-experiment therefore contains $N_{sub} = N_T / N_{exp}$ candidate sampling points.

The discretised structure of the equally divided strategy is illustrated in (5.1):

$$\begin{aligned}
 &w_1, w_2, \dots, w_{N_{sub}}, \dots, w_{(K-1)N_{sub}+1}, \dots, w_{KN_{sub}}, \dots, w_{N_T} \\
 &\underbrace{t_1, t_2, \dots, t_{N_{sub}}}_{\text{first sub-exp}}, \dots, \underbrace{t_{(K-1)N_{sub}+1}, \dots, t_{KN_{sub}}}_{\text{K-th sub-exp}}, \dots, t_{N_T}, \quad K = 1, \dots, N_{exp}
 \end{aligned} \tag{5.1}$$

Assume that N_{st} sampling points are to be selected from the N_T candidates. In the equally divided strategy, each sub-experiment selects an equal number of sampling points, i.e. N_{st} / N_{exp} points from N_{sub} candidates.

The OED problem for the K -th sub-experiment is formulated as:

$$\begin{aligned}
 \mathbf{w}^{[K]} = & \arg \min_{\mathbf{w}} \phi \left(\left[\mathbf{FIM}^{[K]}(\mathbf{w}, \boldsymbol{\theta}) \right]^{-1} \right) \\
 \text{s.t. } & \sum_{l=1}^{N_{sub}} w_l = \frac{N_{st}}{N_{exp}}, \quad w_l \in \{0, 1\}
 \end{aligned} \tag{5.2}$$

where

$$\mathbf{FIM}^{[K]}(\mathbf{w}, \boldsymbol{\theta}) = \sum_{l=(K-1)N_{sub}+1}^{KN_{sub}} w_l \cdot \mathbf{S}^\top(t_l, \boldsymbol{\theta}) \boldsymbol{\Sigma}^{-1} \mathbf{S}(t_l, \boldsymbol{\theta}).$$

For the first sub-experiment, a fixed worst-case maximin design is adopted. The worst-case parameter $\boldsymbol{\theta}^{WC}$ is identified using particle swarm optimisation (PSO), and the sampling design is obtained by solving (5.2) under $\boldsymbol{\theta}^{WC}$. This allows the first-stage design to be naturally integrated into the iterative framework. The overall procedure is summarised in Algorithm 3.

Algorithm 3: Equally divided strategy for midterm adjustment experimental re-design

Data: Parametric uncertainty space $\Theta = \{\boldsymbol{\theta} \mid \boldsymbol{\theta}^L \preceq \boldsymbol{\theta} \preceq \boldsymbol{\theta}^U\}$

- 1 Identify worst-case parameter $\boldsymbol{\theta}^{WC}$ using PSO;
- 2 Initialise $\hat{\boldsymbol{\theta}}^{[1]} = \boldsymbol{\theta}^{WC}$;
- 3 Initialise dataset $\mathbf{D} = \emptyset$;
- 4 Set $K = 1$;
- 5 **while** $K \leq N_{exp}$ **do**
 - 6 Compute $\mathbf{w}^{[K]}$ via (5.2) using $\hat{\boldsymbol{\theta}}^{[K]}$;
 - 7 Collect data $\mathbf{D}^{[K]}$ according to $\mathbf{w}^{[K]}$;
 - 8 Update dataset $\mathbf{D} = [\mathbf{D}, \mathbf{D}^{[K]}]$;
 - 9 **if** $K < N_{exp}$ **then**
 - 10 Estimate parameters $\hat{\boldsymbol{\theta}}^{[K+1]}$ using $\mathbf{D}$ via the MultiStart fmincon-based constrained nonlinear least-squares procedure;
 - 11 **end**
 - 12 $K \leftarrow K + 1$;
- 13 **end**

Result: $\mathbf{w}^* = [\mathbf{w}^{[1]}, \dots, \mathbf{w}^{[N_{exp}]}]$

Practical identifiability analysis should be performed for the first sub-experiment, as it relies on the smallest dataset in the entire procedure. Ensuring identifiability at this stage is critical for obtaining reliable parameter estimates throughout the redesign process. To increase the identifiability in the first stage, one may reduce the number of sub-experiments N_{exp} or increase the total number of sampling points N_{st} .

The primary advantage of the equally divided strategy lies in its operational simplicity and predictability, requiring minimal in-experiment decision-making and enabling straightforward implementation. However, its main limitation is the lack of adaptability: the predefined update schedule does not respond to the actual evolution of parameter estimates or data quality, which may reduce information efficiency. Consequently, this strategy serves as a baseline against which more adaptive redesign strategies are evaluated.

5.3 Auto-updating Redesign Strategy

To enhance the adaptability of the midterm experimental redesign process, an auto-updating redesign strategy is proposed to explicitly address the challenge of practical identifiability. The central idea is to replace the fixed partitioning of the experiment with a dynamic division mechanism, in which the experimental horizon is adaptively segmented into sub-experiments.

During each sub-experiment, the information content of the collected data is evaluated with respect to parameter identifiability. Once the accumulated data provide sufficient information to ensure reliable parameter estimation, the current sub-experiment is terminated, and the model parameters are re-estimated. The updated parameter estimates are then used to redesign the sampling strategy for the subsequent sub-experiment. Unlike the equally divided strategy, each sub-experiment is not predefined but determined by the information content of the data.

Through this adaptive partitioning mechanism, the experimental design is continuously refined based on the evolving information content of the data. This enables the redesign process to maintain practical identifiability throughout the experiment, even under significant parametric uncertainty.

5.3.1 Dividing the sub-experiments

The Fisher Information Matrix (FIM) provides a convenient local measure of information content and can therefore be used to assess practical identifiability during the redesign process. A necessary condition for local practical identifiability is that the FIM is nonsingular (Guedj et al., 2007). Conversely, large or unbounded confidence intervals indicate that certain parameters cannot be reliably estimated under the current experimental setup.

The confidence interval (CI) of the j -th parameter can be approximated from the inverse of the FIM as

$$CI_j = \pm z_{1-\alpha/2} \sqrt{(\mathbf{FIM}^{-1})_{jj}}, \quad (5.3)$$

where $z_{1-\alpha/2}$ is the critical value of the standard normal distribution, e.g. $z_{0.975} = 1.96$ for a 95% confidence level.

A parameter is considered practically non-identifiable if the corresponding CI is excessively large relative to its magnitude or spans physically implausible values. This motivates the following practical identifiability criterion:

$$2z_{1-\alpha/2} \sqrt{(\mathbf{FIM}^{-1})_{jj}} \leq \kappa \cdot \theta_j. \quad (5.4)$$

where κ is a user-defined non-negative scalar that specifies the acceptable relative uncertainty level. For problems with bounded uncertainty $\boldsymbol{\theta}^L \preceq \boldsymbol{\theta} \preceq \boldsymbol{\theta}^U$, nominal parameter values may not be well defined at the initial stage. In this case, the right-hand side of (5.4) is replaced by $\kappa \cdot (\theta_j^U - \theta_j^L)$, which reflects the prior uncertainty range.

The choice of κ should reflect both the degree of parameter uncertainty and the stage of the redesign process. In the first sub-experiment, a relatively small κ is recommended to ensure sufficient information is collected for reliable parameter estimation despite limited data. In subsequent sub-experiments, κ may be decreased to make the redesign criterion more

stringent and thereby avoid overly frequent redesigns, particularly for systems of moderate complexity or low measurement noise.

As in the equally divided strategy, the first sub-experiment is designed using a fixed worst-case maximin approach, where the worst-case parameter is identified using PSO.

The auto-updating redesign strategy is summarised as follows:

1. Initialisation:

- (a) Define the parameter uncertainty space: $\Theta = \{\boldsymbol{\theta} \mid \boldsymbol{\theta}^L \preceq \boldsymbol{\theta} \preceq \boldsymbol{\theta}^U\}$.
- (b) Initialise the nominal parameter estimate using the worst-case parameter: $\hat{\boldsymbol{\theta}}^{[1]} = \boldsymbol{\theta}^{WC}$.
- (c) Select an initial value of κ .

2. Iterative adaptive loop:

For $K = 1, 2, \dots$ until the end of the experiment:

- (a) *Determine sub-experiment duration:* Extend the K -th sub-experiment until the identifiability condition (5.4) is satisfied.
- (b) *Experimental design:* Compute the optimal sampling strategy for the K -th sub-experiment using OED with $\hat{\boldsymbol{\theta}}^{[K]}$.
- (c) *Data acquisition:* Conduct the experiment over the current sub-experiment and collect data according to the designed sampling strategy.
- (d) *Parameter estimation:* Update $\hat{\boldsymbol{\theta}}^{[K+1]}$ using all accumulated data.
- (e) *Termination check:* If the end of the experiment is reached, terminate; otherwise, set $K \leftarrow K + 1$ and continue.

3. Output: The final sampling strategy is obtained by concatenating the sampling strategies from all sub-experiments.

5.3.2 Allocating sampling point numbers for sub-experiments

From the procedure of the auto-updating strategy, the duration of each sub-experiment is determined adaptively to ensure sufficient information for parameter estimation. However, the number of sampling instants within each sub-experiment is not explicitly specified and must be allocated separately.

A simple approach is to assign a fixed number of sampling points to each sub-experiment. Alternatively, the number of samples can be determined adaptively based on the information content of each sub-experiment.

Let $N^{[1]}$ denote the number of samples assigned to the first sub-experiment. For $K \geq 2$, the number of samples for the K -th sub-experiment can be defined as

$$N^{[K]} = \left(\sum_{i=1}^{K-1} N^{[i]} \right) \cdot \frac{\lambda_{\min}(\mathbf{FIM}^{[K]})}{\lambda_{\min}(\sum_{i=1}^{K-1} \mathbf{FIM}^{[i]})}, \quad (5.5)$$

where $\lambda_{\min}(\cdot)$ denotes the smallest eigenvalue. This formulation allocates sampling effort proportionally to the incremental information content of the current sub-experiment relative to previously accumulated information. However, this approach does not provide explicit control over the total number of sampling points. It is therefore more suitable for experimental settings where data collection cost is not tightly constrained.

To enforce a fixed total number of sampling instants, denoted by N_{st} , a normalised allocation strategy can be adopted. Specifically, the number of samples for the K -th sub-experiment is defined as

$$N^{[K]} = \left(N_{st} - \sum_{i=1}^{K-1} N^{[i]} \right) \cdot \frac{\lambda_{\min}(\mathbf{FIM}^{[K]})}{\lambda_{\min}(\sum_{t_i \in \mathcal{T}^{[K]}} \mathbf{FIM}(t_i))}, \quad (5.6)$$

where $\mathcal{T}^{[K]}$ denotes the set of candidate time points from the start of the K -th sub-experiment to the end of the experiment.

In practice, the computed values of $N^{[K]}$ must be rounded to integers. This may introduce additional issues, particularly in early sub-experiments. For instance, if the first sub-experiment contributes relatively little information, the allocation rule in (5.6) may yield $N^{[K]} = 0$, which is not admissible.

To address this, a lower bound N_p should be imposed on the number of samples in the first sub-experiment, ensuring that the collected data are sufficient for parameter estimation (typically exceeding the number of parameters). Also, due to the use of worst-case parameter values in the initial design, the estimated information content may be inaccurate, potentially leading to an excessively large $N^{[1]}$. Therefore, an upper bound on $N^{[1]}$ should also be enforced. As a practical alternative, one may directly prescribe a fixed number of samples for the first sub-experiment, while applying adaptive allocation only to subsequent sub-experiments. This provides a robust initialisation while retaining flexibility in later stages.

5.3.3 Implementation and pseudo-code

The numerical solution of the sampling-time design follows the discretisation of the time horizon introduced in (3.42). Sampling-time optimisation is performed using the Powell-type discrete exchange procedure. Parameter estimation at each redesign point is formulated as a constrained nonlinear least-squares problem and solved using MATLAB `fmincon` with the active-set algorithm and a three-start MultiStart procedure to reduce sensitivity to local minima.

The pseudo-code of the auto-updating strategy is presented in Algorithm 4. Two logical indicators are introduced to control the iterative procedure:

- the experiment-end indicator (*ExpPt*), which is set to 1 when the overall experiment reaches its final time;
- the sub-experiment-end indicator (*SubPt*), which is set to 1 when the identifiability condition in (5.4) is satisfied.

Algorithm 4: Auto-updating strategy for midterm adjustment experimental redesign

Data: Parametric uncertainty space $\Theta = \{\theta \mid \theta^L \preceq \theta \preceq \theta^U\}$

- 1 Find the worst-case parameter θ^{WC} using PSO;
- 2 Initialise $\hat{\theta} \leftarrow \theta^{WC}$;
- 3 Initialise dataset $\mathbf{D} \leftarrow \emptyset$;
- 4 Set $ExpPt \leftarrow 0$, $SubPt \leftarrow 0$;
- 5 Set $K \leftarrow 1$;
- 6 Set starting time $T_s \leftarrow t_1$ and time interval T_{int} ;
- 7 **while** $ExpPt = 0$ **do**
 - 8 Set $L \leftarrow 0$;
 - 9 Set $SubPt \leftarrow 0$;
 - 10 // Determine sub-experiment horizon
 - 11 **while** $SubPt = 0$ **do**
 - 12 Define candidate sub-experiment time grid: $\mathbf{t}_{sub} = [T_s, \dots, T_s + L \cdot T_{int}]$;
 - 13 **if** *identifiability condition (5.4) is satisfied* **then**
 - 14 $SubPt \leftarrow 1$;
 - 15 **end**
 - 16 **if** $T_s + L \cdot T_{int} \geq t_{N_T}$ **then**
 - 17 $SubPt \leftarrow 1$;
 - 18 $ExpPt \leftarrow 1$;
 - 19 **end**
 - 20 $L \leftarrow L + 1$;
 - 21 **end**
 - 22 // Sampling allocation and design
 - 23 Determine the number of samples $N^{[K]}$ for $\mathbf{t}_{sub}$;
 - 24 Obtain optimal sampling strategy $\mathbf{w}^{[K]}$ for $\mathbf{t}_{sub}$ via OED using $\hat{\theta}$ and the Powell-type discrete exchange procedure;
 - 25 // Data acquisition and update
 - 26 Collect data according to $\mathbf{w}^{[K]}$ and update dataset $\mathbf{D}$;
 - 27 Estimate parameters $\hat{\theta}$ using all accumulated data $\mathbf{D}$ via the MultiStart fmincon-based constrained nonlinear least-squares procedure;
 - 28 // Move to next sub-experiment
 - 29 Update $T_s \leftarrow T_s + L \cdot T_{int}$;
 - 30 $K \leftarrow K + 1$;
- 31 **end**

Result: Concatenated sampling strategy $\mathbf{w}^* = [\mathbf{w}^{[1]}, \mathbf{w}^{[2]}, \dots]$

This implementation realises an information-driven partitioning of the experiment, where both the timing and density of measurements are adapted online based on identifiability criteria.

5.4 Condition-triggered Redesign Strategy

The condition-triggered midterm redesign strategy adapts the experimental design in response to changes observed during the experiment. By reacting to in-process variations, this approach enables timely refinement of both parameter estimates and sampling strategies, making it particularly suitable for systems with evolving operating conditions.

In contrast to pre-scheduled partitioning and identifiability-driven partitioning, condition-triggered redesign initiates updates only when a prescribed event occurs during the experiment. In principle, such events may include changes in controllable operating variables (e.g. temperature, pressure, or flow rate), deviations in observed data trends, or external disturbances. In this work, the trigger is defined by a change in the operating conditions. Once the trigger is activated, the current sub-experiment is terminated, the model parameters are re-estimated using all data collected up to that point, and a new sampling time design is computed for the remaining experimental horizon.

As in the equally divided and auto-updating strategies, the first sub-experiment is designed using a fixed worst-case maximin approach in order to provide robustness against the initial parametric uncertainty. After the trigger event, the sampling time design for the subsequent sub-experiment is determined by solving the sub-experiment OED problem in (5.2) using the updated parameter estimates and the candidate time points associated with the remaining horizon. The final sampling strategy is then obtained by concatenating the designs from all triggered sub-experiments.

The number of sampling points assigned to each sub-experiment may be specified in advance or determined according to practical considerations. When the trigger corresponds to a known operating-condition change, a simple and effective choice is to partition the total

number of sampling points between the pre-trigger and post-trigger intervals. If greater flexibility is required, the adaptive allocation rule in (5.6) may also be used.

The overall procedure of the condition-triggered strategy can be summarised as follows:

1. Initialisation:

- (a) Define the parameter uncertainty space $\Theta = \{\theta \mid \theta^L \preceq \theta \preceq \theta^U\}$.
- (b) Identify the worst-case parameter θ^{WC} and initialise the first sub-experiment accordingly.
- (c) Specify the trigger condition for redesign.

2. First sub-experiment:

- (a) Compute the initial sampling design using the fixed worst-case maximin strategy.
- (b) Conduct the experiment and collect data until the trigger condition is met.

3. Triggered redesign:

- (a) Terminate the current sub-experiment once the trigger event occurs.
- (b) Re-estimate the model parameters using all accumulated data.
- (c) Compute a new sampling time design for the remaining experimental horizon using the updated parameter estimates.

4. Termination: Repeat the above procedure until the end of the experiment is reached.

The overall sampling strategy is obtained by concatenating the designs from all sub-experiments.

Through this mechanism, the sampling design can be updated in response to changes in the current system behaviour. The use of automated triggers reduces reliance on manual intervention and enables rapid response to condition changes. However, the effectiveness of this strategy depends on both the reliability of the parameter estimates and the timing of the trigger. When initial uncertainty is large, early-stage parameter estimates may be insufficiently accurate, potentially leading to premature or suboptimal redesign decisions.

Conversely, if the trigger occurs too late, informative sampling windows occurring earlier in the experiment may already have been missed.

5.5 Mid-term Redesign for the Enzyme Reaction System

In this section, the enzyme reaction system introduced in Chapter 4 is used to demonstrate the equally divided and auto-updating strategies for midterm adjustment experimental redesign under parametric uncertainty. The nominal parameter values are listed in Table A.2. The initial concentrations of the controllable species **S**, **N**, and **E** are set to $[\mathbf{S}_0, \mathbf{N}_0, \mathbf{E}_0] = [0.8, 0.9, 1.5 \times 10^{-5}]$ mol/L. The three most sensitive parameters, $[k_2, k_{-3}, k_5W]$, are selected for estimation, with nominal values $\boldsymbol{\theta}^* = [100, 200, 5000]$. These nominal values are treated as the ground truth, and synthetic (in silico) data generated from them are regarded as experimental observations for parameter estimation throughout the midterm redesign process. For each measured output y_i , the measurement noise is assumed to be Gaussian with zero mean and a standard deviation given by $\sigma_i = 0.1 y_i + 10^{-4}$.

This case study enables a direct comparison between static robust designs and adaptive midterm redesign strategies under identical modelling assumptions.

5.5.1 Design methods and results

The measurable time grid is defined as $[10:10:6000]$ s, yielding a total of $N_T = 600$ candidate sampling instants. From these, $N_{st} = 21$ sampling points are selected through experimental design. Four design strategies are applied to the enzyme reaction system for comparison:

- *Classical OED*. The design is obtained using the nominal parameter values $\boldsymbol{\theta}^*$.
- *Maximin design*. The maximin problem is solved using the fixed worst-case strategy, where the worst-case parameter is identified within the uncertainty space using PSO.

Methods	Results (s)	D-value
OED	[570:10:630, 2830:10:2880, 4260:10:4330]	-10.74
Maximin	[300:10:360, 500:10:560, 710:10:770]	-17.54
Midterm (equally)	[320, 330, 520, 530, 730:10:750, 2010:10:2040, 3980:10:4050, 4810, 4820]	-11.15
Midterm (auto)	[330, 340, 500, 510, 670:10:730, 2670:10:2700, 3580:10:3620, 5990]	-12.24

Table 5.1 Sampling time designs for the enzyme reaction system under moderate uncertainty $[0.01\theta^*, 3\theta^*]$

- *Mid-term redesign (equally divided strategy)*. The experimental duration is partitioned into three equal sub-experiments with time grids [10:10:2000], [2010:10:4000], and [4010:10:6000]. The first sub-experiment adopts the maximin design, while subsequent sub-experiments use classical OED based on updated parameter estimates. Each sub-experiment selects seven sampling points.
- *Mid-term redesign (auto-updating strategy)*. The procedure is initialised using the worst-case parameter, with $\kappa = 0.1$. As data accumulate, the identifiability threshold is progressively tightened by updating $\kappa \leftarrow 0.1\kappa$ for subsequent sub-experiments, promoting improved parameter identifiability while avoiding excessive subdivision.

All designs are obtained under the D-optimal criterion using the Powell-type discrete exchange procedure. The resulting sampling strategies and corresponding D-values are reported in Tables 5.1 and 5.2 for two uncertainty levels.

Two uncertainty levels, $[0.01\theta^*, 3\theta^*]$ and $[0.01\theta^*, 10\theta^*]$, are considered to investigate the sensitivity of the design strategies to boundary effects, given that maximin design is inherently driven by boundary parameter settings. The corresponding worst-case parameters identified by PSO are [300, 600, 15000] and [1000, 2000, 50000], respectively.

The detailed results of these experimental design strategies are summarised in Table 5.1 for the uncertainty range $[0.01\theta^*, 3\theta^*]$ and Table 5.2 for $[0.01\theta^*, 10\theta^*]$. The nominal OED result is omitted in Table 5.2 for brevity, as it does not depend on the uncertainty

Methods	Results (s)	D-value
Maximin	[3440, 3470, 3710, 4030, 4450, 4490, 4600:10:4650, 4670, 4690:10:4740, 4770, 5780]	-16.39
Midterm (equally)	[1940:10:2030, 2660, 2670, 3990:10:4050, 4940, 4950]	-14.30
Midterm (auto)	[170:10:230, 1180:10:1200, 2400:10:2420, 3160:10:3190, 4170:10:4190, 5990]	-11.67

Table 5.2 Sampling time designs for the enzyme reaction system under severe uncertainty $[0.01\theta^*, 10\theta^*]$

range and is identical to that reported in Table 5.1. For these two uncertainty settings, the auto-updating strategy determines the sub-experiment boundaries at $[690, 3940, 6000]$ s and $[300, 3150, 5980, 6000]$ s, respectively, reflecting its adaptive response to the evolving information content.

The two tables also report the D-values (logarithmic determinants of the FIM) evaluated at the nominal parameter values. As expected, the classical OED achieves the highest D-values in both cases, since it is optimised at the nominal parameters and therefore yields the largest information content. In contrast, the maximin design produces the lowest D-values, reflecting its conservative focus on worst-case parameter realisations. The midterm redesign strategies, although initialised from the same worst-case conditions, recover a substantial portion of the nominal information content and consistently outperform the maximin design.

To visualise the sampling patterns, Figures 5.3 and 5.4 present the sampling designs under the two uncertainty settings. The circles indicate the selected measurement time points, while the absolute parameter sensitivities are also shown in Figure 5.3 for reference.

The classical OED (blue circles) concentrates sampling points near the peaks of the sensitivity functions, thereby maximising local information content. In addition, it selects sampling times within 4260:10:4330 s, where the measurement noise—being proportional to the state values—is relatively small, leading to a larger FIM. In contrast, the maximin designs (red circles) exhibit strong dependence on the prescribed uncertainty bounds, resulting in markedly different sampling patterns across the two uncertainty ranges.

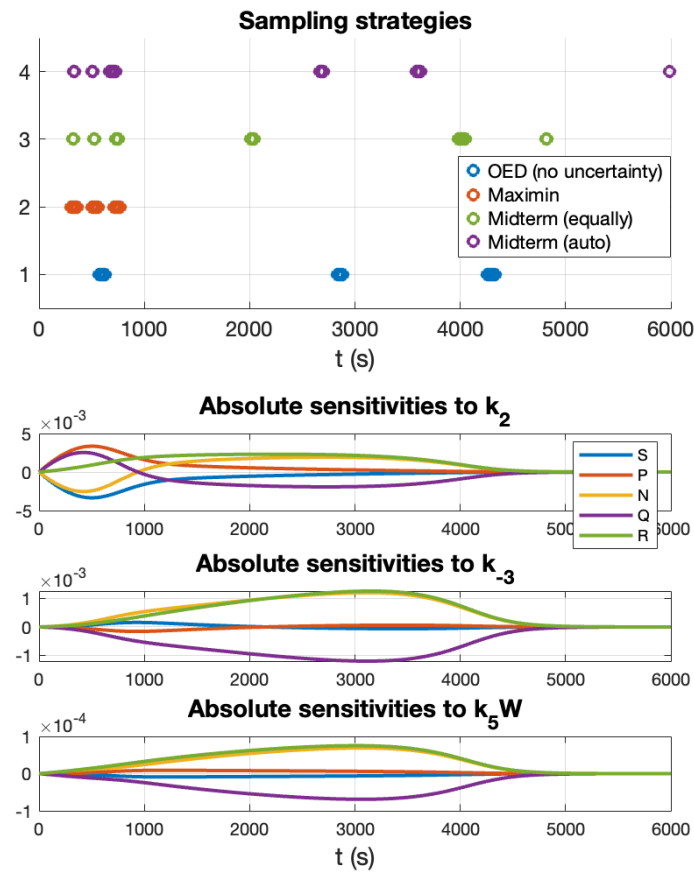


Fig. 5.3 Sampling patterns for enzyme reaction system with parametric uncertainty $[0.01\theta^*, 3\theta^*]$ (nominal OED, maximin, equally divided and auto-updating midterm re-design)

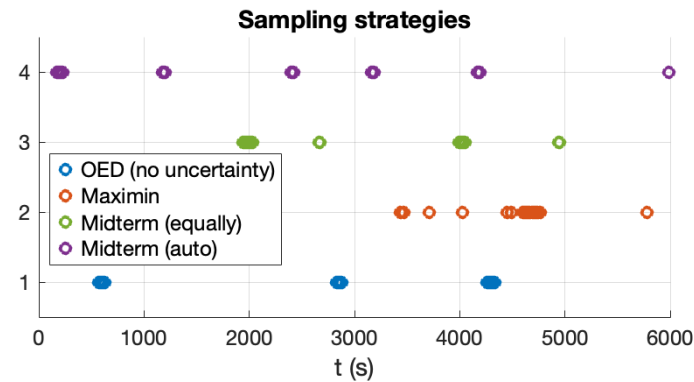


Fig. 5.4 Sampling patterns for enzyme reaction system with parametric uncertainty $[0.01\theta^*, 10\theta^*]$ (nominal OED, maximin, equally divided and auto-updating midterm re-design)

For the moderate uncertainty range $[0.01\theta^*, 3\theta^*]$, both midterm redesign strategies initially follow the maximin design in the early stage, ensuring robustness, while subsequently incorporating informative regions identified by classical OED, such as 570:10:630 s. This combination enables reliable parameter estimation after the first sub-experiment.

When the uncertainty range is expanded to $[0.01\theta^*, 10\theta^*]$, clearer differences emerge. The equally divided strategy allocates excessive early sampling points to low-information regions, reducing the effectiveness of the initial parameter update. In contrast, the auto-updating strategy triggers an earlier refinement (around 300 s) and progressively shifts sampling towards more informative regions that align more closely with classical OED. Meanwhile, the maximin design concentrates most sampling points in the later stages of the experiment, thereby failing to exploit early-time regions with strong parameter sensitivities.

As discussed in Chapter 4, the clustered sampling patterns obtained here should be interpreted within the discretised in-silico design setting. For the enzyme system, the 10 s candidate interval defines the temporal resolution of the optimisation problem rather than a universal experimental sampling requirement. In practical applications, feasibility constraints, such as a minimum interval between consecutive samples, a maximum number of measurements within a prescribed time window, and limitations associated with sample acquisition and processing, can be incorporated explicitly into the sampling-time design.

5.5.2 Performance Analysis

The enzyme reaction system serves as an illustrative benchmark in which the nominal parameter values (Table A.2) are treated as the “true” parameters. This enables direct evaluation of parameter estimation quality through the CIs.

Confidence ellipsoids for the parameter pairs (k_2, k_{-3}) and (k_{-3}, k_5W) are shown in Figure 5.5 for the uncertainty range $[0.01\theta^*, 3\theta^*]$, and in Figure 5.6 for $[0.01\theta^*, 10\theta^*]$. The classical OED (solid blue) serves as the reference, with nominal parameter values indicated by blue markers, while the maximin, equally divided, and auto-updating midterm strategies

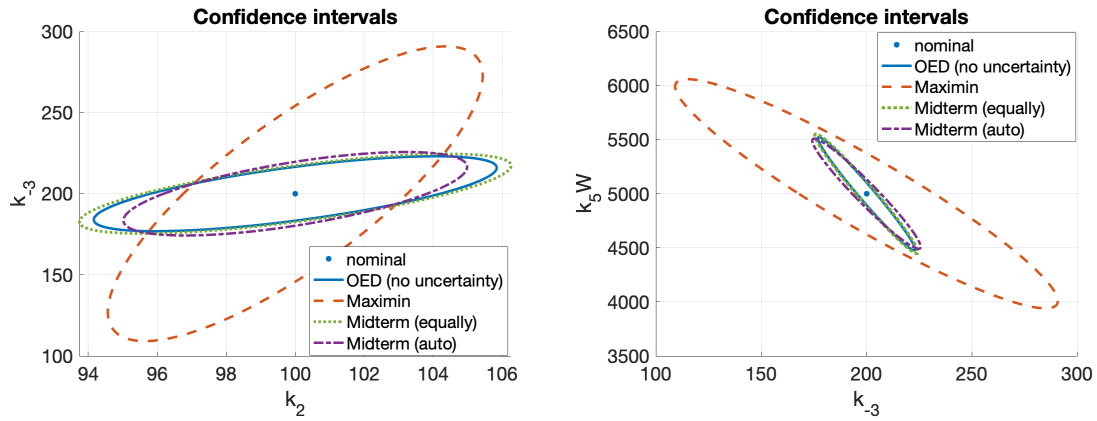


Fig. 5.5 Confidence ellipses for $k_2 - k_{-3}$ and $k_{-3} - k_5W$ plane of sampling strategy obtained by OED, maximin, equally divided midterm redesign and auto-updating midterm redesign for the enzyme reaction system under parametric uncertainty $[0.01\theta^*, 3\theta^*]$

Parameter (nominal)	Design strategy	CI	Percentage
k_2 (100)	OED (nominal)	± 4.68	4.68%
	Maximin	± 4.35	4.35%
	Midterm (equally)	± 5.01	5.01%
	Midterm (auto)	± 3.99	3.99%
k_{-3} (200)	OED (nominal)	± 18.49	9.25%
	Maximin	± 72.76	36.38%
	Midterm (equally)	± 19.64	9.82%
	Midterm (auto)	± 20.60	10.30%
k_5W (5000)	OED (nominal)	± 419.2	8.38%
	Maximin	± 848.4	16.97%
	Midterm (equally)	± 442.8	8.86%
	Midterm (auto)	± 407.8	8.16%

Table 5.3 The 95% CI, the percentages of the CI w.r.t. the nominal value of the parameters of sampling strategy obtained by OED, maximin, equally divided midterm redesign and auto-updating midterm redesign under parametric uncertainty $[0.01\theta^*, 3\theta^*]$

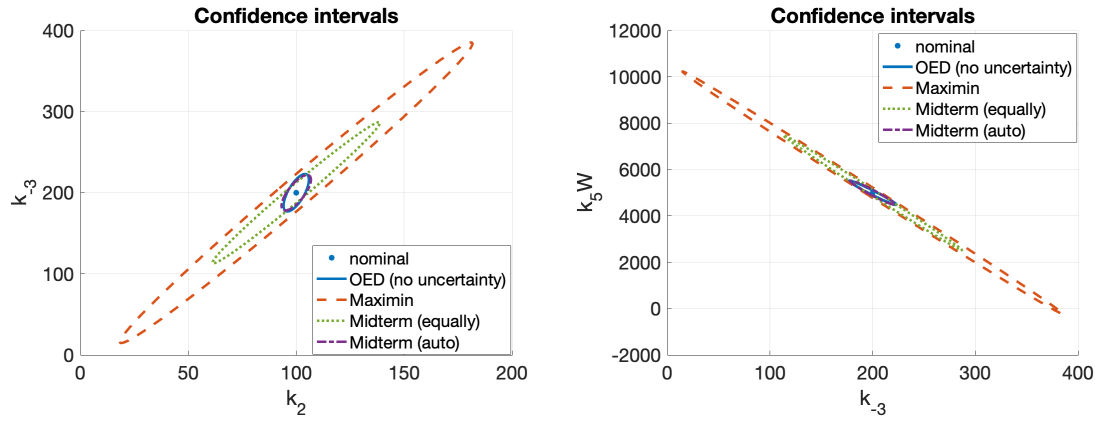


Fig. 5.6 Confidence ellipses for (k_2, k_{-3}) and (k_{-3}, k_5W) sampling strategy obtained by OED, maximin, equally divided midterm redesign and auto-updating midterm redesign for the enzyme reaction system under parametric uncertainty $[0.01\theta^*, 10\theta^*]$

Parameter (nominal)	Design strategy	CI	Percentage
k_2 (100)	OED (nominal)	± 4.68	4.68%
	Maximin	± 65.41	65.4%
	Midterm (equally)	± 31.03	31.03%
	Midterm (auto)	± 5.45	5.45%
k_{-3} (200)	OED (nominal)	± 18.49	9.25%
	Maximin	± 148.4	74.2%
	Midterm (equally)	± 69.65	34.83%
	Midterm (auto)	± 17.50	8.75%
k_5W (5000)	OED (nominal)	± 419.2	8.38%
	Maximin	± 4192	83.84%
	Midterm (equally)	± 1987	39.74%
	Midterm (auto)	± 416.3	8.32%

Table 5.4 The 95% confidence interval (CI), the percentages of the CI w.r.t. the nominal value of the parameters of sampling strategy obtained by maximin, equally divided midterm redesign and auto-updating midterm redesign for the enzyme reaction system under parametric uncertainty $[0.01\theta^*, 10\theta^*]$

are represented by red dashed, green dashed, and purple dash-dotted ellipses, respectively. To quantify the FIM-based predicted parameter precision, the CIs of the three unknown parameters are computed using (5.3) and summarised in Tables 5.3 and 5.4.

Across both uncertainty levels, the auto-updating midterm redesign produces confidence regions nearly identical to those of the classical OED, achieving comparable CIs despite the absence of accurate initial parameter knowledge. This indicates that adaptive redesign can effectively recover near-optimal sampling strategies under uncertainty.

The equally divided strategy performs similarly under moderate uncertainty but degrades under severe uncertainty. The CI percentages increase substantially (e.g. from 4.68% to 31.03% for k_2 , 9.25% to 34.83% for k_{-3} , and 8.38% to 39.74% for k_5W), indicating reduced robustness. The maximin design generally yields the largest confidence regions, particularly for k_{-3} and k_5W and under severe uncertainty, reflecting its conservative worst-case formulation and the associated reduction in local parameter estimation precision near the nominal regime.

These trends are broadly consistent with the D-values reported in Tables 5.1 and 5.2. The classical OED achieves the highest D-values, as expected because it is optimised directly at the nominal parameter values used for this evaluation, while the maximin design yields the lowest. Among the midterm strategies, the auto-updating method performs best under severe uncertainty, whereas under moderate uncertainty the equally divided strategy attains a D-value slightly closer to classical OED. This indicates that the auto-updating strategy shows the more robust trend as the uncertainty level increases.

Overall, both midterm redesign strategies improve upon the maximin design, but the auto-updating approach uniquely maintains near-optimal performance under substantial parametric uncertainty through adaptive refinement during the experiment.

5.6 Mid-term redesign for the biodiesel production system

In this section, midterm redesign strategies are applied to determine optimal sampling time points for the enzymatic biodiesel production system under parametric uncertainty. Compared with the enzyme reaction system, this model is higher-dimensional, involves a larger set of parameters, and exhibits wider parameter magnitude variations, making it a more challenging test case.

Nominal parameter values are given in Table B.3, and the experimental configuration follows Exp. 8 in Table B.2. Exp. 8 is selected because its prescribed methanol-feed change provides a suitable setting for evaluating the condition-triggered midterm redesign strategy. The methanol feed rate F_a is maintained at 0.185 Eq./h for the first two hours and then reduced to 0.06 Eq./h. The initial conditions are $\mathbf{CH}(0) = 0.2$ eq, $\mathbf{W}(0) = 5$ wt.% oil, and $\mathbf{E}_{bulk}(0) = 0.5$ wt.% oil.

Since the methanol feed rate F_a changes at 120 min, this time is used as the trigger point for the condition-triggered redesign strategy. Based on the sensitivity analysis in Yu et al. (2018a), four kinetic parameters, k_2 , k_6 , k_8 , and k_9 , are selected for estimation, with nominal values $\boldsymbol{\theta}^* = [1.69 \times 10^6, 9.13 \times 10^4, 2.36 \times 10^4, 2.54 \times 10^4]$. Measurement noise is assumed to be independent and Gaussian with zero mean, and a standard deviation given by $\sigma_i = 0.05y_i + 0.01$.

5.6.1 Design methods and results

The measurable sampling instants are defined as $[5:5:1500]$ min, yielding $N_T = 300$ candidate points, from which $N_{st} = 28$ sampling instants are selected. Parametric uncertainty is assumed to be uniformly distributed within $\boldsymbol{\theta}^L = 0.01\boldsymbol{\theta}^*$ and $\boldsymbol{\theta}^U = 100\boldsymbol{\theta}^*$.

Five design strategies are considered:

- *Classical OED (nominal)* using $\boldsymbol{\theta}^*$.

Methods	Results (min)	D-value
OED	[35:5:115, 615:5:665]	-53.91
Maximin	[5:5:25, 555:5:665]	-56.09
Midterm (equally)	[5:5:20, 585:5:630, 755:5:820]	-56.88
Midterm (auto)	[5:5:25, 210:5:300, 540:5:550, 790]	-55.77
Midterm (condition)	[5:5:25, 80:5:170, 540:5:555]	-54.96

Table 5.5 Sampling time design for biodiesel production system with parametric uncertainty $[0.01\theta^*, 100\theta^*]$

- *Maximin design.* Solved via the fixed worst-case approach over $\Theta = \{\theta \mid \theta^L \preceq \theta \preceq \theta^U\}$ with an equally divided initial design. The worst-case parameter $[1.69 \times 10^8, 9.13 \times 10^6, 2.36 \times 10^6, 2.54 \times 10^6]$ is identified using PSO.
- *Mid-term redesign (equally divided strategy).* The horizon is split into two equal intervals, $[5:5:750]$ min and $[755:5:1500]$ min, with 14 sampling points selected in each sub-experiment.
- *Mid-term redesign (auto-updating strategy).* Using Algorithm 4 with initial $\kappa = 0.01$, the horizon is partitioned into three sub-experiments: $[5:5:250]$ min, $[255:5:785]$ min, and $[790:5:1500]$ min. The corresponding numbers of samples are 14, 13, and 1, determined by (5.6) under the constraint $N_{st} = 28$.
- *Mid-term redesign (condition-triggered strategy).* The redesign is triggered at 120 min due to the change in methanol feed rate F_a , resulting in two sub-experiments: $[5:5:120]$ min and $[125:5:1500]$ min, each with 14 sampling points.

All OED problems are solved using the Powell-type discrete exchange procedure under the D-optimality criterion. The final sampling designs and their corresponding D-values (log-determinants of the FIM evaluated at the nominal parameters) are summarized in Table 5.5. For visualization, the resulting sampling instants are plotted together with the absolute sensitivities in Figure 5.7. Sampling instants selected by nominal-parameter OED, maximin design, equally divided redesign, auto-updating redesign, and condition-triggered redesign are shown using blue, red, green, purple, and yellow markers, respectively.

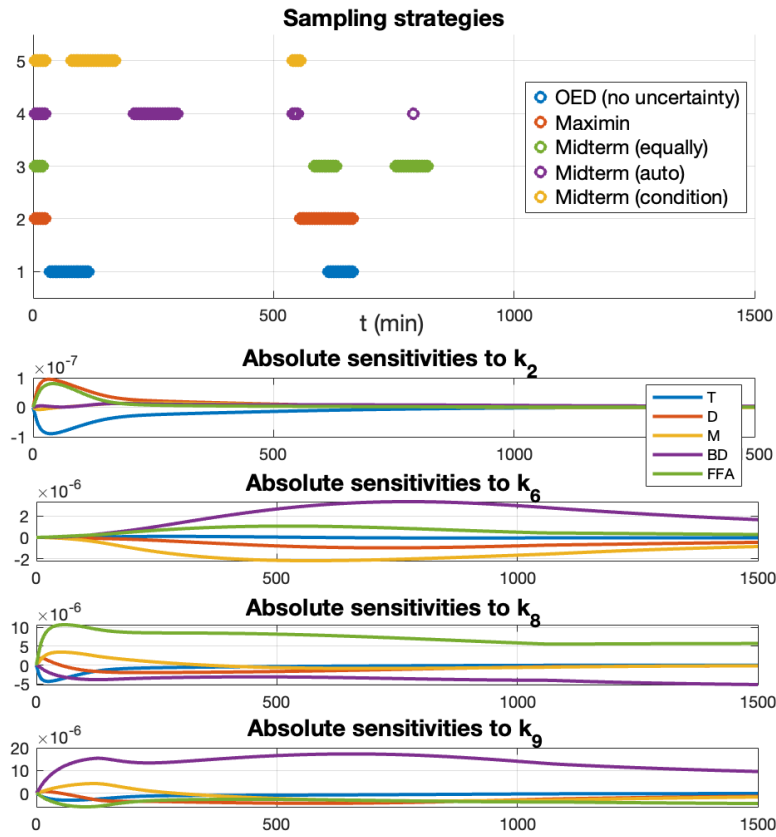


Fig. 5.7 Sampling time design results for biodiesel production system with parametric uncertainty $[0.01\theta^*, 100\theta^*]$

As seen in Figure 5.7, both the classical OED and the maximin design place all 28 sampling points within the early stage of the experiment (first half of the horizon), where the sensitivities are maximal. Moreover, all three midterm redesign methods include sampling points coinciding with the maximin design within the first 25 minutes, confirming their consistency under high uncertainty.

The D-values in Table 5.5 further distinguish the performance among strategies. The equally divided redesign exhibits the lowest D-value, worse even than the maximin design, because half of its sampling points are forced into the late stage of the experiment (after 750min), where information content is low. Note that all 28 sampling points are selected in the first 700 min by OED using nominal parameters. The condition-triggered redesign

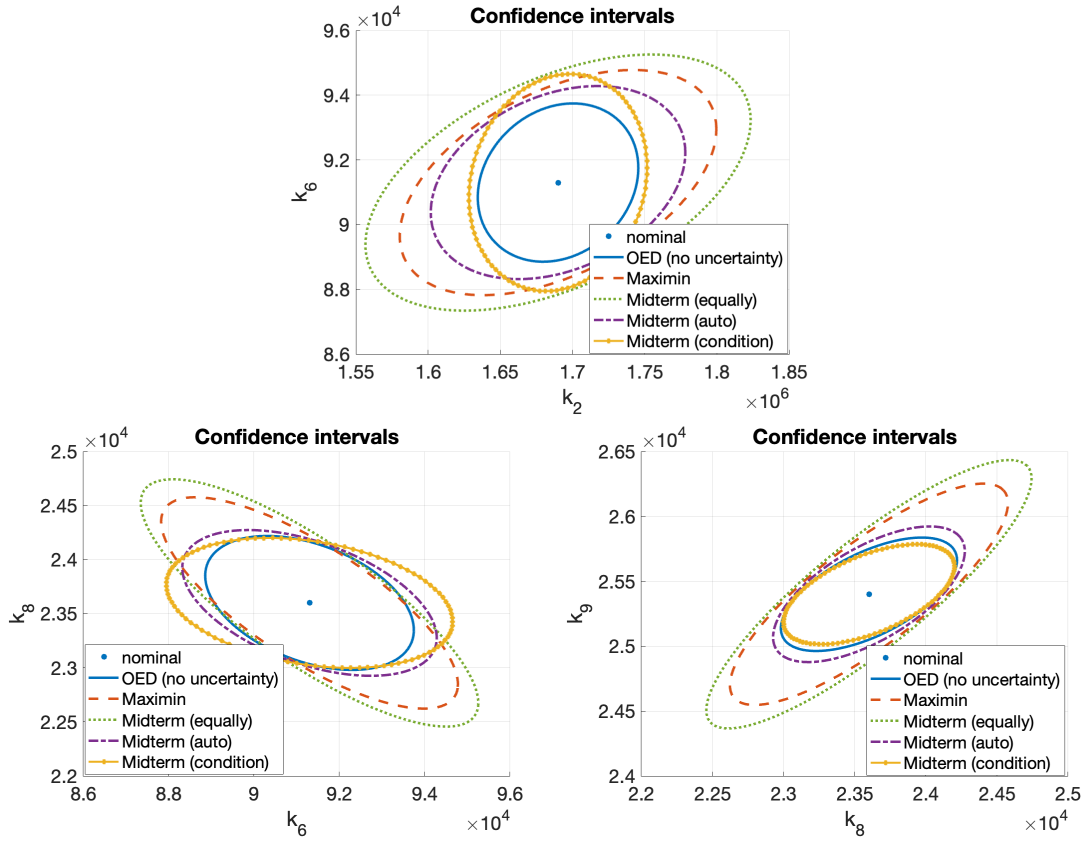


Fig. 5.8 Confidence ellipse on k_2 - k_6 , k_6 - k_8 and k_8 - k_9 surface of the sampling strategies obtained by OED, maximin, equally divided midterm redesign, auto-updating midterm redesign and condition-triggered midterm redesign for the biodiesel production system under parametric uncertainty $[0.01\theta^*, 100\theta^*]$

achieves the highest D-value among the redesign methods in this case. Its relatively early redesign at the prescribed 120-min operating-condition change allows the remaining sampling schedule to be re-optimised before the informative early-time region for k_2 is completely missed. The auto-updating strategy yields intermediate performance, reflecting its adaptive yet conservative allocation across the three inferred sub-experiments.

5.6.2 Performance Analysis

The nominal parameter values in Table B.3 are treated as the true values for constructing confidence hyper-ellipsoids of the estimated parameters under each design strategy. These are visualised through selected parameter pairs, namely, (k_2, k_6) , (k_6, k_8) , and (k_8, k_9)

Parameter (nominal)	Design strategy	CI	Percentage
k_2 (1.69×10^6)	OED (nominal)	$\pm 4.45 \times 10^4$	2.63%
	Maximin	$\pm 8.78 \times 10^4$	5.20%
	Midterm (equally)	$\pm 1.07 \times 10^5$	6.33%
	Midterm (auto)	$\pm 7.05 \times 10^4$	4.17%
	Midterm (condition)	$\pm 4.94 \times 10^4$	2.92%
k_6 (9.13×10^4)	OED (nominal)	$\pm 1.96 \times 10^3$	2.15%
	Maximin	$\pm 2.79 \times 10^3$	3.06%
	Midterm (equally)	$\pm 3.17 \times 10^3$	3.47%
	Midterm (auto)	$\pm 2.39 \times 10^3$	2.62%
	Midterm (condition)	$\pm 2.69 \times 10^3$	2.95%
k_8 (2.36×10^4)	OED (nominal)	± 495.8	2.1%
	Maximin	± 782.6	3.32%
	Midterm (equally)	± 915.6	3.88%
	Midterm (auto)	± 539.7	2.29%
	Midterm (condition)	± 480.9	2.04%
k_9 (2.54×10^4)	OED (nominal)	± 350.0	1.38%
	Maximin	± 682.9	2.69%
	Midterm (equally)	± 827.9	3.26%
	Midterm (auto)	± 418.4	1.65%
	Midterm (condition)	± 308.2	1.21%

Table 5.6 The 95% CI, the percentages of the CI w.r.t. the nominal value of the parameters of sampling strategy obtained by OED, maximin, equally divided midterm redesign, auto-updating midterm redesign and condition-triggered midterm redesign for the biodiesel production system under parametric uncertainty $[0.01\theta^*, 100\theta^*]$

(Figure 5.8). The classical OED, maximin, equally divided, auto-updating, and condition-triggered strategies are represented by solid blue, dashed red, dotted green, dash-dotted purple, and yellow asterisk markers, respectively. To provide a quantitative comparison, the corresponding 95% CIs, computed using (5.3), are reported in Table 5.6.

The results show that both the condition-triggered and auto-updating strategies achieve parameter-estimation precision close to that of the classical OED, while clearly outperforming the maximin design.

The condition-triggered strategy yields the narrowest confidence intervals for k_8 and k_9 , and also gives a narrower interval for k_2 than the auto-updating strategy, whereas its interval for k_6 is slightly wider. Its favourable performance in this case is associated with

the relatively early redesign at 120 min, which helps avoid missing informative early-time sampling regions, particularly for k_2 .

The auto-updating strategy produces slightly larger but more evenly balanced confidence intervals across all parameters.

By contrast, the equally divided strategy performs worst overall in terms of parameter-estimation precision. Its rigid partitioning allocates a substantial portion of samples to less informative regions, limiting the effectiveness of parameter updates and leading to uniformly larger confidence intervals.

5.7 Practical implementation and computational feasibility

In practical implementation, the dynamic system is assumed to continue evolving during parameter estimation and sampling-time redesign; the experiment is not paused while these calculations are performed. At the end of each sub-experiment, all measurements collected up to that point are used to update the parameter estimates, after which the remaining sampling schedule is re-optimised. The redesigned schedule is then applied from the next admissible candidate sampling instant.

The computational time required for one update was therefore compared with the candidate sampling interval in each case study. For the enzyme reaction system, parameter estimation required 3.7–9.5 s and sampling-time re-optimisation required 0.4–2.1 s, with a maximum combined update time of 9.9 s. This remains within the 10 s candidate sampling interval. For the biodiesel production system, the corresponding times were 44.1–57.2 s for parameter estimation and 1.8–3.7 s for redesign, giving a maximum combined time of approximately 59 s, well below the 5 min candidate interval. Consequently, no admissible sampling instant is missed because of computation in the two case studies considered here.

For applications in which parameter estimation and redesign cannot be completed before the next admissible sampling instant, an explicit fallback policy would be required, for

Table 5.7 Computational time required for one midterm redesign update in the two case studies.

Computational task	Enzyme reaction	Biodiesel production
Parameter estimation	3.7–9.5 s	44.1–57.2 s
Sampling-time redesign	0.4–2.1 s	1.8–3.7 s
Maximum total update time	9.9 s	59 s
Candidate sampling interval	10 s	5 min

example by retaining the previously planned sampling schedule until the updated design becomes available. Such a case is not encountered in the present numerical studies.

5.8 Summary

This chapter introduced an adaptive midterm experimental redesign framework for sampling time optimisation under parametric uncertainty. Unlike the static robust designs in Chapter 4, the proposed approach updates parameter estimates during a single experimental run and incorporates this information into subsequent design stages.

The core concept is to partition the experimental horizon into sequential sub-experiments. Each stage consists of experimental design, data acquisition, and parameter estimation, with updated parameter estimates informing the design of the next stage. This adaptive mechanism progressively reduces the impact of initial uncertainty and enables the sampling strategy to evolve toward increasingly informative configurations.

Three redesign strategies were developed. The equally divided strategy partitions the time horizon uniformly and provides a simple and predictable baseline, but lacks flexibility in adapting to system dynamics. The auto-updating strategy determines sub-experiment boundaries based on identifiability criteria, enabling adaptive allocation of sampling effort and consistent improvement in estimation accuracy. The condition-triggered strategy activates redesign at a prescribed change in operating conditions, using this point to update the parameter estimates and redesign the remaining sampling schedule.

The proposed methods were evaluated on two case studies with different levels of complexity. For the enzyme reaction system, the auto-updating strategy consistently recovered near-nominal OED performance despite large initial uncertainty, while the equally divided strategy degraded under severe uncertainty due to inefficient early-stage sampling. For the biodiesel production system, the condition-triggered strategy achieved good performance because the prescribed redesign occurred sufficiently early to avoid missing informative early-time sampling regions, particularly for k_2 , while the auto-updating strategy maintained more balanced performance across the parameters.

Overall, the results demonstrate that adaptive midterm redesign can improve parameter estimation quality compared with static robust designs while avoiding the need for multiple experimental runs. In particular, the auto-updating and condition-triggered strategies achieve a favourable balance between robustness and efficiency by allowing the sampling schedule to be updated during the experiment. The favourable performance of the condition-triggered strategy in the biodiesel case is mainly associated with the relatively early trigger time and should therefore be interpreted as case-specific.

Despite these advantages, several challenges remain. The framework requires repeated solution of nonlinear optimisation and parameter estimation problems, which may become computationally demanding for large-scale systems. Its performance also depends on appropriate selection of design parameters, such as identifiability thresholds, which may require problem-specific tuning.

Future work will focus on enhancing automation and scalability. Potential directions include adaptive determination of sub-experiment boundaries based on online information metrics, self-tuning of algorithmic parameters using real-time uncertainty estimates, and integration of surrogate or machine-learning models to reduce computational cost. Extending the framework to multi-objective settings and embedding it within automated experimental platforms would further enable efficient and intelligent experimental design for complex systems.

Chapter 6

Sampling Time Design with Misspecified Cramér–Rao Bounds under Input Uncertainty

While Chapters 4 and 5 focused on parametric uncertainty, this Chapter addresses a fundamentally different challenge arising from model misspecification due to input uncertainty. In the previous chapters, experimental design methods were developed to address parametric uncertainty in the model. In practical experiments, however, uncertainty may also arise in the inputs, such as dynamic stimuli or initial conditions. Input uncertainty directly affects the physical execution of the experiment and propagates nonlinearly through the system dynamics. As a result, the distribution of the measured data may deviate significantly from the assumed statistical model. This mismatch invalidates the use of the standard Cramér–Rao bound (CRB), whose computation relies on a correctly specified likelihood and corresponding Fisher Information Matrix (FIM).

To address this issue, this chapter adopts the Misspecified Cramér–Rao bound (MCRB) as an alternative performance bound under input uncertainty. The use of the MCRB for sampling time design under input uncertainty was previously introduced in (Wang and Yue, 2024). Building on that work, this chapter provides a more detailed derivation of the full-

trajectory MCRB, analyses how input uncertainty changes the statistical structure of the pseudo-data, and compares the resulting sampling design with classical optimal experimental design (OED), existing input-uncertainty methods, and standard robust experimental design (RED) formulations.

First, the theoretical basis of the MCRB is introduced to justify its use under model misspecification. Then, a full-trajectory MCRB-based sampling time design formulation is developed for nonlinear dynamic systems, in which the MCRB is computed from the stacked measurement vector over all selected sampling times. Existing input-uncertainty design methods are then reviewed as benchmarks, and the proposed framework is demonstrated on the enzyme reaction system.

6.1 Introduction of Misspecified Cramér–Rao Bounds

As discussed previously, nonlinear system dynamics imply that input uncertainty propagates to the measurement space in a nontrivial manner, potentially violating the assumed Gaussian noise model. Since the classical CRB relies on a correctly specified statistical model of the observations, such misspecification renders the bound unreliable. In particular, the resulting variance lower bound may become unattainable in practice, as it is computed under incorrect likelihood assumptions and does not reflect the true information content of the data. Consequently, its use in the OED formulation (3.40) loses practical relevance.

To address this limitation, the MCRB provides a variance bound that remains valid under model misspecification, allowing the assumed data model to differ from the true one (Fortunati et al., 2017). The theoretical foundation originates from the study of maximum likelihood estimation under misspecified models (Huber, 1967; White, 1982), where estimators converge to a *pseudo-true parameter*, defined as the closest element in the assumed model family in terms of Kullback–Leibler divergence (KLD) (Vuong, 1986). Under this framework, the asymptotic covariance of the estimator leads to the MCRB, which generalises the classical CRB.

Subsequent studies have extended and applied the MCRB in several signal-processing settings, including parameter bounds under model misspecification, constrained estimation, scatter-matrix estimation under non-Gaussian distributions, and communication-channel estimation problems (Fortunati et al., 2016, 2017; Richmond and Horowitz, 2015; Thanh et al., 2021). These studies show that the MCRB can provide a more relevant performance bound than the classical CRB when the assumed likelihood differs from the true data-generating process.

Despite these advances, the use of MCRB in OED remains largely unexplored. Existing work has primarily focused on estimation or model selection problems (Rosenthal and Tabrikian, 2022), with limited attention to its role in sampling design for parameter estimation. This gap motivates its integration into the OED framework in this chapter.

This section introduces the formulation of the MCRB for systems with input-induced model misspecification. The following assumptions are adopted:

- The true measurement distribution is denoted by pdf of $\mathbf{x}(t)$, $p(\mathbf{x}(t))$, with mean $\boldsymbol{\mu}(t)$ and covariance $\boldsymbol{\Sigma}_x(t)$.
- The assumed statistical distribution model of measurement is denoted by pdf, $f(\mathbf{x}(t) | \boldsymbol{\theta}) \sim N(\mathbf{x}(\boldsymbol{\theta}, t), \boldsymbol{\Sigma})$, where $p \notin f(\mathbf{x} | \boldsymbol{\theta})$ for all $\boldsymbol{\theta} \in \Theta$.
- Under the assumed measurement model, measurement errors at different time points are independent. Under the true data-generating process, however, input uncertainty may induce dependence between measurements at different sampling times.

6.2 Unbiasedness and Covariance Inequality under Misspecification

6.2.1 Misspecified unbiasedness

Under input uncertainty, the true measurement distribution p does not belong to the assumed model family $f(\mathbf{x} | \boldsymbol{\theta})$ for any $\boldsymbol{\theta} \in \Theta$. As a result, the classical notion of unbiasedness, defined with respect to a true parameter within the model, no longer applies. Instead, inference is centred around the *pseudo-true parameter* $\boldsymbol{\theta}^*$, defined as the minimiser of the KLD between p and f :

$$\boldsymbol{\theta}^* = \arg \min_{\boldsymbol{\theta} \in \Theta} D(p \| f) = \arg \min_{\boldsymbol{\theta} \in \Theta} \mathbb{E}_p \{ -\ln f \}. \quad (6.1)$$

This parameter serves as the natural reference point under model misspecification. Accordingly, an estimator $\hat{\boldsymbol{\theta}}(\mathbf{x})$ is said to be *misspecified-unbiased* (MS-unbiased) if

$$\mathbb{E}_p \{ \hat{\boldsymbol{\theta}}(\mathbf{x}) \} = \boldsymbol{\theta}^*. \quad (6.2)$$

In practice, the true distribution p is generally unavailable, as it results from nonlinear propagation of input uncertainty through the system dynamics. Monte Carlo methods can be used to approximate expectations under p , but may introduce bias for finite samples. Therefore, asymptotic MS-unbiasedness is typically considered:

$$\lim_{M \rightarrow \infty} \mathbb{E}_p \{ \hat{\boldsymbol{\theta}}_M \} = \boldsymbol{\theta}^*. \quad (6.3)$$

Under model misspecification, MS-unbiased estimators provide the relevant benchmark for parameter estimation. The objective of experimental design is therefore to minimise the covariance of such estimators. In the following section, it will be shown that the MCRB provides a lower bound on the covariance of (asymptotically) MS-unbiased estimators. This establishes the theoretical basis for replacing the classical CRB with the MCRB in the presence of input uncertainty.

6.2.2 Covariance inequality in the misspecified condition

Let the true probability density function (pdf) of the measurements be denoted by $p(\mathbf{x})$, and the assumed (misspecified) model by $f(\mathbf{x} | \boldsymbol{\theta})$. The estimator $\hat{\boldsymbol{\theta}}_f(\mathbf{x})$ is derived under the assumed model f , while its expectation is taken with respect to the true distribution:

$$\boldsymbol{\mu}_p = \mathbb{E}_p \left\{ \hat{\boldsymbol{\theta}}_f(\mathbf{x}) \right\}. \quad (6.4)$$

Since the covariance inequality (3.36) holds for any underlying distribution, replacing $\mathbb{E}_f\{\cdot\}$ with $\mathbb{E}_p\{\cdot\}$ yields the misspecified covariance inequality:

$$\mathbb{E}_p \left\{ \boldsymbol{\zeta} \boldsymbol{\zeta}^\top \right\} \succeq \mathbb{E}_p \left\{ \boldsymbol{\zeta} \boldsymbol{\eta}^\top \right\} \mathbb{E}_p^{-1} \left\{ \boldsymbol{\eta} \boldsymbol{\eta}^\top \right\} \mathbb{E}_p \left\{ \boldsymbol{\eta} \boldsymbol{\zeta}^\top \right\} \triangleq \text{MCRB}. \quad (6.5)$$

Here, the estimation error and score function are defined as

$$\boldsymbol{\zeta} = \hat{\boldsymbol{\theta}}_f(\mathbf{x}) - \mathbb{E}_p \left\{ \hat{\boldsymbol{\theta}}_f(\mathbf{x}) \right\} = \hat{\boldsymbol{\theta}}_f(\mathbf{x}) - \boldsymbol{\mu}_p, \quad (6.6)$$

$$\boldsymbol{\eta} = \left(\frac{\partial \ln f(\mathbf{x} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \right)^\top - \mathbb{E}_p \left\{ \left(\frac{\partial \ln f(\mathbf{x} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \right)^\top \right\}. \quad (6.7)$$

The second term in $\boldsymbol{\eta}$ ensures $\mathbb{E}_p\{\boldsymbol{\eta}\} = 0$, accounting for the mismatch between p and f .

When the assumed model is correctly specified ($p = f$), and under standard regularity conditions, $\hat{\boldsymbol{\theta}}_f$ is unbiased and the score function has zero mean. In this case,

$$\boldsymbol{\zeta} = \hat{\boldsymbol{\theta}}_f(\mathbf{x}) - \boldsymbol{\theta}, \quad \boldsymbol{\eta} = \left(\frac{\partial \ln f(\mathbf{x} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \right)^\top, \quad (6.8)$$

which recovers the classical CRB. Therefore, the MCRB can be interpreted as a generalisation of the CRB under model misspecification, although equality between the two does not necessarily imply perfect model matching (Fortunati et al., 2017). This result establishes the theoretical basis for using the MCRB in experimental design under input uncertainty.

In practice, the true distribution $p(\mathbf{x})$ is rarely available in analytical form due to nonlinear propagation of input uncertainty. Consequently, expectations with respect to p are typically approximated using Monte Carlo sampling (Dijkstra, 1984).

6.3 MCRB for the Maximum Likelihood Estimator

6.3.1 Misspecified maximum likelihood estimator

The maximum likelihood (ML) estimator is widely used for parameter estimation. Under model misspecification, where the measurement data $\mathbf{x}$ follow the true distribution $p(\mathbf{x})$ rather than the assumed model $f(\mathbf{x} | \boldsymbol{\theta})$, the resulting estimator is referred to as the Misspecified maximum likelihood (MML) estimator:

$$\hat{\boldsymbol{\theta}}_{MML} = \arg \max_{\boldsymbol{\theta} \in \Theta} \sum_{m=1}^M \ln f(\mathbf{x}^{(m)} | \boldsymbol{\theta}), \quad \text{with } \mathbf{x}^{(m)} \sim p. \quad (6.9)$$

The MML estimator maximises the sample log-likelihood under the assumed model, which is equivalent to minimising the empirical KLD. As the sample size $M \rightarrow \infty$, this empirical objective converges to its population counterpart in (6.1). It has been shown (Huber, 1967; White, 1981) that

$$\hat{\boldsymbol{\theta}}_{MML} \xrightarrow[M \rightarrow \infty]{a.s.} \boldsymbol{\theta}_{KLD} = \boldsymbol{\theta}^*, \quad (6.10)$$

i.e., the MML estimator converges almost surely to the pseudo-true parameter. Therefore, the MML estimator is asymptotically MS-unbiased and provides the natural foundation for deriving the MCRB under model misspecification.

6.3.2 MCRB

Suppose the following regularity conditions hold (Richmond, 2018; Vuong, 1986):

- The KLD, $D(p||f)$, has a unique minimum at $\boldsymbol{\theta}^*$ in the parameter space Θ .

- The log-likelihood $\ln f(\mathbf{x} | \boldsymbol{\theta})$ is twice differentiable at $\boldsymbol{\theta}^*$.
- The expected Hessian under p is nonsingular, i.e.

$$\mathbb{E}_p \left\{ \frac{\partial^2 \ln f(\mathbf{x} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta} \partial \boldsymbol{\theta}^\top} \middle| \boldsymbol{\theta}^* \right\}$$

is invertible.

- There exists a neighbourhood of $\boldsymbol{\theta}^*$ such that $\left| \frac{1}{f} \frac{\partial f}{\partial \boldsymbol{\theta}} \right|$ is dominated by a square-integrable function under p .

The MML estimator satisfies the first-order condition:

$$\sum_{m=1}^M \frac{\partial \ln f(\mathbf{x}^{(m)} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \bigg|_{\hat{\boldsymbol{\theta}}_{MML}} = 0. \quad (6.11)$$

Applying a first-order Taylor expansion of the score function around $\boldsymbol{\theta}^*$ gives

$$\left(\sum_{m=1}^M \frac{\partial \ln f(\mathbf{x}^{(m)} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \bigg|_{\boldsymbol{\theta}^*} \right)^\top + \left(\sum_{m=1}^M \frac{\partial^2 \ln f(\mathbf{x}^{(m)} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}^2} \bigg|_{\tilde{\boldsymbol{\theta}}_M} \right) (\hat{\boldsymbol{\theta}}_{MML} - \boldsymbol{\theta}^*) = 0, \quad (6.12)$$

where $\tilde{\boldsymbol{\theta}}_M$ lies on the line segment between $\hat{\boldsymbol{\theta}}_{MML}$ and $\boldsymbol{\theta}^*$. Hence,

$$\boldsymbol{\zeta} = \hat{\boldsymbol{\theta}}_{MML} - \boldsymbol{\theta}^* = - \left(\sum_{m=1}^M \frac{\partial^2 \ln f(\mathbf{x}^{(m)} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}^2} \bigg|_{\tilde{\boldsymbol{\theta}}_M} \right)^{-1} \left(\sum_{m=1}^M \frac{\partial \ln f(\mathbf{x}^{(m)} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \bigg|_{\boldsymbol{\theta}^*} \right)^\top. \quad (6.13)$$

Under the consistency of $\hat{\boldsymbol{\theta}}_{MML}$ and the continuity and integrability conditions on the Hessian, $\tilde{\boldsymbol{\theta}}_M \rightarrow \boldsymbol{\theta}^*$ as $M \rightarrow \infty$. Therefore,

$$-\frac{1}{M} \sum_{m=1}^M \frac{\partial^2 \ln f(\mathbf{x}^{(m)} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta} \partial \boldsymbol{\theta}^\top} \bigg|_{\tilde{\boldsymbol{\theta}}_M} \xrightarrow[M \rightarrow \infty]{p} \mathbf{A}(\boldsymbol{\theta}^*) = -\mathbb{E}_p \left\{ \frac{\partial^2 \ln f(\mathbf{x} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta} \partial \boldsymbol{\theta}^\top} \bigg|_{\boldsymbol{\theta}^*} \right\}. \quad (6.14)$$

By the central limit theorem,

$$\frac{1}{\sqrt{M}} \sum_{m=1}^M \left(\frac{\partial \ln f(\mathbf{x}^{(m)} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \bigg|_{\boldsymbol{\theta}^*} \right)^\top \xrightarrow{d} N(0, \mathbf{B}(\boldsymbol{\theta}^*)), \quad (6.15)$$

where

$$\mathbf{B}(\boldsymbol{\theta}^*) = \mathbb{E}_p \left\{ \left(\frac{\partial \ln f(\mathbf{x} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \bigg|_{\boldsymbol{\theta}^*} \right)^\top \cdot \frac{\partial \ln f(\mathbf{x} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \bigg|_{\boldsymbol{\theta}^*} \right\}. \quad (6.16)$$

Since $\boldsymbol{\theta}^*$ minimises the KLD, we have

$$\mathbb{E}_p \left\{ \frac{\partial \ln f(\mathbf{x} | \boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \bigg|_{\boldsymbol{\theta}^*} \right\} = 0, \quad (6.17)$$

and thus the score function simplifies to

$$\boldsymbol{\eta} = \left(\sum_{m=1}^M \frac{\partial \ln f(\mathbf{x}^{(m)})}{\partial \boldsymbol{\theta}^*} \right)^\top. \quad (6.18)$$

Using (6.13)–(6.15), we obtain

$$\mathbb{E}_p \{ \boldsymbol{\zeta} \boldsymbol{\eta}^\top \} = \mathbf{A}^{-1}(\boldsymbol{\theta}^*) \mathbf{B}(\boldsymbol{\theta}^*), \quad \mathbb{E}_p \{ \boldsymbol{\eta} \boldsymbol{\eta}^\top \} = M \mathbf{B}(\boldsymbol{\theta}^*). \quad (6.19)$$

Substituting (6.19) into the covariance inequality yields the MCRB:

$$MCRB = \mathbb{E}_p \{ \boldsymbol{\zeta} \boldsymbol{\eta}^\top \} \mathbb{E}_p^{-1} \{ \boldsymbol{\eta} \boldsymbol{\eta}^\top \} \mathbb{E}_p \{ \boldsymbol{\eta} \boldsymbol{\zeta}^\top \} = \frac{1}{M} \mathbf{A}^{-1}(\boldsymbol{\theta}^*) \cdot \mathbf{B}(\boldsymbol{\theta}^*) \cdot \mathbf{A}^{-1}(\boldsymbol{\theta}^*), \quad (6.20)$$

which corresponds to Huber's sandwich covariance (Huber, 1967).

Moreover, according to the covariance inequality,

$$\mathbb{V}\{\hat{\boldsymbol{\theta}}_{MML}\} \succeq MCRB. \quad (6.21)$$

We can see from (6.14) and (6.15) that the equality holds for the MML estimator. In fact, the MML estimator is asymptotically normal and centred at the pseudo-true parameter $\boldsymbol{\theta}^*$, with its asymptotic covariance characterised by the MCRB:

$$\sqrt{M} \left(\hat{\boldsymbol{\theta}}_{MML} - \boldsymbol{\theta}^* \right) \xrightarrow{d} N \left(\mathbf{0}, \mathbf{A}^{-1} \mathbf{B} \mathbf{A}^{-1} \right). \quad (6.22)$$

Equivalently, for large M ,

$$\hat{\boldsymbol{\theta}}_{MML} \sim N \left(\boldsymbol{\theta}^*, \frac{1}{M} \mathbf{A}^{-1} \mathbf{B} \mathbf{A}^{-1} \right). \quad (6.23)$$

6.4 Sampling Time Design with MCRB

When input uncertainty is present, RED is commonly employed to ensure acceptable estimation performance over the uncertainty space, for example by optimising worst-case or average criteria. However, existing RED approaches rely on the classical FIM, whose validity depends on a correctly specified statistical model of the measurements.

Under input uncertainty, this assumption is generally violated, as the uncertainty propagates nonlinearly through the system dynamics and distorts the measurement distribution. Consequently, FIM-based criteria may no longer provide reliable measures of estimation performance. In such misspecified settings, the MCRB offers a more appropriate alternative, as it accounts for discrepancies between the assumed and true data-generating processes.

This section extends the MCRB framework to nonlinear dynamic systems described by ordinary differential equations (ODEs) by treating the measurements collected at different sampling times as a joint trajectory vector. This formulation allows the propagated effect of input uncertainty on cross-time measurement dependence to be retained in the design criterion. The resulting sampling time design problem is then formulated directly in terms of the trajectory-level MCRB.

6.4.1 Full-trajectory MCRB for nonlinear dynamic systems

This section derives an approximate trajectory-level MCRB for nonlinear dynamic systems described by ODEs. Consider a sampling set, $\mathcal{T} = \{t_1, t_2, \dots, t_{N_{st}}\}$, and define the stacked measurement vector

$$\mathbf{D}_{\mathcal{T}} = \begin{bmatrix} \mathbf{D}(t_1) \\ \mathbf{D}(t_2) \\ \vdots \\ \mathbf{D}(t_{N_{st}}) \end{bmatrix} \in \mathbb{R}^{N_x N_{st}}. \quad (6.24)$$

Similarly, define the stacked model output

$$\mathbf{x}_{\mathcal{T}}(\boldsymbol{\theta}) = \begin{bmatrix} \mathbf{x}(\boldsymbol{\theta}, t_1) \\ \mathbf{x}(\boldsymbol{\theta}, t_2) \\ \vdots \\ \mathbf{x}(\boldsymbol{\theta}, t_{N_{st}}) \end{bmatrix}. \quad (6.25)$$

Under the assumed model, the stacked measurement vector follows

$$\mathbf{D}_{\mathcal{T}} \mid \boldsymbol{\theta} \sim N(\mathbf{x}_{\mathcal{T}}(\boldsymbol{\theta}), \boldsymbol{\Sigma}_{\mathcal{T}}), \quad (6.26)$$

where $\boldsymbol{\Sigma}_{\mathcal{T}}$ denotes the assumed covariance matrix of the measurement noise. If the assumed measurement noise is independent across time points, then $\boldsymbol{\Sigma}_{\mathcal{T}}$ is block diagonal. The corresponding log-likelihood is

$$\ln f(\mathbf{D}_{\mathcal{T}} \mid \boldsymbol{\theta}) \propto -\frac{1}{2} [\mathbf{D}_{\mathcal{T}} - \mathbf{x}_{\mathcal{T}}(\boldsymbol{\theta})]^\top \boldsymbol{\Sigma}_{\mathcal{T}}^{-1} [\mathbf{D}_{\mathcal{T}} - \mathbf{x}_{\mathcal{T}}(\boldsymbol{\theta})]. \quad (6.27)$$

To handle nonlinearity, the stacked model output is linearised at the initial parameter guess $\boldsymbol{\theta}_0$:

$$\mathbf{x}_{\mathcal{T}}(\boldsymbol{\theta}) \approx \mathbf{x}_{\mathcal{T}}(\boldsymbol{\theta}_0) + \mathbf{S}_{\mathcal{T}}(\boldsymbol{\theta}_0)(\boldsymbol{\theta} - \boldsymbol{\theta}_0), \quad (6.28)$$

where

$$\mathbf{S}_{\mathcal{T}}(\boldsymbol{\theta}_0) = \left. \frac{\partial \mathbf{x}_{\mathcal{T}}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \right|_{\boldsymbol{\theta}_0}. \quad (6.29)$$

Substituting this linearisation into the assumed likelihood yields the approximate MML estimator

$$\hat{\boldsymbol{\theta}}_{MML} \approx \boldsymbol{\theta}_0 + \mathbf{A}_{\mathcal{T}}^{-1} \mathbf{S}_{\mathcal{T}}^{\top} \boldsymbol{\Sigma}_{\mathcal{T}}^{-1} [\mathbf{D}_{\mathcal{T}} - \mathbf{x}_{\mathcal{T}}(\boldsymbol{\theta}_0)], \quad (6.30)$$

where

$$\mathbf{A}_{\mathcal{T}} = \mathbf{S}_{\mathcal{T}}^{\top} \boldsymbol{\Sigma}_{\mathcal{T}}^{-1} \mathbf{S}_{\mathcal{T}}. \quad (6.31)$$

Let the mean and covariance of the stacked measurement vector under the true distribution p be

$$\bar{\mathbf{D}}_{\mathcal{T}} = \mathbb{E}_p\{\mathbf{D}_{\mathcal{T}}\}, \quad \boldsymbol{\Gamma}_{\mathcal{T}} = \text{Cov}_p(\mathbf{D}_{\mathcal{T}}). \quad (6.32)$$

In general, $\bar{\mathbf{D}}_{\mathcal{T}} \neq \mathbf{x}_{\mathcal{T}}(\boldsymbol{\theta}_0)$ due to model misspecification induced by input uncertainty. Moreover, unlike the assumed covariance matrix $\boldsymbol{\Sigma}_{\mathcal{T}}$, the true covariance matrix $\boldsymbol{\Gamma}_{\mathcal{T}}$ is generally not block diagonal, since uncertainty in the inputs may induce dependence between measurements collected at different sampling times after nonlinear propagation through the system dynamics.

The expectation of the approximate MML estimator under p is

$$\boldsymbol{\mu}_p = \mathbb{E}_p\{\hat{\boldsymbol{\theta}}_{MML}\} = \boldsymbol{\theta}_0 + \mathbf{A}_{\mathcal{T}}^{-1} \mathbf{S}_{\mathcal{T}}^{\top} \boldsymbol{\Sigma}_{\mathcal{T}}^{-1} [\bar{\mathbf{D}}_{\mathcal{T}} - \mathbf{x}_{\mathcal{T}}(\boldsymbol{\theta}_0)]. \quad (6.33)$$

The estimation error and centred score are therefore approximated by

$$\boldsymbol{\zeta} = \hat{\boldsymbol{\theta}}_{MML} - \boldsymbol{\mu}_p = \mathbf{A}_{\mathcal{T}}^{-1} \mathbf{S}_{\mathcal{T}}^{\top} \boldsymbol{\Sigma}_{\mathcal{T}}^{-1} [\mathbf{D}_{\mathcal{T}} - \bar{\mathbf{D}}_{\mathcal{T}}], \quad (6.34)$$

$$\boldsymbol{\eta} = \mathbf{S}_{\mathcal{T}}^{\top} \boldsymbol{\Sigma}_{\mathcal{T}}^{-1} [\mathbf{D}_{\mathcal{T}} - \bar{\mathbf{D}}_{\mathcal{T}}]. \quad (6.35)$$

Hence,

$$\mathbb{E}_p\{\boldsymbol{\zeta} \boldsymbol{\eta}^{\top}\} = \mathbf{A}_{\mathcal{T}}^{-1} \mathbf{S}_{\mathcal{T}}^{\top} \boldsymbol{\Sigma}_{\mathcal{T}}^{-1} \boldsymbol{\Gamma}_{\mathcal{T}} \boldsymbol{\Sigma}_{\mathcal{T}}^{-1} \mathbf{S}_{\mathcal{T}} \triangleq \mathbf{A}_{\mathcal{T}}^{-1} \mathbf{B}_{\mathcal{T}}, \quad (6.36)$$

with

$$\mathbf{B}_{\mathcal{T}} = \mathbf{S}_{\mathcal{T}}^{\top} \mathbf{\Sigma}_{\mathcal{T}}^{-1} \mathbf{\Gamma}_{\mathcal{T}} \mathbf{\Sigma}_{\mathcal{T}}^{-1} \mathbf{S}_{\mathcal{T}}. \quad (6.37)$$

Similarly,

$$\mathbb{E}_p\{\boldsymbol{\eta} \boldsymbol{\eta}^{\top}\} = \mathbf{B}_{\mathcal{T}}. \quad (6.38)$$

Therefore, the trajectory-level approximate MCRB is

$$\text{MCRB}(\mathcal{T}) \approx \mathbf{A}_{\mathcal{T}}^{-1} \mathbf{B}_{\mathcal{T}} \mathbf{A}_{\mathcal{T}}^{-1}. \quad (6.39)$$

This expression arises from local linearisation at $\boldsymbol{\theta}_0$ and is therefore more accurate when $\boldsymbol{\theta}_0$ is close to the pseudo-true parameter.

In practice, $\tilde{\mathbf{D}}_{\mathcal{T}}$ and $\mathbf{\Gamma}_{\mathcal{T}}$ are unavailable analytically and are instead estimated empirically from simulated or experimental trajectories under input uncertainty.

6.4.2 Sampling time design based on the full-trajectory MCRB

The trajectory-level MCRB provides a natural criterion for sampling time design under input uncertainty. Let $\mathcal{C} = \{t_1, t_2, \dots, t_{N_T}\}$ denote the set of candidate sampling times, and let $\mathcal{T} \subseteq \mathcal{C}$ be a selected sampling set with cardinality $|\mathcal{T}| = N_{st}$. The optimal sampling time design problem is formulated as

$$\mathcal{T}^* = \underset{\mathcal{T} \subseteq \mathcal{C}, |\mathcal{T}|=N_{st}}{\text{arg min}} \quad \varphi(\mathbf{A}_{\mathcal{T}}^{-1} \mathbf{B}_{\mathcal{T}} \mathbf{A}_{\mathcal{T}}^{-1}), \quad (6.40)$$

where $\varphi(\cdot)$ denotes a scalar design criterion such as the D-, A-, or E-optimal criterion.

Unlike the classical discretised sampling time design problem, the present formulation is not additive over individual candidate time points. This is because $\mathbf{B}_{\mathcal{T}}$ depends on the full covariance matrix $\mathbf{\Gamma}_{\mathcal{T}}$ of the selected trajectory, which generally contains off-diagonal terms induced by input uncertainty. Consequently, the design criterion depends on the selected sampling set as a whole rather than on independent contributions from individual sampling

times. The resulting optimisation problem is therefore a non-convex combinatorial problem. In practice, it may be solved by derivative-free discrete search methods or metaheuristic algorithms, such as greedy exchange procedures (Fedorov, 1972), genetic algorithms, particle swarm optimisation, or simulated annealing (García-Ródenas et al., 2020).

Compared with covariance-corrected FIM formulations that only modify the marginal measurement variance at each sampling time, the proposed trajectory-level MCRB formulation additionally accounts for cross-time dependence induced by input uncertainty after nonlinear propagation through the system dynamics. It therefore provides a more complete measure of estimation performance under model misspecification.

6.5 Existing Experimental Design Methods for Input Uncertainty

6.5.1 Standard robust experimental designs for input uncertainty

The standard RED frameworks introduced in Chapter 4 can be extended to handle input uncertainty. In particular, maximin and Bayesian designs can be formulated with respect to uncertain initial conditions.

Let $\mathfrak{E}$ denote the input uncertainty space. The maximin design seeks to optimise performance under the worst-case realisation:

$$\mathbf{t}_{sp}^* = \arg \min_t \max_{\mathbf{x}_0 \in \mathfrak{E}} \phi(\mathbf{FIM}^{-1}(t, \mathbf{x}_0)). \quad (6.41)$$

Under the discretised sampling framework (cf. (3.42)), this becomes:

$$\mathbf{w}^* = \arg \max_{\mathbf{w}} \min_{\mathbf{x}_0 \in \mathfrak{E}} \phi \left(\sum_{i=1}^{N_T} w_i \mathbf{FIM}(t_i, \mathbf{x}_0) \right). \quad (6.42)$$

Similarly, the Bayesian design maximises the expected information over the uncertainty space:

$$\begin{aligned}\mathbf{w}^* &= \arg \max_{\mathbf{w}} \mathbb{E}_{\mathbf{x}_0} \{ \phi(\mathbf{FIM}(\mathbf{w}, \mathbf{x}_0)) \} \\ &= \arg \max_{\mathbf{w}} \mathbb{E}_{\mathbf{x}_0} \left\{ \phi \left(\sum_{i=1}^{N_T} w_i \mathbf{FIM}(t_i, \mathbf{x}_0) \right) \right\}.\end{aligned}\tag{6.43}$$

These approaches require prior knowledge of the uncertainty set or distribution. More importantly, they rely on the mapping from initial states to the FIM, which is generally nonlinear and not available in closed form for dynamic systems. As a result, both maximin and Bayesian formulations lead to non-convex optimisation problems.

In practice, numerical approximations are required. Typical approaches include sampling-based approximations of the uncertainty space (e.g. sample-average or worst-case evaluation) combined with repeated model simulations and sensitivity analysis. Heuristic optimisation methods, such as particle swarm optimisation (PSO), are often employed. However, these approaches can be computationally expensive, particularly for high-dimensional or strongly nonlinear systems.

6.5.2 Optimal experimental design using sample covariance matrix

A pragmatic approach to handle input uncertainty is to retain the classical OED framework while approximating the measurement covariance using a sample covariance matrix Σ_D . This matrix is obtained by propagating sampled initial conditions through the model to generate pseudo-data, from which the empirical covariance is computed for each time point. Under this approximation, the design problem becomes:

$$\boldsymbol{\varphi}^* = \arg \max_{\boldsymbol{\varphi}} \phi \left(\mathbf{S}^\top(\boldsymbol{\varphi}, \boldsymbol{\theta}) \Sigma_D^{-1} \mathbf{S}(\boldsymbol{\varphi}, \boldsymbol{\theta}) \right).\tag{6.44}$$

For dynamic systems with discretised sampling candidates, this leads to:

$$\begin{aligned} \mathbf{w}^* = \arg \max_{\mathbf{w}} \quad & \phi \left(\sum_{i=1}^{N_T} w_i \mathbf{S}^\top(\boldsymbol{\theta}_0, t_i) \boldsymbol{\Sigma}_D^{-1}(t_i) \mathbf{S}(\boldsymbol{\theta}_0, t_i) \right) \\ \text{s.t.} \quad & \sum_{i=1}^{N_T} w_i = N, \quad w_i \in \{0, 1\}. \end{aligned} \quad (6.45)$$

Under the E-optimality criterion, the continuous relaxation of this formulation can be expressed as a semi-definite programming (SDP), analogous to (3.45); with binary sampling variables, the formulation is a mixed-integer semidefinite optimisation problem. However, this approach does not correct the underlying model misspecification and may still lead to biased or misleading information measures. Moreover, because $\boldsymbol{\Sigma}_D(t_i)$ is estimated separately at each candidate time point, this formulation retains only the within-time covariance and neglects cross-time correlations induced by input uncertainty.

6.5.3 Smallest covariance deviation design

An alternative approach is to select sampling times that minimise the covariance perturbation induced by input uncertainty (Wang and Yue, 2021). This leads to the smallest covariance deviation design:

$$\boldsymbol{\varphi}^* = \arg \min_{\boldsymbol{\varphi}} \phi(\boldsymbol{\Sigma}_D - \boldsymbol{\Sigma}), \quad (6.46)$$

where $\phi(\cdot)$ is a scalar measure, chosen here as the determinant.

For dynamic systems with discretised candidate points, the problem becomes:

$$\begin{aligned} \mathbf{w}^* = \arg \min_{\mathbf{w}} \quad & \sum_{i=1}^{N_T} w_i \phi(\boldsymbol{\Sigma}_D(t_i) - \boldsymbol{\Sigma}(t_i)), \\ \text{s.t.} \quad & \sum_{i=1}^{N_T} w_i = N, \quad w_i \in \{0, 1\}. \end{aligned} \quad (6.47)$$

The method has been applied to measurement-set selection (Wang and Yue, 2021), where it favours variables that are less sensitive to input uncertainty. While effective in that context

(e.g. for L_1 -based parameter estimation), its applicability to sampling time design is limited. In particular, it does not account for parameter sensitivities and may therefore exclude highly informative time points in sampling time design. Besides, it also does not consider the possible correlations between time points due to input uncertainty.

6.6 Case Study for Enzyme Reaction System under Input Uncertainty

The enzyme reaction system and its sampling design task are described in Section 4.5 and Appendix A. The following assumptions define the experimental setting considered for sampling time design under input uncertainty:

- The experimental duration is 6,000s, ensuring that all state variables reach steady state.
- The candidate sampling grid consists of 600 time points $[10:10:6,000]$ s, from which 21 sampling instants are selected.
- All five measurable states are sampled simultaneously.
- Measurement error is assumed independent and Gaussian: $\xi(t) \sim N(0, \Sigma(t))$, where $\Sigma(t) = \text{diag}([\sigma_1^2(t), \dots, \sigma_5^2(t)])$.
- The standard deviation of measurement error follows the linear model:

$$\sigma_i(t) = 0.1 x_i(t) + 10^{-4}, \quad (6.48)$$

where $x_i(t)$ denotes the i -th measurable state. The constant term prevents the variance from becoming zero when $x_i(t)$ approaches zero.

These assumptions define the nominal measurement model. However, when input uncertainty is propagated through the nonlinear system, the effective data-generating process no longer

fully satisfies these assumptions. This induces misspecification in the design stage and motivates the use of MCRB-based experimental design.

6.6.1 Impact of input uncertainty on measurements

In this case study, input uncertainty arises from uncertain initial states. The nominal initial condition is $\mathbf{x}_{0,nom} = [E_0, S_0, N_0]^\top = [1.5 \times 10^{-5}, 0.8, 0.9]^\top$. The uncertainty is assumed to be independently Gaussian: $\mathbf{x}_0 \sim N(\mathbf{x}_{0,nom}, \mathbf{\Sigma}_0)$, where $\mathbf{\Sigma}_0 = \text{diag}((\gamma_u \mathbf{x}_{0,nom})^2)$. The relative uncertainty level is set to $\gamma_u = 0.05$, implying that approximately 95% of initial values lie within $[0.9\mathbf{x}_{0,nom}, 1.1\mathbf{x}_{0,nom}]$. In addition, the uncertain initial states are truncated to the interval $[0.8\mathbf{x}_{0,nom}, 1.2\mathbf{x}_{0,nom}]$.

Summary statistics of pseudo-data

To quantify the impact of input uncertainty, Monte Carlo simulation is employed. A total of 50,000 samples are drawn from the input distribution, propagated through the system ODEs, and corrupted by measurement noise to generate pseudo-experimental data. The resulting distributions with and without input uncertainty are compared in Figure 6.1. This figure shows that, although the central trajectories remain close to the true state responses in both cases, the pseudo-data bands generally become broader when input uncertainty is included. This broadening is state- and time-dependent, and is particularly pronounced over certain time windows for S , N , and Q .

The differences in summary statistics are further shown in Figure 6.2, where each curve is defined as the statistic obtained with input uncertainty minus that obtained without input uncertainty. The results show that input uncertainty has only a limited effect on the mean and median, but can noticeably change the interquartile range and standard deviation over specific time regions. This indicates that input uncertainty primarily alters the spread and dispersion structure of the pseudo-data, rather than simply shifting their central tendency.

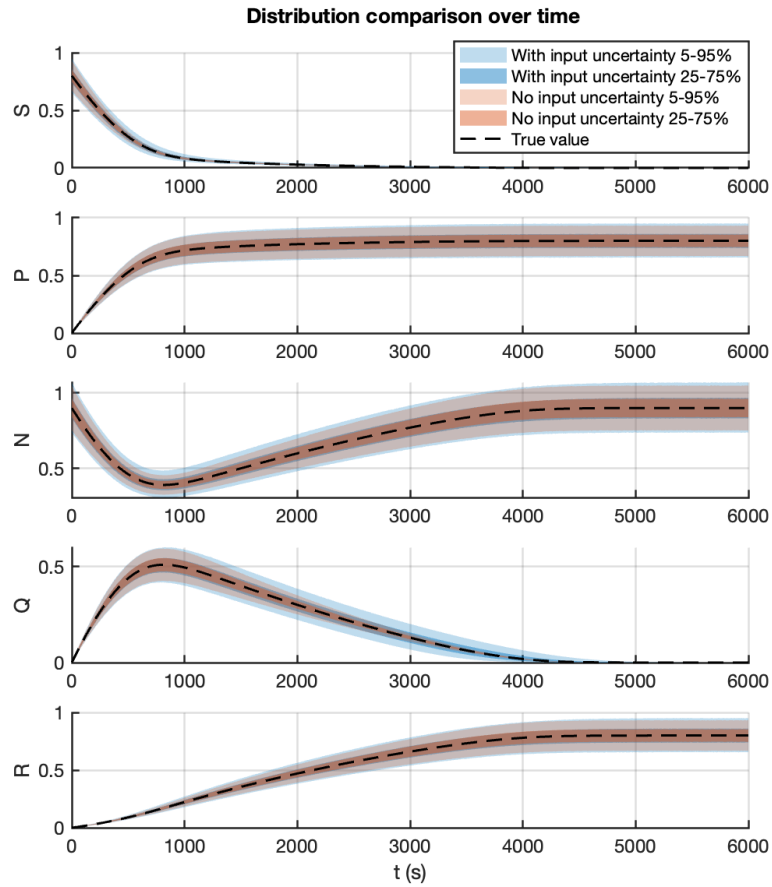


Fig. 6.1 Temporal comparison of pseudo-data distributions with and without input uncertainty for the measured states S , P , N , Q and R . The shaded bands denote the 5th–95th and 25th–75th percentile intervals. Blue and orange correspond to the cases with and without input uncertainty, respectively, and the dashed black line shows the true state trajectory.

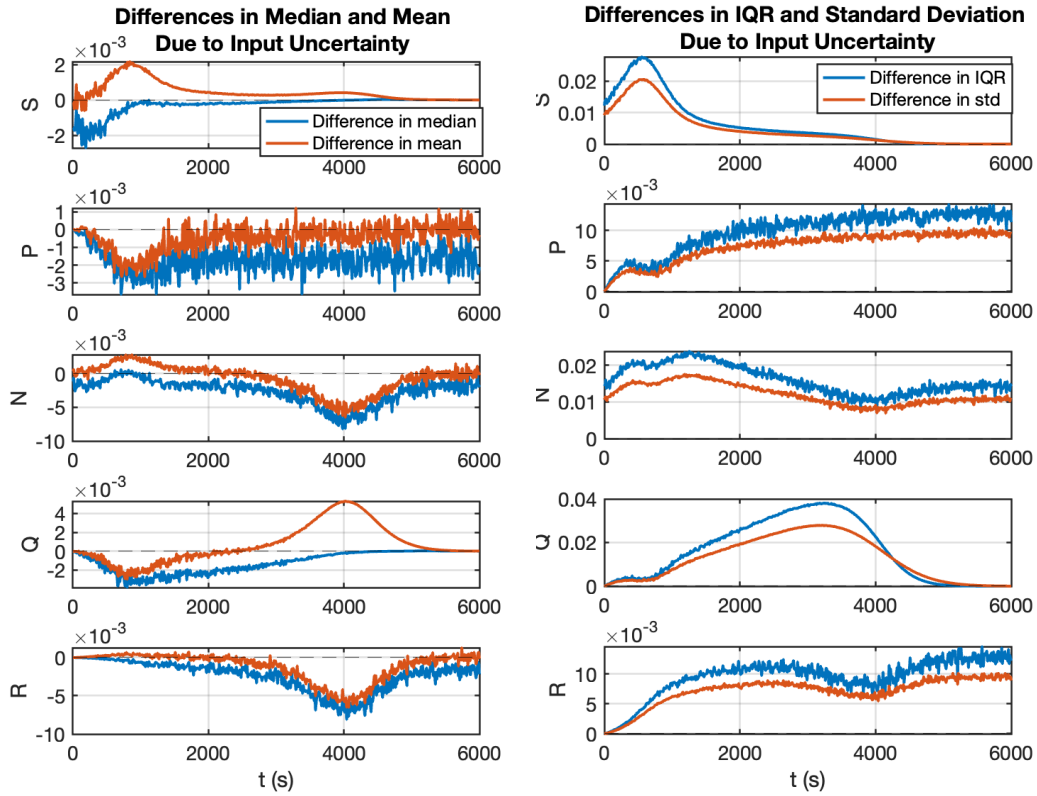


Fig. 6.2 Time-dependent differences in summary statistics of pseudo-data induced by input uncertainty for the measured states S , P , N , Q and R . The left column shows the differences in the median and mean, while the right column shows the differences in the interquartile range (IQR) and standard deviation.

Taken together, these results show that the inclusion of input uncertainty changes the statistical structure of the pseudo-data in a time- and state-dependent manner. Consequently, the resulting measurements are no longer fully consistent with the originally assumed measurement model.

Distributional properties of pseudo-data

To examine the Gaussian assumption in measurement distributions, Figure 6.3 compares the standardized pseudo-data distributions with and without input uncertainty.

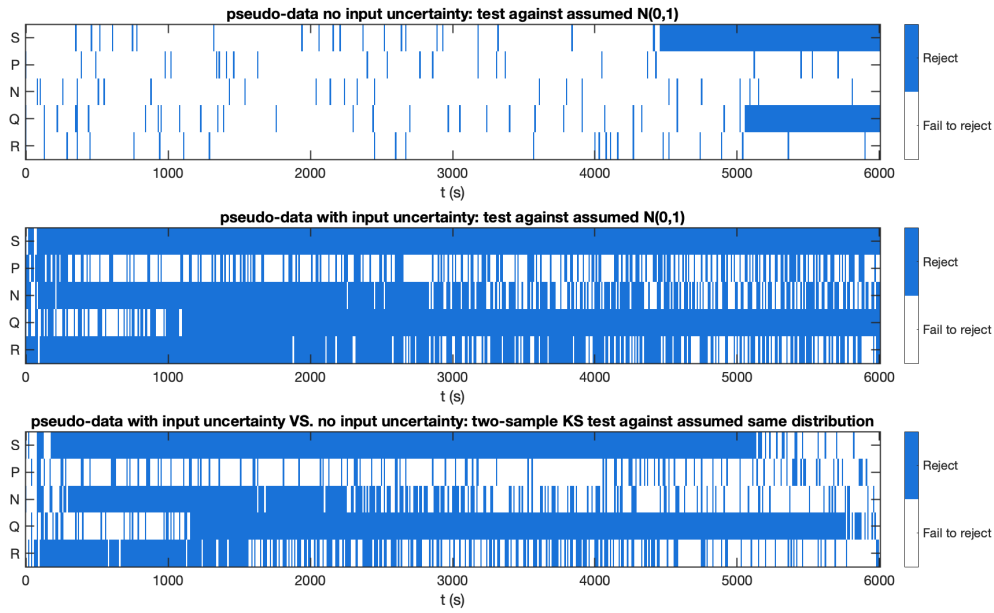


Fig. 6.3 Distributional assessment of pseudo-data with and without input uncertainty based on standardized deviations from the reference trajectory for the measured states S , P , N , Q and R . The top and middle panels show normality test results for the cases without and with input uncertainty, respectively, and the bottom panel shows the two-sample Kolmogorov–Smirnov test comparing the two standardized distributions. Blue indicates rejection of the null hypothesis. Negative pseudo-data values were corrected when states approached zero, so strict Gaussianity is not expected in those regions.

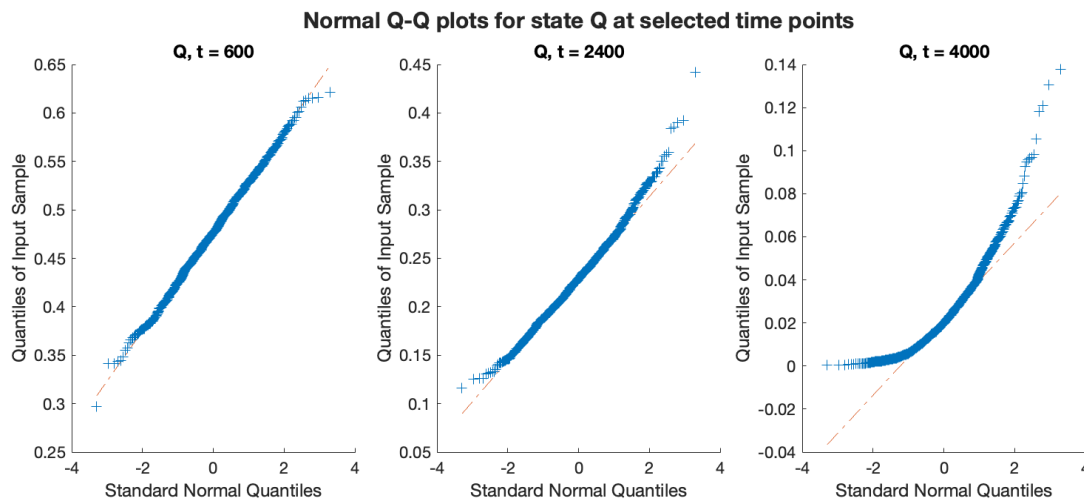


Fig. 6.4 Normal Q–Q plots for state Q at selected time points. The sample quantiles are compared with the corresponding standard normal quantiles to assess deviations from Gaussianity.

For pseudo-data generated without input uncertainty, where only the assumed measurement noise is present, the standardized deviations are broadly consistent with the assumed $N(0, 1)$ distribution over most of the time horizon. Nevertheless, deviations from Gaussianity are observed in some regions, particularly when the corresponding state approaches zero. This is because negative pseudo-data values generated by the Gaussian noise model are physically infeasible and were therefore corrected, which distorts the resulting distribution.

When input uncertainty is included, the standardized pseudo-data exhibit substantially more frequent rejections of the assumed $N(0, 1)$ distribution. The two-sample Kolmogorov–Smirnov (KS) test further shows that the distributions of data with and without input uncertainty differ significantly over wider time windows for several states. These results indicate that input uncertainty alters the Gaussianity in data distribution in a state- and time-dependent manner, so that the resulting pseudo-data can no longer be adequately characterised by the assumed measurement-error model alone.

The normal quantile–quantile (Q–Q) plots for state Q in Figure 6.4 further illustrate this behaviour. The sample quantiles are compared with the theoretical normal quantiles, with the red line indicating the Gaussian reference. At $t = 600$ s, the pseudo-data remain close to Gaussian. At $t = 2,400$ s, moderate deviations are visible, while at $t = 4,000$ s, the distribution becomes clearly skewed and truncated. This confirms that input uncertainty can induce non-Gaussian features after propagation through the nonlinear dynamics.

Temporal correlations in pseudo-data

Figure 6.5 shows the time-point correlation structure of the pseudo-data generated under input uncertainty. Under the nominal measurement model, measurement errors at different sampling times are assumed to be independent. However, once uncertain inputs are propagated through the nonlinear dynamic model, this assumption no longer holds. The reason is that each realization of the uncertain input affects the full state trajectory rather than an isolated time point. As a result, pseudo-data values at different sampling times become statistically coupled, which leads to the temporal correlation patterns observed in Figure 6.5.

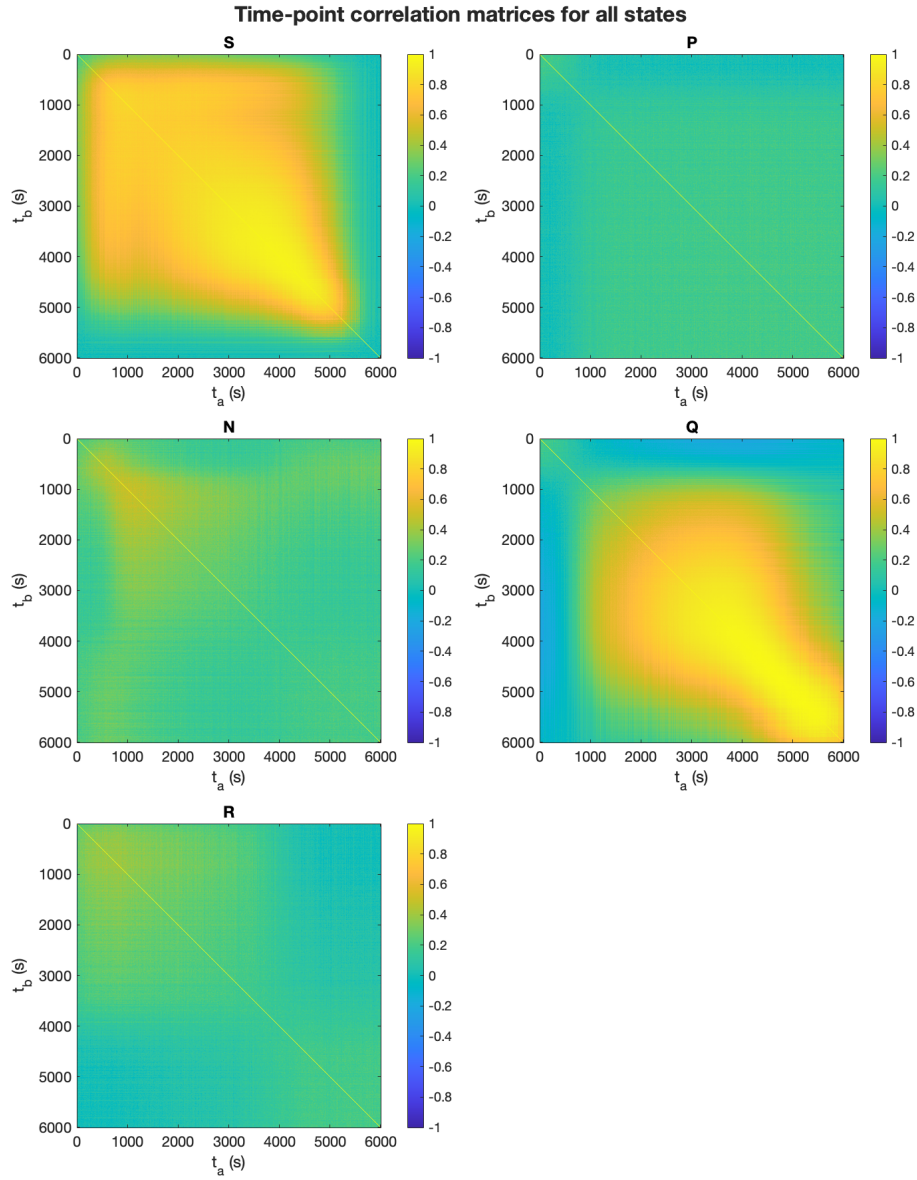


Fig. 6.5 Time-point correlation matrices of pseudo-data with input uncertainty for the measured states S , P , N , Q and R . Correlations are computed across the Monte Carlo ensemble between pseudo-data values at time points t_a and t_b .

Table 6.1 Sampling strategies of the no-design, classical OED, and MCRB-based designs.

Design method	Sampling strategy (s)
no design	[0:300:6000]
classical OED	[570:10:630, 2830:10:2880, 4260:10:4330]
MCRB	[480, 500:10:560, 3470:10:3590]

The strength of this induced dependence is state-dependent. States S and Q exhibit strong and persistent positive correlations across broad time regions, indicating that input uncertainty affects these trajectories coherently over time. In contrast, P remains comparatively weakly correlated, suggesting that its response is less sensitive to trajectory-wide propagation of input uncertainty. States N and R show intermediate behaviour, with moderate temporal correlation over selected time windows.

These results show that input uncertainty does not merely increase the variance of the measurements. After propagation through the nonlinear model, it changes the dispersion of the pseudo-data, introduces deviations from Gaussianity, and induces temporal correlations between measurements. Therefore, the assumptions underlying the classical FIM-based design are no longer fully satisfied. A design based only on the nominal FIM may therefore select sampling times that appear informative under the assumed model but are less suitable for the actual estimation problem. This motivates the use of the MCRB-based design.

6.6.2 Comparison of MCRB-based OED with classical OED

The misspecified sampling time design is formulated as (6.40), with input uncertainty defined in Section 6.6.1. The true covariance matrix is approximated using the sample covariance of pseudo-data with input uncertainty. The resulting non-convex combinatorial optimisation problem is solved using the Powell-type discrete exchange procedure under the D-optimality criterion.

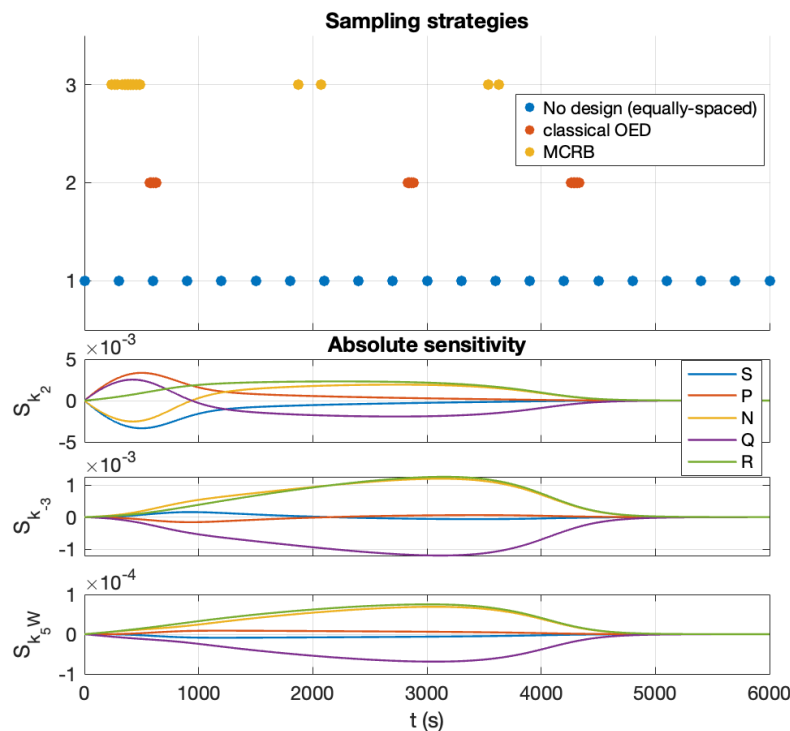


Fig. 6.6 Sampling strategies of the no-design, classical OED, and MCRB-based designs, together with the relative parameter sensitivities.

The obtained MCRB-based sampling strategy is shown in Figure 6.6 (yellow circles), alongside classical OED (red) and no design (blue). Details are summarised in Table 6.1. The MCRB-based design concentrates sampling in high-sensitivity regions, placing greater emphasis on the early transient phase compared to classical OED, which tends to favour later-stage dynamics.

To evaluate the effect of the sampling time design on parameter estimation, 5,000 pseudo-experiments were generated for each strategy and the resulting parameter estimates were analysed using boxplots in Figure 6.7, pairwise scatter plots with empirical 95% contours in Figure 6.8, and the numerical metrics reported in Table 6.2, including relative bias (rBias), root mean square error (RMSE), and empirical 95% intervals. Overall, the MCRB-based design gives the most reliable estimation results. Its main advantage is not a large change in the median estimates, but a clear reduction in estimation spread, extreme outliers, and joint parameter uncertainty.

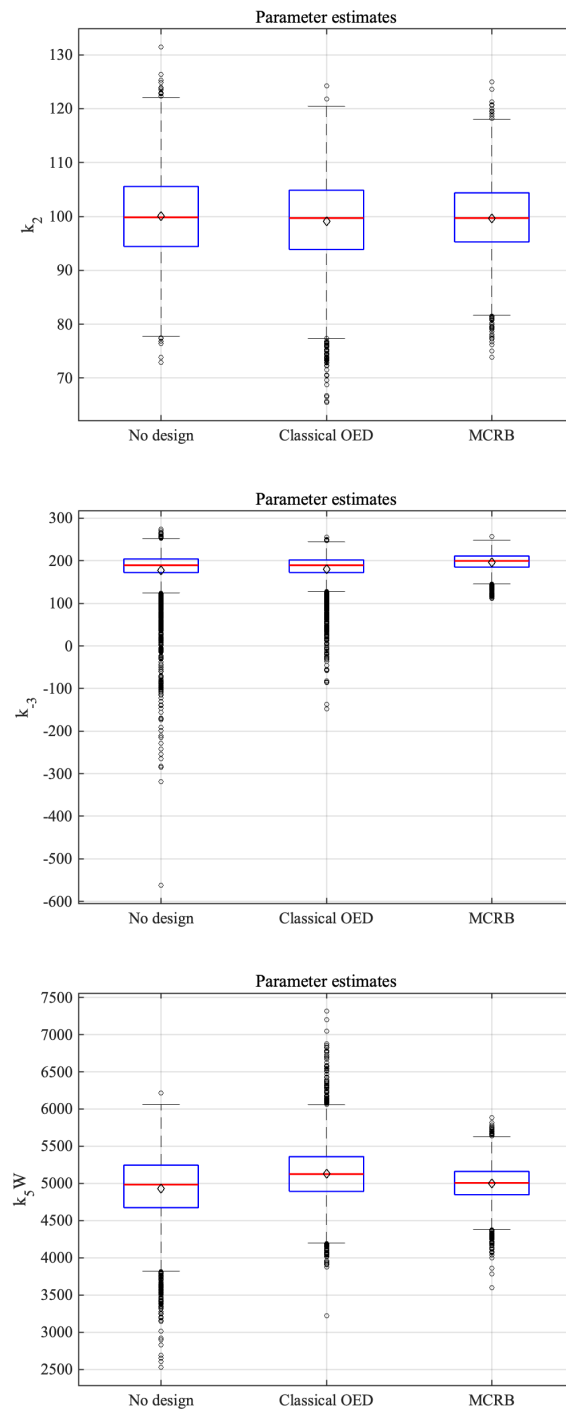


Fig. 6.7 Boxplots of the parameter estimates obtained from 5,000 pseudo-experiments under the no-design (equally spaced), classical OED, and MCRB-based sampling strategies under input uncertainty. The red line indicates the median estimate and the diamond indicates the mean.

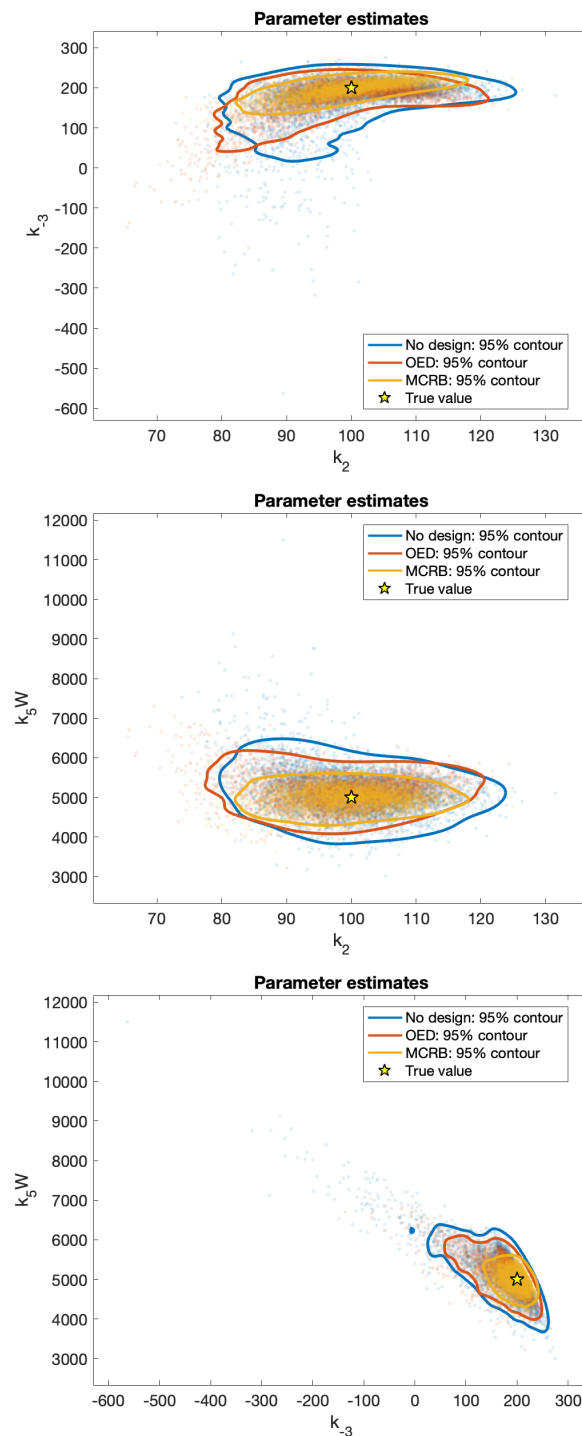


Fig. 6.8 Pairwise scatter plots of the parameter estimates obtained from 5,000 pseudo-experiments under the no-design, classical OED, and MCRB-based sampling strategies, together with the corresponding empirical 95% contours. The star denotes the true parameter value.

The boxplots in Figure 6.7 show that the MCRB-based design gives the most concentrated estimate distributions among the three strategies. For k_2 , the differences between the three designs are relatively small because all estimates are already centred close to the true value. Nevertheless, the MCRB-based design still gives the narrowest spread. The improvement is more pronounced for k_{-3} and k_5W . For k_{-3} , the no-design gives a broad distribution with a strong lower tail, while classical OED partially reduces this behaviour. The MCRB-based design gives a much tighter distribution and substantially reduces the extreme low estimates. For k_5W , the MCRB estimates are also more concentrated around the true value and show a clearly narrower overall spread than both the no-design and classical OED cases.

The pairwise scatter plots in Figure 6.8 show the consistent behaviour in joint parameter space. For (k_2, k_{-3}) , the main improvement of the MCRB design is the suppression of the lower tail in k_{-3} . For (k_2, k_5W) , the MCRB contour is the most compact. For (k_{-3}, k_5W) , a negative correlation remains under all three strategies, but the MCRB design gives the smallest contour and the estimates are closest to the true parameter pair. The MCRB design therefore improves the concentration of the joint estimate distribution, rather than completely removing the correlation structure.

These results can be explained by the difference between the classical OED and MCRB-based criteria. Classical OED selects sampling times using the nominal FIM, which assumes that the measurement errors are independent and described by the prescribed measurement-noise covariance. Under input uncertainty, however, the pseudo-data no longer follow this assumed error structure. The uncertainty in the initial states changes the effective covariance of the data, distorts the distribution of the pseudo-data, and introduces temporal correlation between measurements. Therefore, time points that appear highly informative under the nominal FIM may not lead to stable parameter estimates when the data are generated with input uncertainty.

The MCRB-based design addresses this mismatch by incorporating the covariance structure of the pseudo-data into the design criterion. It therefore balances local sensitivity information against the additional variability introduced by input uncertainty. This explains

Table 6.2 Summary statistics of the parameter estimates obtained from 5,000 pseudo-experiments under the three sampling strategies: no design, classical OED and MCRB-based design. The empirical 95% interval width is defined as the difference between the 97.5th and 2.5th percentiles of the estimate distribution.

Parameter (nominal)	Design strategy	rBias %	RMSE	95% interval width
k_2 (100)	no design	0.08	8.14	31.38
	classical OED	-0.92	8.34	27.98
	MCRB	-0.39	6.86	26.56
k_{-3} (200)	no design	-11.01	58.57	206.43
	classical OED	-9.69	43.11	157.53
	MCRB	-1.70	20.39	78.25
k_5W (5,000)	no design	-1.37	458.8	1782
	classical OED	2.62	404.3	1510
	MCRB	-0.05	249.2	986

why the improvement is strongest for k_{-3} and k_5W , where classical OED still leaves substantial spread and tail behaviour. The summary metrics in Table 6.2 support this interpretation: the MCRB design gives the smallest RMSE and narrowest empirical 95% interval for all three parameters. Thus, the advantage of the MCRB-based design comes from using an information measure that better reflects the effective uncertainty structure of the pseudo-data.

6.6.3 Comparison of MCRB-based OED with existing input-uncertainty design methods

This section compares the MCRB-based sampling design (result shown in Table 6.1) with two alternative approaches introduced in Section 6.5: (i) OED using sample covariance, and (ii) smallest covariance deviation design. The corresponding sampling strategies are shown in Figure 6.9, with sampling details provided in Table 6.3. Figure 6.9 shows that the three methods produce noticeably different sampling patterns. The CRB design using sample covariance allocates samples to both the early and late stages, the smallest covariance deviation design concentrates mainly in an earlier window, and the MCRB-based design places most samples in the early stage with a few additional points elsewhere. This suggests that the three criteria emphasise different parts of the dynamic trajectory under input uncertainty.

Table 6.3 Sampling strategies of the CRB using sample covariance and smallest covariance deviation used for comparison with the MCRB-based design.

Design method	Sampling strategy (s)
CRB using sample covariance	[60:10:140, 170, 3130, 3200, 3210, 3230:10:3250, 3290, 3310, 3330, 3350, 3390]
Smallest covariance deviation	[640, 730, 750, 770:10:790, 870, 890, 910, 920, 950, 970:10:990, 1040, 1050, 1090, 1100, 1130, 1290, 1730]

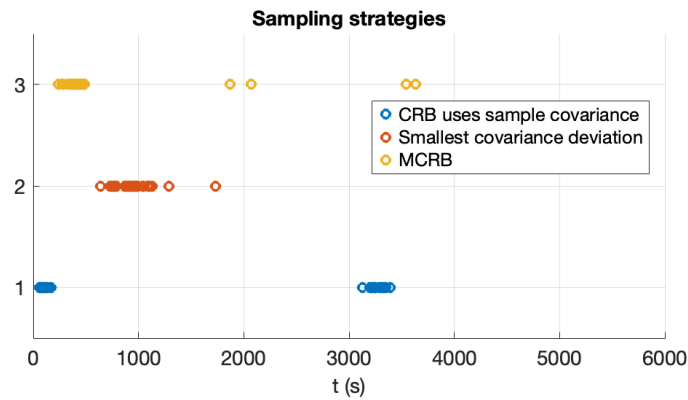


Fig. 6.9 Sampling strategies of the CRB using sample covariance, smallest covariance deviation, and MCRB-based designs.

Similarly, to evaluate estimation performance, 5,000 parameter estimates are generated for each strategy. The resulting distributions are shown in Figure 6.10 and Figure 6.11, with the corresponding numerical summaries reported in Table 6.4. The results show that the MCRB-based design gives the most balanced estimation performance among the three methods. For k_2 and k_{-3} , the CRB design using sample covariance gives slightly smaller RMSE and narrower empirical intervals than the MCRB-based design. This is because replacing the nominal measurement covariance with the sample covariance can improve the weighting of information at individual sampling times. However, this method still treats the selected time points as independent contributions to the information matrix. It therefore does not fully account for the temporal correlations between measurements induced by input uncertainty. This limitation becomes clear for k_5W , where the same design gives a much wider distribution and larger joint contours than the MCRB-based design.

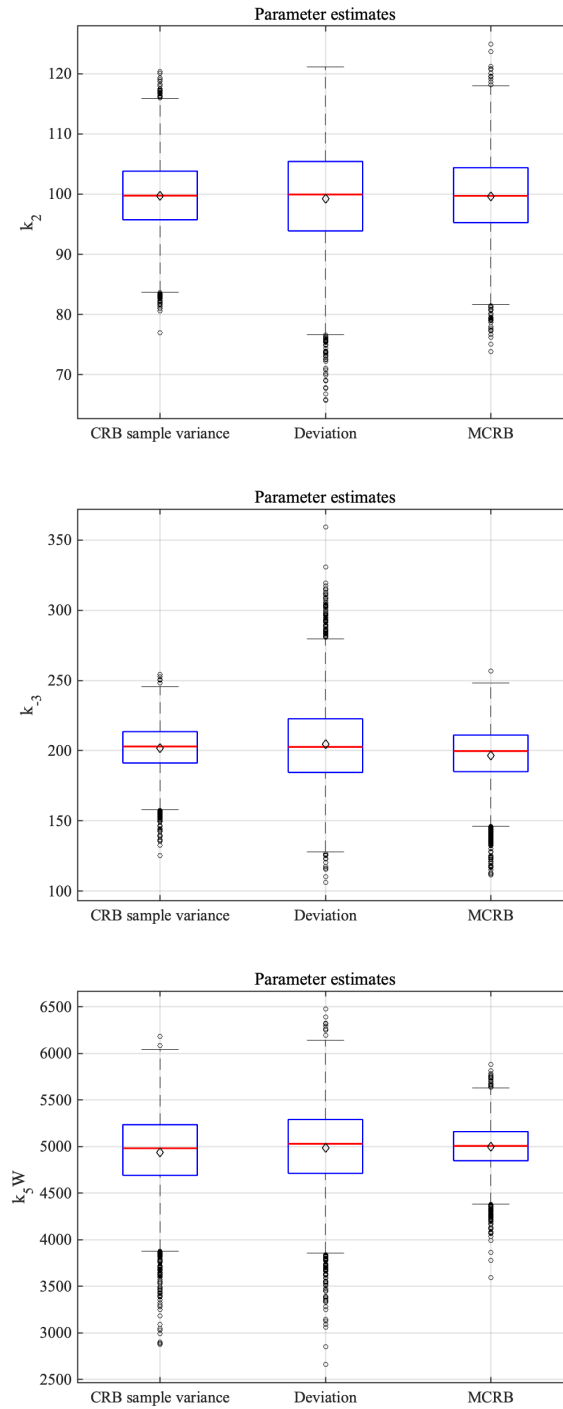


Fig. 6.10 Boxplots of the parameter estimates obtained from 5,000 pseudo-experiments under the CRB using sample covariance, smallest covariance deviation, and MCRB-based designs.

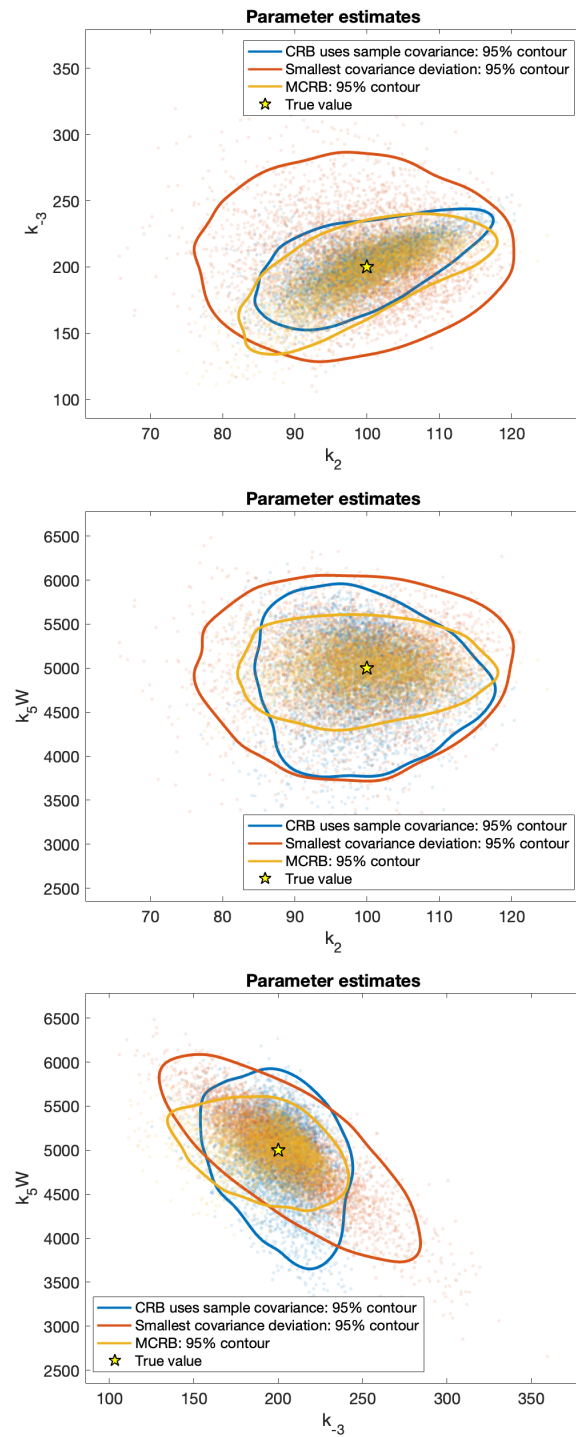


Fig. 6.11 Pairwise scatter plots of the parameter estimates obtained from 5,000 pseudo-experiments under the CRB using sample covariance, smallest covariance deviation, and MCRB-based sampling strategies. The solid lines denote empirical 95% contours and the star denotes the true parameter value.

Table 6.4 Summary statistics of the parameter estimates obtained from 5,000 pseudo-experiments under the three sampling strategies: CRB using sample covariance, smallest covariance deviation and MCRB-based design. The empirical 95% interval width is defined as the difference between the 97.5th and 2.5th percentiles of the estimate distribution.

Parameter (nominal)	Design strategy	rBias %	RMSE	95% interval width
k_2 (100)	CRB uses sample covariance	-0.26	6.11	24.00
	Smallest covariance deviation	-0.72	8.49	33.07
	MCRB	-0.39	6.86	26.56
k_{-3} (200)	CRB uses sample covariance	0.92	17.19	68.12
	Smallest covariance deviation	2.37	29.97	117.78
	MCRB	-1.70	20.39	78.25
k_5W (5,000)	CRB uses sample covariance	-1.31	434.1	1694
	Smallest covariance deviation	-0.25	449.0	1776
	MCRB	-0.05	249.2	986

The smallest covariance deviation design provides less favourable overall performance. Its purpose is to select sampling times where the covariance distortion due to input uncertainty is relatively small. This can avoid strongly affected regions of the trajectory, but it does not necessarily select the most informative times for parameter estimation. As a result, the estimate distributions are generally wider, especially for k_{-3} and k_5W . This shows that reducing the effect of input uncertainty alone is not sufficient if the selected samples do not also provide strong parameter sensitivity information.

The advantage of the MCRB-based design is that it incorporates the covariance structure of the full pseudo-data vector into the design criterion. It therefore accounts not only for changes in variance at individual time points, but also for correlations between measurements at different times. This is different from the CRB design using sample covariance, which improves the local covariance weighting but still treats the selected time points as independent contributions to the information matrix. The smallest covariance deviation design also has a different limitation: it avoids regions with strong covariance distortion, but does not necessarily select the most informative samples for parameter estimation. By incorporating the covariance of the full pseudo-data vector, the MCRB-based design gives a more suitable compromise and provides more stable estimation performance, especially for k_5W .

Table 6.5 Sampling strategies of the standard RED methods used for comparison with the MCRB-based design.

Design method	Sampling strategy (s)
Maximin fixed WC	[390:10:450, 1460:10:1510, 2450:10:2520]
Pseudo-Bayesian	[10, 20, 190, 260, 570, 580, 730, 1700, 2090, 2820, 3200, 3210, 3230, 3530, 3880, 4030, 4440, 4460, 4690, 4820, 5310]

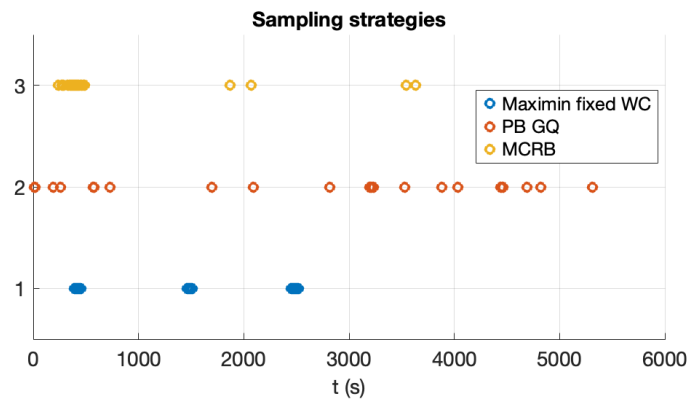


Fig. 6.12 Sampling strategies of the standard RED methods and the MCRB-based design.

6.6.4 Comparison of MCRB-based OED with standard RED methods

This subsection compares the MCRB-based design with the two RED approaches, maximin and pseudo-Bayesian D-mean designs. The maximin design is solved using the fixed worst-case method, and the pseudo-Bayesian design is solved using 5-point Gaussian quadrature (GQ). The sampling strategies are shown in Figure 6.12 and summarised in Table 6.5. Figure 6.12 shows that the three robust designs produce different sampling patterns. The maximin fixed worst-case design forms several compact clusters in the early-to-middle time range, while the pseudo-Bayesian design spreads samples more broadly across the full horizon. The MCRB-based design mainly concentrates samples in the early transient region, with a few additional later samples. Thus, the three methods identify different informative regions under input uncertainty.

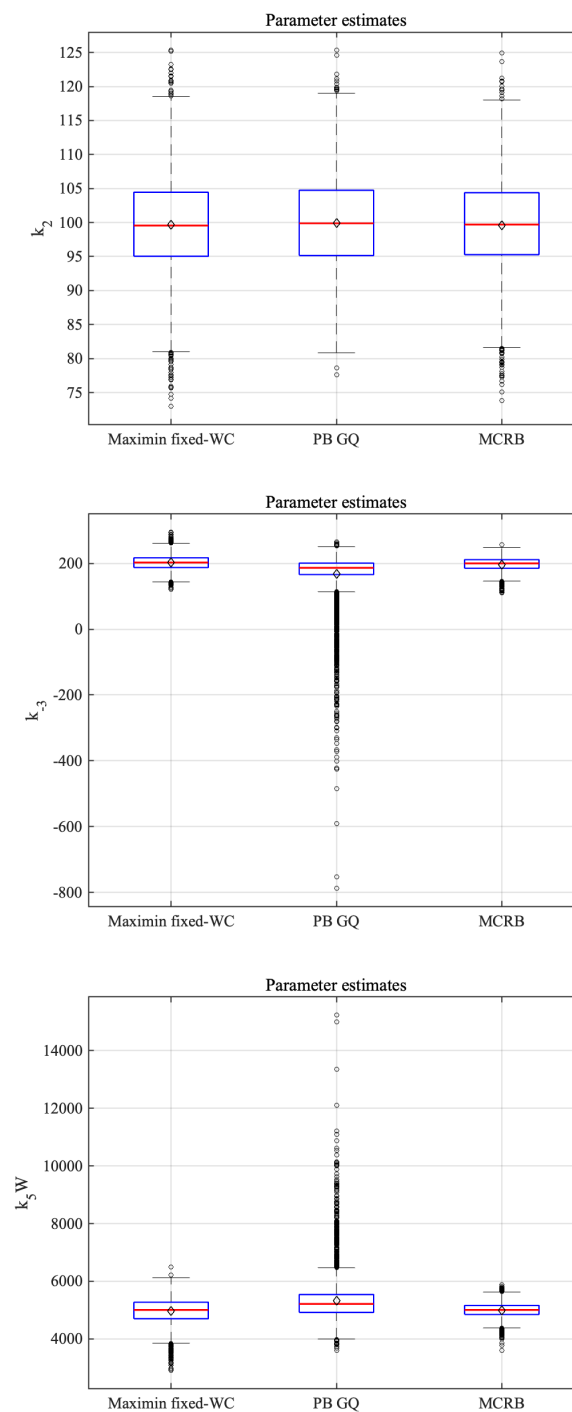


Fig. 6.13 Boxplots of the parameter estimates obtained from 5,000 pseudo-experiments under the maximin, pseudo-Bayesian, and MCRB-based sampling strategies under input uncertainty. The red line indicates the median estimate and the diamond indicates the mean.

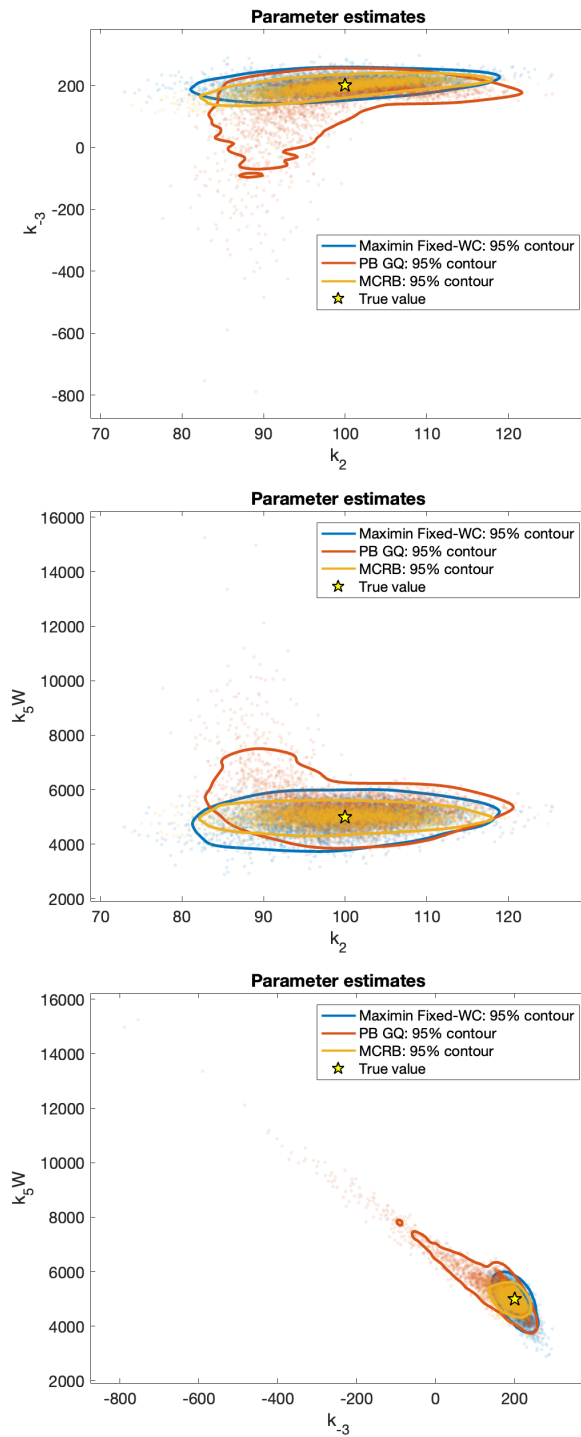


Fig. 6.14 Pairwise scatter plots of the parameter estimates obtained from 5,000 pseudo-experiments under the maximin, pseudo-Bayesian, and MCRB-based sampling strategies, together with the corresponding empirical 95% contours. The star denotes the true parameter value.

Table 6.6 Summary statistics of the parameter estimates obtained from 5,000 pseudo-experiments under the three sampling strategies: maximin, pseudo-Bayesian and MCRB-based design. The empirical 95% interval width is defined as the difference between the 97.5th and 2.5th percentiles of the estimate distribution.

Parameter (nominal)	Design strategy	rBias %	RMSE	95% interval width
k_2 (100)	Maximin	-0.37	7.17	28.48
	Pseudo-Bayesian	-0.06	6.80	26.21
	MCRB	-0.39	6.86	26.56
k_{-3} (200)	Maximin	1.19	22.31	86.77
	Pseudo-Bayesian	-16.36	80.69	285.10
	MCRB	-1.70	20.39	78.25
k_5W (5,000)	Maximin	-0.73	442.0	1707
	Pseudo-Bayesian	6.41	822.2	2958
	MCRB	-0.05	249.2	986

Parameter estimation performance is evaluated using 5,000 pseudo-data realisations. The resulting parameter distributions are shown in Figure 6.13 and Figure 6.14, for single parameter and pairwise parameters respectively. Relevant statistics are reported in Table 6.6.

For k_2 , all three robust designs give similar results, indicating that this parameter is relatively insensitive to the design criterion. For k_{-3} , the MCRB-based design gives a compact distribution, comparable to the maximin design and much tighter than the pseudo-Bayesian design. For k_5W , the improvement is clearer: the MCRB-based design gives the narrowest boxplot, smaller joint contours, and the lowest RMSE and empirical interval width among the three methods.

The results also show that standard RED methods do not necessarily improve over classical OED in this input-uncertainty problem, as shown by comparison with the classical OED results in Table 6.2. The maximin design performs worse than classical OED for k_5W , while the pseudo-Bayesian design performs worse for both k_{-3} and k_5W . This suggests that, in this input-uncertainty case, applying a worst-case or expectation-based formulation does not necessarily improve parameter-estimation performance when the underlying information measure is still based on the classical FIM/CRB.

Although maximin and pseudo-Bayesian designs account for input uncertainty through worst-case protection or averaging over the input-uncertainty space, they still evaluate information under the nominal measurement-error assumption. They therefore do not directly account for the effective covariance change, distributional distortion, or temporal correlation induced in the pseudo-data. By contrast, the MCRB-based design modifies the information measure itself by using the pseudo-data covariance under input uncertainty. This makes the design criterion more consistent with the actual parameter estimation problem and explains its more stable performance, especially for k_5W .

6.7 Summary

This chapter addressed sampling time design for nonlinear dynamic systems under input uncertainty. Unlike the parametric uncertainty considered in Chapters 4 and 5, input uncertainty affects the execution of the experiment and can alter the data-generating process. In the enzyme reaction system, uncertainty in the initial states was shown to change the dispersion of pseudo-data, violate the assumed Gaussian measurement model, and induce temporal correlations between measurements. As a result, the nominal FIM/CRB-based design criterion may no longer reliably reflect estimation performance.

To address this, the MCRB was adopted as a performance bound under model misspecification. A trajectory-level approximation was developed by stacking measurements across sampling times and incorporating the empirical covariance of pseudo-data. This formulation captures both marginal variance and cross-time dependence induced by input uncertainty. The resulting design problem is non-additive and combinatorial, and was solved numerically using the Powell-type discrete exchange procedure under D-optimality.

The case study showed that the MCRB-based design improves parameter estimation compared with equally spaced sampling and classical OED. The main benefit lies in reduced estimation spread, tail behaviour, and joint uncertainty, particularly for k_{-3} and k_5W , where classical OED retains substantial variability.

Comparison with existing methods reveals a more nuanced picture. The sample-covariance OED performs well for k_2 and k_{-3} but poorly for k_5W . The smallest covariance deviation design avoids regions sensitive to input uncertainty but may miss informative sampling points. Standard RED methods account for input uncertainty through worst-case or expectation-based formulations but remain tied to the nominal FIM/CRB. In contrast, the MCRB-based design achieves more consistent performance by modifying the information measure itself.

In summary, input uncertainty should not be treated solely as a perturbation to sensitivity or variance. Its nonlinear propagation alters the statistical structure of the data, which must be reflected in the design criterion. The proposed MCRB-based framework provides a principled approach to account for this effect. Its current limitations include reliance on local linearisation and empirical covariance estimation, which warrant further investigation for larger systems, stronger uncertainties, and integration with sequential redesign and parametric uncertainty.

Chapter 7

Summary and Future Work

This chapter provides concluding remarks on the work presented in this thesis and outlines directions for future research.

7.1 Summary and Conclusion

This thesis develops robust sampling time design strategies for model-based design of experiments (MBDoE) in nonlinear dynamic systems under uncertainty. It addresses two key limitations of classical Fisher Information Matrix (FIM)-based MBDoE: sensitivity to parametric uncertainty and the breakdown of assumed measurement models under input uncertainty.

The main contributions are summarised as follows:

- **Foundational framework.** Chapters 2 and 3 established the theoretical basis of MBDoE, including modelling workflows, sensitivity analysis, identifiability, parameter estimation, and classical FIM-based design. These provide the foundation for subsequent developments under uncertainty.
- **Standard robust experimental design (RED) with distribution-aware evaluation.** Chapter 4 formulates maximin and pseudo-Bayesian designs and develops numeri-

cal solution methods. A key contribution is the introduction of a distribution-based evaluation framework that analyses the performance of sampling strategies across the parameter uncertainty space, rather than relying on a single scalar metric. This enables robustness to be examined through multiple lenses, such as worst-case behaviour, average performance, and variability, providing a more comprehensive and discriminative comparison between classical and robust designs. Case studies on two benchmark systems show that, although standard RED improves robustness, it may reduce nominal accuracy and incur significant computational cost.

- **Adaptive midterm redesign.** Chapter 5 introduced a midterm redesign framework that updates parameter estimates within a single experiment and re-optimises sampling strategies accordingly. Three redesign strategies were investigated: equally divided, auto-updating, and condition-triggered redesign. The equally divided and auto-updating strategies provide predefined and information-driven redesign policies, respectively, while the condition-triggered strategy uses a change in operating conditions as the redesign point. In the biodiesel case, the favourable performance of the condition-triggered strategy was associated with the relatively early redesign time, which helped avoid missing an informative early-time region, particularly for k_2 .
- **Misspecified Cramér–Rao bound (MCRB)-based design for input uncertainty.** Chapter 6 addressed measurement model misspecification caused by input uncertainty. It showed that uncertainty in the inputs can change the effective measurement distribution by altering the dispersion of pseudo-data, introducing departures from the assumed Gaussian error model, and inducing temporal correlations between measurements at different sampling times. To account for these effects, a full-trajectory (stacked-measurement) MCRB-based sampling time design was developed. Compared with classical optimal experimental design (OED), this design provides a more appropriate criterion when the data-generating process no longer matches the assumed measurement model.

Overall, this thesis extends MBDoE from static, model-reliant formulations to adaptive and uncertainty-aware frameworks. It contributes both new methodologies (midterm redesign and MCRB-based design) and systematic evaluations of existing robust design approaches.

The central conclusion is that effective sampling time design in nonlinear systems requires moving beyond static nominal formulations. Under substantial parametric uncertainty, a design based on the FIM evaluated only at a single nominal parameter vector may lack robustness, while under measurement model misspecification caused by input uncertainty, the classical FIM/Cramér–Rao bound (CRB) framework may no longer provide an appropriate description of estimation performance.

The midterm redesign framework demonstrates that sequential updating within a single experiment can reduce dependence on prior parameter estimates and improve robustness without requiring multiple experimental runs. In parallel, the MCRB-based approach addresses limitations arising from misspecified data models by using a performance bound that is more consistent with the effective data-generating process under input uncertainty.

Together, these developments provide a unified perspective on robust MBDoE, emphasising adaptive design, appropriate uncertainty modelling, and statistically consistent design criteria for reliable parameter estimation in practical settings. In the broader model-development process, data obtained from informative experiments support parameter recalibration, after which independent data can be used to assess the predictive performance of the recalibrated model.

7.2 Open Challenges and Future Perspectives

While this thesis advances robust sampling time design, several important challenges remain and motivate future research:

- **Integration of multiple uncertainties.** This work treats parametric and input uncertainties separately. In practice, experiments often involve multiple interacting sources, including structural uncertainty, correlated noise, and operational variability. Develop-

ing a unified framework that handles these uncertainties in a consistent manner remains an open problem.

- **Multi-objective robust design.** The proposed methods focus on single robustness criteria (e.g., D-optimality under different formulations). Extending these approaches to multi-objective settings—balancing estimation accuracy, robustness, experimental cost, and feasibility—would improve practical applicability.
- **Extension to multiple experimental design variables.** This thesis focuses on sampling-time optimisation while the operating conditions, input profiles, and measured outputs are prescribed. The robust design formulations considered here can, in principle, be extended to other experimental design variables, including initial conditions, input profiles, and measurement selection. Joint optimisation of sampling times with these variables may provide more informative experiments, although it would also increase the dimensionality of the design problem and introduce additional practical constraints.
- **Computational scalability.** Robust and Bayesian designs are computationally demanding, especially for nonlinear systems with high-dimensional parameter spaces. Techniques such as surrogate modelling, reduced-order models, and machine learning-based accelerators (e.g., Gaussian processes or reinforcement learning) offer promising directions to improve efficiency.
- **Theoretical extensions of MCRB.** The current formulation uses a local linearisation of the nonlinear dynamic model and estimates the pseudo-data covariance empirically from simulated trajectories. Future work should examine the accuracy of this approximation under stronger input uncertainty, larger sampling sets, and higher-dimensional systems. Extensions to non-Gaussian assumed likelihoods, nonparametric misspecification, and hybrid model–data-driven settings would further broaden the applicability of the MCRB-based design framework.

- **Integration with autonomous experimentation.** The midterm redesign framework is naturally suited to closed-loop experimental platforms. Embedding RED and MCRB-based strategies into automated laboratories would enable real-time decision-making and more efficient data acquisition.
- **Cross-disciplinary applications.** Although demonstrated on biochemical systems, the proposed methods are applicable to other domains such as energy systems, aerospace, and climate modelling. Adapting the framework to domain-specific constraints and uncertainty structures offers significant opportunities for further validation.

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Appendix A

Enzyme Reaction System

A.1 System and Model Descriptions

The enzyme reaction system introduced here is an exemplary kinetically controlled synthesis system. Many essential enzymatic processes are believed to adhere to this reaction scheme or a closely related one, e.g., in the preparation of semi-synthesis penicillin, **S** is hydroxyphenylglycine methyl ester and **N** is 6-APA, etc. (Yu et al., 2018a). This appendix provides the complete dynamic model and auxiliary analyses of the enzyme reaction system employed throughout Chapters 4–6.

The reaction scheme of the enzyme reaction system is shown in Figure 4.1. The donor substrate **S**, the nucleophile **N**, and the enzyme catalyst **E** (red font) are initial reactants. The initial concentration of these three reactants is user-controllable and represented by S_0 , N_0 , and E_0 . The final product is marked with green font, which includes the desired product **Q** and a hydrolysis by-product **R**. The species **ES**, **E***, **EQ**, and **ER** denote different enzyme–substrate complexes, while **E** represents the free enzyme. The other state variables shown in the figure are the leaving group product **P** and the water **W**, which is treated as constant due to its large amount compared to other variables. The kinetic reaction rates of the system are represented by k_1 to k_6 .

This chemical process can be written into the following six groups of reactions:



For completeness, a brief qualitative description of the reaction mechanism is provided below. Assume all reactants are well mixed in the reactor. At the onset, the substrate **S** binds with the enzyme **E**, forming the enzyme-substrate complex **ES**. Subsequently, **ES** can break down into another compound **E***, and the leaving group product **P**. The enzyme compound **E*** can then either engage with the nucleophile **N** to form **EQ** or undergo hydrolysis to produce **ER**. The compound **EQ** may decompose into the necessary product and enzyme, whereas **ER** can decompose into the hydrolysis by-product **R** and enzyme **E**. Throughout the entire reaction process, all the reactions are reversible, except for the decomposition of **ER** to yield **E** and **R**. The characteristics of the enzyme mean it only catalyses the reactions, which means the amount of enzyme remains the same at the end of the reaction as at the beginning.

Based on mass-balance relations, the dynamic behaviour of the enzyme reaction system is described by the following set of ordinary differential equations (ODEs):

$$\frac{dE}{dt} = -k_1 E \cdot S + k_{-1} ES + k_4 EQ - k_{-4} E \cdot Q + k_6 ER \quad (A.7)$$

$$\frac{dES}{dt} = k_1 E \cdot S - k_{-1} ES - k_2 ES + k_{-2} E^* \cdot P \quad (A.8)$$

Table A.1 Nominal value of initial state

<i>Reactants</i>	E^*	S	P	N	Q	R	E	ES	EQ	ER
<i>Initial states (mol/L)</i>	0	0.8	0	0.9	0	0	$1.5e-5$	0	0	0

Table A.2 Nominal values of reaction rate parameters

<i>Parameters</i>	k_1	k_{-1}	k_2	k_{-2}	k_3	k_{-3}	k_4	k_{-4}	k_5W	k_{-5}	k_6
<i>Nominal</i>	1e5	1e3	100	1e4	5e4	200	1e3	2e4	5e3	100	500

$$\frac{dE^*}{dt} = k_2ES - k_{-2}E^* \cdot P - k_3E^* \cdot N + k_{-3}EQ - k_5W \cdot E^* + k_{-5}ER \quad (A.9)$$

$$\frac{dEQ}{dt} = k_3E^* \cdot N - k_{-3}EQ - k_4EQ + k_{-4}E \cdot Q \quad (A.10)$$

$$\frac{dER}{dt} = k_5W \cdot E^* - k_{-5}ER - k_6ER \quad (A.11)$$

$$\frac{dS}{dt} = -k_1E \cdot S + k_{-1}ES \quad (A.12)$$

$$\frac{dP}{dt} = k_2ES - k_{-2}E^* \cdot P \quad (A.13)$$

$$\frac{dN}{dt} = -k_3E^* \cdot N + k_{-3}EQ \quad (A.14)$$

$$\frac{dQ}{dt} = k_4EQ - k_{-4}E \cdot Q \quad (A.15)$$

$$\frac{dR}{dt} = k_6ER \quad (A.16)$$

All state variables are expressed in mol/L, and rate constants follow the units specified in Table A.2.

Among those variables, only **S**, **P**, **N**, **Q**, and **R** are measurable in the lab experiments since measuring different forms of enzymes is challenging due to their very low concentrations. State variable **S**, **N** and **E** have non-zero initial values. The other state variables are considered to have zero initial states. The nominal values of the initial states and kinetic parameters adopted in this thesis are summarised in Tables A.1 and A.2, respectively.

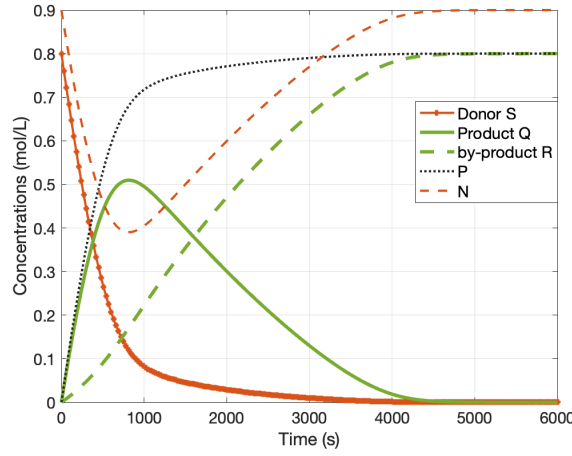


Fig. A.1 Time profile of donor substrate **S**, desired product **Q** and by-product **R**

Environmental effects such as temperature, pH variation, and enzyme deactivation are neglected in the present model formulation. These effects are addressed implicitly through parametric uncertainty in the experimental design studies reported in the main chapters.

A.2 Equilibrium Analysis

For reference, the steady-state behaviour of the enzyme reaction system is obtained by setting the time derivatives in Eq. (A.7) to (A.16) to zero, yielding:

$$\begin{aligned} ES(\infty) = E^*(\infty) = EQ(\infty) = ER(\infty) = S(\infty) = Q(\infty) = 0 \\ P(\infty) = R(\infty) = S_0, N(\infty) = N_0, E(\infty) = E_0 \end{aligned} \quad (\text{A.17})$$

The time profile of donor substrate **S**, product **Q** and by-product **R**, together with the nucleophile **N** and leaving group product **P** are presented in Figure A.1, the dynamics of different forms of enzymes are plotted in Figure A.2 due to their magnitude. It is evident from the figures that, at the early stage, the donor substrate **S** and free form of enzyme **E** reacts quickly, and the produced compound enzyme **ES** reaches its peak at almost the beginning of the reaction. Then the **ES** starts to produce the leaving group **P** and compound enzyme **E***, the latter quickly reacts with **N** to product the desired product **Q** (formation through v_3 and

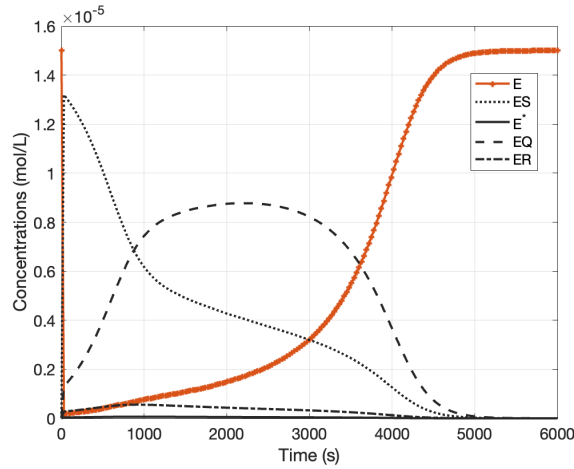


Fig. A.2 Time profile of different forms of enzymes

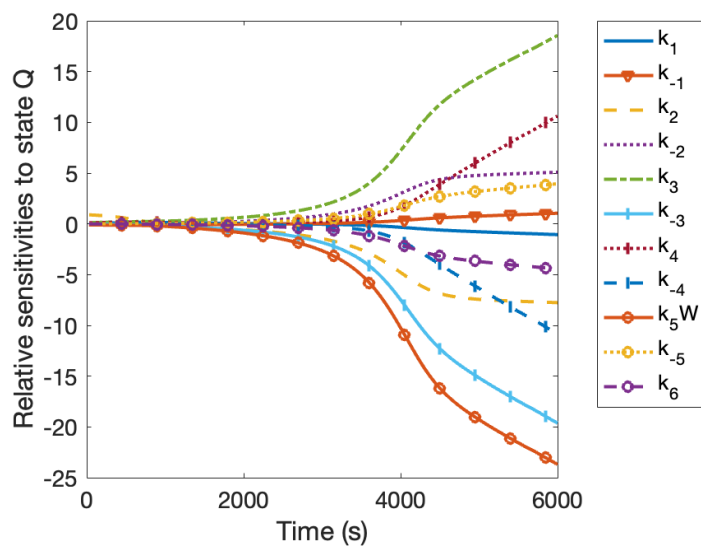
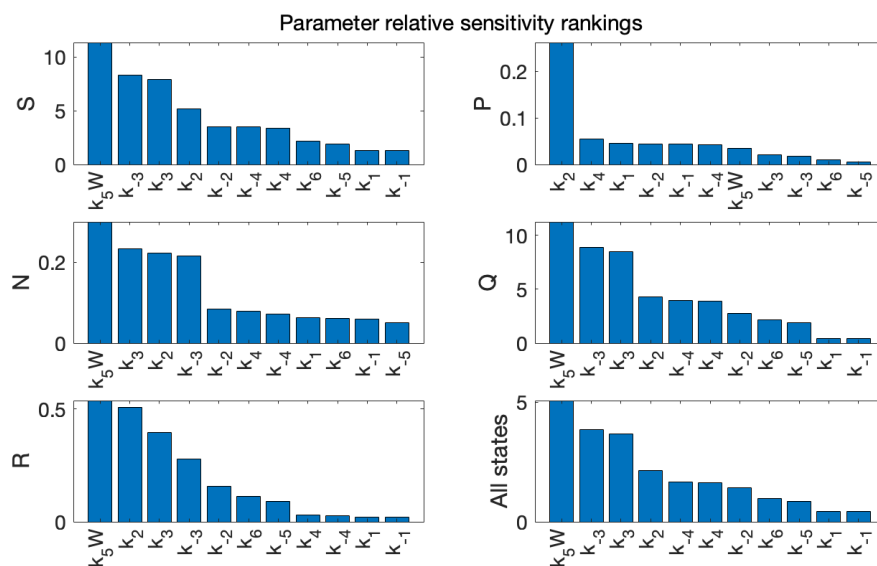
v_4). However, after **S** is used up, the reversible reactions (v_4 and v_3) that lead to **Q** begin to reverse. The produced **E*** reacts with water **W** (v_5) and irreversibly go on to form by-product **R** (v_6).

Therefore, the main product of interest, **Q**, accumulated in the early stage of the reaction and then decreased gradually to zero. On the other hand, the by-product **R** increased slowly until the donor substrate **S** was fully depleted. This indicates that the desired product **Q** is not the thermodynamically most favourable since the equilibrium position will eventually consist almost entirely of by-product **R**. Enhancing product quality in this enzymatic process can maximise the Q/S_0 ratio or minimise the time required to reach peak value (Yue et al., 2013).

A.3 Local Sensitivity Analysis

In this section, the parametric sensitivity of the enzyme reaction system will be studied to explore the importance of each parameter. Based on reported kinetic ranges in the literature, the second-order rate constants k_1 , k_{-2} , k_3 , and k_{-4} are typically bounded above by 10^9 . No clear theoretical upper limits are available for the other parameters.

The nominal value of these parameters is usually determined from the previous experiment data. For a feasible process, the rate of **Q** formation should be larger than the rate of **R**

Fig. A.3 Relative local sensitivity of state Q Fig. A.4 Parameter relative sensitivity rankings to states S , P , N , Q , R separately and all together

formation. However, if the rate of **Q** formation is much faster than the rate of **R** formation, the side reaction is insignificant and results in no complications of the kinetically controlled process.

The dynamic relative sensitivity to state **Q** is shown in Figure A.3, calculated by (3.7). It shows that the sensitivity is quite different along the time scale, which means the information content varies at different time points, and the sampling time design is beneficial. The importance rankings of parameters for all measurable states are shown in Figure A.4. It shows that parameters k_5W , k_{-3} , k_3 and k_2 have the largest impact. With the identifiability analysis and correlation analysis, which can be found in detail in Yue et al. (2013) and Yu et al. (2018a), parameters k_5W , k_{-3} and k_2 are selected as target parameters that need to be precisely estimated. Other parameters are set at their nominal value.

Appendix B

Enzymatic Biodiesel Production System

This appendix documents the complete model formulation and experimental settings of the enzymatic biodiesel production case study employed throughout the main chapters.

B.1 Kinetic Model

The kinetic model is adopted from the literature (Lv et al., 2010; Price et al., 2014) and describes enzymatic transesterification in a biphasic oil–water system using a liquid lipase formulation (CalleraTM Trans L). For completeness, this appendix summarises the modelling assumptions, reaction mechanism, governing equations, measurement definition, and the experimental configurations used for parameter estimation.

The model is developed under the following assumptions (Cheirsilp et al., 2008; Fedosov et al., 2013):

- The reaction proceeds via a Ping-Pong Bi-Bi mechanism.
- Alcohol inhibition is competitive.
- Deactivation caused by alcohol can be ignored at low methanol concentrations.

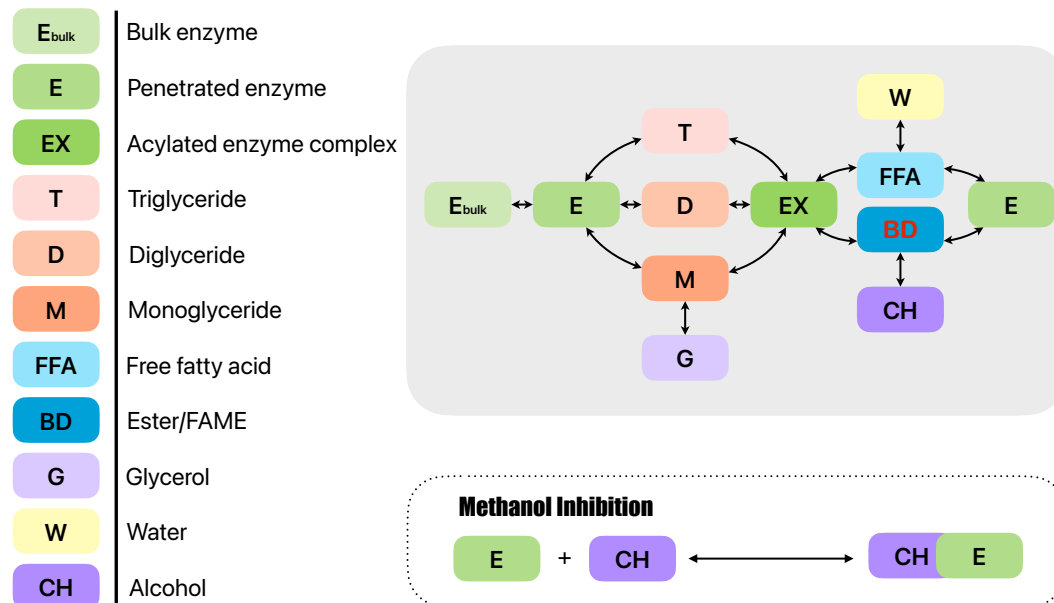


Fig. B.1 Transesterification reaction scheme

- Same interfacial and bulk concentrations of the substrate and products, that is instantaneous mass transfer from the bulk to the interface.
- Acyl migration is neglectable.
- All reaction steps are reversible.
- All reactor mixture are homogeneous with constant density.

A schematic representation of the reaction network is shown in Figure B.1.

The kinetic description explicitly accounts for enzyme interaction at the oil–water interface. The free enzyme contained in the polar phase E_{bulk} is absorbed at the free specific oil–water inter-facial area A_f and forms the penetrated enzyme E . Then the penetrated enzyme E reacts with the triglyceride T , diglyceride D and monoglyceride M and generates the enzyme complex ET , ED and EM . These enzyme complexes further decompose to form the acylated enzyme complex EX and diglyceride D , monoglyceride M and glycerol G , respectively. The acylated enzyme complex EX reacts with the water W and methanol CH to

produce the free fatty acid **FA** and biodiesel **BD**. Remind that there is a reversible competitive methanol inhibition in which the enzyme **E** reacts with the methanol **CH**.

The detailed reaction set and corresponding rate expressions are listed in Table B.1. In reaction r_1 , the free specific interfacial area is expressed as a volumetric concentration ($A_f, [mol/m^3]$), which uses the enzyme coverage to estimate a theoretical upper limit of the moles of enzyme molecules that can occupy the free interfacial area:

$$A_f = \frac{a_f}{A_e}, \quad (B.1)$$

where A_e is the enzyme coverage, $2.98 \times 10^7 m^2/mol$, representing the interfacial area required for the adsorption of 1 mol of enzyme (Jurado et al., 2008), a_f is free specific interfacial area $[mol/m^3]$:

$$a_f = a_T - A_e \cdot (E + EX + ET + ED + EM + ECH), \quad (B.2)$$

in which a_T is the specific interfacial area per unit volume of oil-water mixture $[m^2/m^3]$:

$$a_T = \frac{6}{d_s} \cdot \frac{V_p}{V}, \quad (B.3)$$

where d_s is the Sauter mean diameter of the droplets in the system (unit: m), V_p is the polar volume (unit: m^3), V is the bulk volume (unit: m^3).

Table B.1 Kinetic mechanism for the enzymatic biodiesel production system

Reactions	Rate of reactions
$E_{bulk} + A_f \xrightleftharpoons[k_{-1}]{k_1} E$	Enzyme in bulk E_{bulk} absorbed in the interface A_f to form penetrated enzyme E $r_1 = k_1 \cdot E_{bulk} \cdot A_f - k_{-1} \cdot E$
$T + E \xrightleftharpoons[k_{-2}]{k_2} ET$	The reactions r_2, r_4, r_6 are reactions of penetrated enzyme E with triglyceride T , diglyceride D and monoglyceride M to form enzyme substrate complex ET , ED , EM (Ping); $r_2 = k_2 \cdot T \cdot E - k_{-2} \cdot ET$
$ET \xrightleftharpoons[k_{-3}]{k_3} EX + D$	$r_3 = k_3 \cdot ET - k_{-3} \cdot EX \cdot D$
$D + E \xrightleftharpoons[k_{-4}]{k_4} ED$	$r_4 = k_4 \cdot D \cdot E - k_{-4} \cdot ED$
$ED \xrightleftharpoons[k_{-5}]{k_5} EX + M$	The reactions r_3, r_5, r_7 are the enzyme substrate complex ET , ED , EM forming the acyl enzyme complex EX and releasing the first product D , M , G , respectively (Pong) $r_5 = k_5 \cdot ED - k_{-5} \cdot EX \cdot M$
$M + E \xrightleftharpoons[k_{-6}]{k_6} EM$	$r_6 = k_6 \cdot M \cdot E - k_{-6} \cdot EM$
$EM \xrightleftharpoons[k_{-7}]{k_7} EX + G$	$r_7 = k_7 \cdot EM - k_{-7} \cdot EX \cdot G$
$EX + W \xrightleftharpoons[k_{-8}]{k_8} FA + E$	The EX can then react with water W or methanol CH and release the second product free fatty acid FA and biodiesel BD $r_8 = k_8 \cdot EX \cdot W - k_{-8} \cdot FFA \cdot E$
$EX + CH \xrightleftharpoons[k_{-9}]{k_9} BD + E$	$r_9 = k_9 \cdot EX \cdot CH - k_{-9} \cdot BD \cdot E$
$CH + E \xrightleftharpoons[k_{-10}]{k_{10}} ECH$	Reversible competitive methanol inhibition $r_{10} = k_{10} \cdot CH \cdot E - k_{-10} \cdot ECH$
Note: Units for the concentrations are $mol \cdot L^{-1}$.	

The governing ODEs are given in (B.4).

$$\begin{aligned}
\frac{d(T \cdot V)}{dt} &= -V \cdot r_2, \\
\frac{d(D \cdot V)}{dt} &= V \cdot (r_3 - r_4), \\
\frac{d(M \cdot V)}{dt} &= V \cdot (r_5 - r_6), \\
\frac{d(BD \cdot V)}{dt} &= V \cdot r_9, \\
\frac{d(FA \cdot V)}{dt} &= V \cdot r_8, \\
\frac{d(G \cdot V)}{dt} &= V \cdot r_7, \\
\frac{d(W \cdot V)}{dt} &= -V \cdot r_8, \\
\frac{d(CH \cdot V)}{dt} &= -V \cdot (r_9 + r_{10}), \\
\frac{d(E \cdot V)}{dt} &= V \cdot (r_1 - r_2 - r_4 - r_6 + r_8 + r_9 - r_{10}) \\
\frac{d(EX \cdot V)}{dt} &= V \cdot (r_3 + r_5 + r_7 - r_8 - r_9), \\
\frac{d(ET \cdot V)}{dt} &= V \cdot (r_2 - r_3), \\
\frac{d(ED \cdot V)}{dt} &= V \cdot (r_4 - r_5), \\
\frac{d(EM \cdot V)}{dt} &= V \cdot (r_6 - r_7), \\
\frac{d(ECH \cdot V)}{dt} &= V \cdot r_{10}, \\
\frac{d(E_{bulk} \cdot V)}{dt} &= -V \cdot r_1, \\
\frac{dV_p}{dt} &= R_G + R_W, \\
\frac{dV}{dt} &= F_a.
\end{aligned} \tag{B.4}$$

In these ODE, r_i , $i = 1, \dots, 10$ are the rates of reactions that given in Table B.1; R_G , R_W and F_a are volumetric flow rate of methanol, volumetric net rates of the production of G and W respectively.

The measurement vector $\mathbf{Y}$ (unit: mass %) and measurement function $\mathbf{h}(\cdot)$ are:

$$y_i = \frac{x_{m_i} V \cdot rmm_i}{\sum_{j=1}^5 x_{m_j} V \cdot rmm_j}, \mathbf{Y} = \begin{bmatrix} TAG \\ DAG \\ MAG \\ FAME \\ FFA \end{bmatrix}, \mathbf{X}_m = \begin{bmatrix} T \\ D \\ M \\ BD \\ FA \end{bmatrix}, \quad (\text{B.5})$$

where $\mathbf{X}_m$ is the measurable state variable, V is the bulk volume and rmm_i is the relative molecular mass of x_{m_i} .

B.2 Experimental Settings and Parameter Estimation

Following (Price et al., 2014), parameter estimation is conducted based on a set of experiments under different operating conditions. The experimental configurations used for data fitting and validation are summarised in Table B.2. The parameter estimates reported in (Price et al., 2014) are adopted as nominal values in this thesis and are listed in Table B.3.

Table B.2 Preliminary experiments for data fitting and validation

Exp.	Methanol feed rate [Eq./h]	Initial dose methanol [Eq.]	Water [wt.% oil]	Enzyme [wt.% oil]
1	0.06	0.2	3	0.1
2	0.06	0.2	3	0.2
3	0.06	0.2	3	0.3
4	0.06	0.2	5	0.2
5	0.06	0.2	5	0.5
6	0.1	0.2	5	0.3
7	0.185 first 2hrs. 0.06 thereafter	0.2	5	0.2
8	0.185 first 2hrs. 0.06 thereafter	0.2	5	0.5
9	0.185 first 2hrs. 0.06 thereafter	0.2	5	0.3
10	0.06	0.4	5	0.5
11	0.06	0.4	7	0.2
12	0.06	0.4	7	0.3

Table B.3 Nominal parameter values estimated from measurement data following experiments 1 to 8

Kinetic parameters	nominal values	units
k_1	4.95e4	$L \cdot mol^{-1} \cdot min^{-1}$
k_{-1}	6.6	min^{-1}
k_2	1.69e6	$L \cdot mol^{-1} \cdot min^{-1}$
k_{-2}	1.11e4	min^{-1}
k_3	2.07e7	min^{-1}
k_{-3}	2.20e7	$L \cdot mol^{-1} \cdot min^{-1}$
k_4	3.41e6	$L \cdot mol^{-1} \cdot min^{-1}$
k_{-4}	1.33e7	min^{-1}
k_5	1.55e7	min^{-1}
k_{-5}	1.81e5	$L \cdot mol^{-1} \cdot min^{-1}$
k_6	9.13e4	$L \cdot mol^{-1} \cdot min^{-1}$
k_{-6}	5.43e5	min^{-1}
k_7	7.06e6	$L \cdot mol^{-1} \cdot min^{-1}$
k_{-7}	4.93	$L \cdot mol^{-1} \cdot min^{-1}$
k_8	2.36e4	$L \cdot mol^{-1} \cdot min^{-1}$
k_{-8}	3.51e6	$L \cdot mol^{-1} \cdot min^{-1}$
k_9	2.54e4	$L \cdot mol^{-1} \cdot min^{-1}$
k_{-9}	2.05e5	$L \cdot mol^{-1} \cdot min^{-1}$
k_{10}	3.23e-2	$L \cdot mol^{-1} \cdot min^{-1}$
k_{-10}	4.39e-4	min^{-1}