

PhD Thesis

Numerical Methods of Optimum Experimental Design Based on a Second-Order Approximation of Confidence Regions



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vorgelegt von
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aus
Wipperfürth

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Dissertation

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Abstract

A successful application of model-based simulation and optimization of dynamic processes requires an exact calibration of the underlying mathematical models. Here, a fundamental task is the estimation of unknown and nature given model coefficients by means of real observations. After an appropriate numerical treatment of the differential systems, the parameters can be estimated as the solution of a finite dimensional nonlinear constrained parameter estimation problem. Due to the fact that the measurements always contain defects, the resulting parameter estimate cannot be seen as an ultimate solution and a sensitivity analysis is required, to quantify the statistical accuracy. The goal of the design of optimal experiments is the identification of those measurement times and experimental conditions, which allow a parameter estimate with a maximized statistical accuracy. Also the design of optimal experiments problem can be formulated as an optimization problem, where the objective function is given by a suitable quality criterion based on the sensitivity analysis of the parameter estimation problem.

In this thesis, we develop a quadratic sensitivity analysis to enable a better assessment of the statistical accuracy of a parameter estimate in the case of highly nonlinear model functions. The newly introduced sensitivity analysis is based on a quadratically approximated confidence region which is an expansion of the commonly used linearized confidence region. The quadratically approximated confidence region is analyzed extensively and adequate bounds are established. It is shown that exact bounds of the quadratic components can be obtained by solving symmetric eigenvalue problems. One main result of this thesis is that the quadratic part is essentially bounded by two Lipschitz constants κ and ω , which also characterize the *Gauss-Newton* convergence properties. This bound can also be used for an approximation error of the validity of the linearized confidence regions. Furthermore, we compute a quadratic approximation of the covariance matrix, which delivers another possibility for the statistical assessment of the solution of a parameter estimation problem. The good approximation properties of the newly introduced sensitivity analysis are illustrated in several numerical examples.

In order to robustify the design of optimal experiments, we develop a new objective function—the Q-criterion—based on the introduced sensitivity analysis. Next to the trace of the linear approximation of the covariance matrix, the Q-criterion consists of the Lipschitz constants κ and ω . Here, we especially focus on a numerical computation of an adequate approximation of κ . The robustness properties of the new objective function in terms of parameter uncertainties is investigated and compared to a *worst-case* formulation of the design of optimal experiments problem. It is revealed that the Q-criterion covers the *worst-case* approach of the design of optimal experiments problem based on the A-criterion. Moreover, the properties of the new objective function are considered in several

examples. Here, it becomes evident that the Q-criterion leads to a drastic improve of the *Gauss-Newton* convergence rate at the following parameter estimation.

Furthermore, in this thesis we consider efficient and numerically stable methods of parameter estimation and the design of optimal experiments for the treatment of multiple experiment parameter estimation problems. In terms of parameter estimation and sensitivity analysis, we propose a parallel computation of the *Gauss-Newton* increments and the covariance matrix based on orthogonal decompositions. Concerning the design of optimal experiments, we develop a parallel approach to compute the trace of the covariance matrix and its derivative.

Zusammenfassung

Der erfolgreiche Einsatz modellbasierter Simulationen und Prozess-Optimierungen von dynamischen Prozessen erfordert eine präzise Kalibrierung der zugrundeliegenden mathematischen Modelle. Eine grundlegende Schwierigkeit ist dabei die Identifikation von unbekanntem und naturgegebenen Modellkoeffizienten anhand von realen Beobachtungen. Nach einer geeigneten numerischen Behandlung des Differentialgleichungssystems können diese Parameter als Lösung eines endlich dimensionalen, nichtlinearen und beschränkten Optimierungsproblems geschätzt werden. Da die Messwerte stets mit Messfehlern behaftet sind, kann die resultierende Schätzung nicht als endgültig angesehen werden und es bedarf einer Sensitivitätsanalyse, um den Einfluss der Messfehler auf die Parameterschätzung zu quantifizieren. Das Ziel der optimalen Versuchsplanung ist die Identifikation derjenigen Messzeitpunkte und experimentellen Bedingungen, welche eine Parameterschätzung mit einer maximalen statistischen Güte erlauben. Auch das Versuchsplanungsproblem kann als beschränktes Optimierungsproblem formuliert werden, dessen Zielfunktion auf einem geeigneten Gütekriterium auf Basis der Sensitivitätsanalyse des Parameterschätzproblems basiert.

Zur besseren Einschätzung der statistischen Güte der Parameterschätzungen bei hochgradig nichtlinearen Modellfunktionen wird in dieser Arbeit eine quadratische Sensitivitätsanalyse entwickelt. Basis der neu eingeführten Sensitivitätsanalyse ist ein quadratisch approximiertes Konfidenzgebiet, welches eine Erweiterung der üblicherweise verwendeten linearisierten Konfidenzgebiete darstellt. Das neu definierte Konfidenzgebiet wird ausführlich analysiert und geeignete Schranken werden hergeleitet. Dabei wird gezeigt, dass exakte Schranken für die quadratischen Anteile des Konfidenzgebietes auf die Lösungen von symmetrischen Eigenwertproblemen zurückgeführt werden können. Ein weiteres grundlegendes Resultat ist, dass der quadratische Anteil im Wesentlichen durch zwei Lipschitzkonstanten κ und ω beschränkt ist, welche auch die Konvergenzeigenschaften des *Gauß-Newton*-Verfahrens charakterisieren. Diese Schranke kann auch als Fehlerabschätzung für die Gültigkeit der linearisierten Konfidenzgebiete herangezogen werden. Zusätzlich wird eine quadratische Approximation der Kovarianzmatrix berechnet, welche eine weitere Möglichkeit zur Einschätzung der statistischen Güte von Lösungen von Parameterschätzproblemen darstellt. Auch hier werden Parameterabhängigkeiten des Modells bis zur zweiten Ordnung berücksichtigt. Die guten Approximationseigenschaften der neu eingeführten Sensitivitätsanalyse werden an mehreren Beispielen demonstriert.

Zur Robustifizierung der optimalen Versuchsplanung wird in dieser Arbeit eine neue Zielfunktion - das Q-Kriterium - auf Basis der eingeführten Sensitivitätsanalyse entwickelt. Neben der Spur der linearen Approximation der Kovarianzmatrix sind die Lipschitzkonstanten κ und ω wesentliche Bestandteile des Q-Kriteriums. Hierbei wird insbesondere

auf die numerische Berechnung bzw. eine geeignete Approximation der Lipschitzkonstanten κ eingegangen. Die Robustheit der neuen Zielfunktion gegenüber Unsicherheiten in den Parameterwerten wird untersucht und mit einer *Worst-Case*-Formulierung des Versuchsplanungsproblems unter Verwendung des A-Kriteriums verglichen. Dabei stellt sich heraus, dass die Verwendung des Q-Kriteriums die *Worst-Case*-Robustifizierung der optimalen Versuchsplanung unter Verwendung des A-Kriteriums bereits beinhaltet. Die Eigenschaften der neuen Zielfunktion der optimalen Versuchsplanung werden an diversen Beispielen untersucht. Hier zeigt sich insbesondere, dass bei der anschließenden Parameterschätzung die Anzahl der benötigten *Gauß-Newton*-Iterationsschritte deutlich reduziert werden kann.

Des Weiteren werden in dieser Arbeit effiziente und numerisch stabile Berechnungsmethoden der Parameterschätzung und der optimalen Versuchsplanung für Parameterschätzprobleme mit einer Mehrfachexperimentstruktur betrachtet. Für die Parameterschätzung und Sensitivitätsanalyse werden eine parallele Berechnung der *Gauß-Newton*-Inkremente sowie der Kovarianzmatrix auf Basis von orthogonalen Zerlegungen vorgeschlagen. Schließlich wird für die optimale Versuchsplanung eine parallele Vorgehensweise zur Berechnung der Spur der Kovarianzmatrix bzw. deren Ableitung entwickelt.

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List of Symbols

$\ \cdot\ _2$	<i>Euclidean norm</i> ($\ x\ = \sqrt{\sum_i x_i^2}$)
α	probability level ($\in [0, 1]$)
A_p^k	Jacobi matrix of the function F_1^k wrt. p
A_x^k	Jacobi matrix of the function F_1^k wrt. x_x
b_j^k	<i>Multiple Shooting</i> continuity conditions of the k -th experiment
B	deterministic part of the Hessian of the PE problem
B_p^k	Jacobi matrix of the function F_2^k wrt. p
B_x^k	Jacobi matrix of the function F_2^k wrt. x_x
χ	DoE inequality constraints
χ^k	DoE inequality constraints of the k -th experiment
\mathcal{C}	linear approximation of the covariance matrix
\mathcal{C}_2	quadratic approximation of the covariance matrix
Δp	<i>Gauss-Newton</i> increment of the global parameter vector p
Δx^k	<i>Gauss-Newton</i> increments of the local parameter vectors x^k
dJ	total derivative of the Jacobian J
dJ^+	total derivative of the generalized inverse J^+
$\overline{\mathcal{D}}_{lin}$	linearized confidence region (constrained case)
$\overline{\mathcal{D}}_{lin}$	linearized confidence region (constrained case)
$\overline{\mathcal{D}}_{lin}$	linearized confidence region (unconstrained case)
$\overline{\mathcal{D}}_{lr}$	likelihood ratio confidence region (constrained case)
$\overline{\mathcal{D}}_{lr}$	likelihood ratio confidence region (unconstrained case)
$\overline{\mathcal{D}}_{quad}$	quadratic approximation of confidence region (constrained case)
$\overline{\mathcal{D}}_{quad}$	quadratic approximation of confidence region (unconstrained case)
ε	vector of all the measurement errors $\varepsilon^T = ((\varepsilon^1)^T, \dots, (\varepsilon^M)^T)$
ε^k	measurement errors of the k -th experiment
η	vector of all the measurements $\eta^T = ((\eta^1)^T, \dots, (\eta^M)^T)$
η^k	measurements of the k -th experiment
E	random part of the Hessian of the PE problem
f^k	right hand side of the differential equations of the k -th experiment
F	PE function $F^T = (F_1^T, F_2^T)$
F_1	PE objective function $F_1^T = ((F_1^1)^T, \dots, (F_1^M)^T)$
F_1^k	PE objective function of the k -th experiment
F_2	PE equality constraints $F_2^T = ((F_2^1)^T, \dots, (F_2^M)^T)$
F_2^k	PE equality constraints of the k -th experiment
γ_n^2	$(1 - \alpha)$ -quantile of the χ^2 -distribution and the F-distribution, respectively
h^k	observation functions of the k -th experiment
J	Jacobi matrix of the function F
\mathcal{J}	KKT matrix of the parameter estimation problem

J_1	Jacobi matrix of the function F_1
J_2	Jacobi matrix of the function F_2
J^+	generalized inverse of the Jacobians J
κ	Lipschitz constant of the generalized inverse J^+
K^k	number of possible measurement times of the k -th experiment in DoE
$l_k + 1$	number of <i>Multiple Shooting</i> nodes of the k -th experiment
m_1	number of measurement times
m^k	number of measurement times of the k -th experiment
m_2	dimension of the function F_2
m_ψ^k	lower bound of the function ψ^k
$m_{q_i}^k$	lower bound of the controls q^k
m_r^k	dimension of the function r^k
$m_{u_i}^k$	lower bound of the control function u_i^k
m_w^k	minimum number of allowed measurements of the k -th experiment
M	number of different experimental conditions
M_ψ^k	upper bound of the function ψ^k
$M_{q_i}^k$	upper bound of the controls q^k
$M_{u_i}^k$	upper bound of the control function u_i^k
M_w^k	maximum number of allowed measurements of the k -th experiment
n_χ	dimension of the function χ
n_χ^k	dimensions of the functions χ^k
n_p	number of the global parameters p
$n_{\tilde{p}}^k$	number of the local parameters \tilde{p}^k
n_ϕ	dimension of the function ϕ
n_ψ	dimension of the function ψ
n_ψ^k	dimensions of the functions ψ^k
n_q^k	number of the control variables q^k
n_u^k	dimension of the control functions u^k
n_x	number of the optimization variables x
n_x^k	number of the local optimization variables x^k
n_ξ	number of the design variables ξ
n_y^k	number of the states y^k
ω	Lipschitz constant of the Jacobian J
p	vector of the global parameters
\tilde{p}^k	vector of the local parameters of the k -th experiment
ϕ	DoE objective function
ψ^k	DoE equality constraints
ψ^k	DoE equality constraints of the k -th experiment
q^k	control variables of the k -th experiment
r^k	PE equality constraints of the k -th experiment
s^k	<i>Single Shooting</i> or <i>Multiple Shooting</i> discretization variables of the k -th experiment

σ^k	standard deviations of ε^k of the k -th experiment
Σ^k	diagonal matrix of the standard deviations $\Sigma^k = \text{diag}(\sigma^k)$ of the k -th experiment
Σ	diagonal matrix of all standard deviations $\Sigma = \text{diag}(\Sigma^1, \dots, \Sigma^M)$
t^k	measurement times $t^k \in [t_a^k, t_e^k]$ of the k -th experiment
t_a^k	initial time of the measurement times of the k -th experiment
t_e^k	final time of the measurement times of the k -th experiment
τ_j^k	<i>Multiple Shooting</i> nodes of the k -th experiment $j = 1, \dots, l_k$
u^k	control function of the k -th experiment
w^k	sampling-variables for measurement selection
W	diagonal matrix of all the sampling-variables $W_k = \text{diag}(W_1, \dots, W_M)$
W_k	diagonal matrix of the sampling-variables $W_k = \text{diag}(w^k)$ of the k -th experiment
x	PE optimization variables $(x^k)^T = ((x^1)^T, \dots, (x^M)^T, p^T)$
x_k	local optimization variables $x_k^T = ((s^k)^T, (\tilde{p}^k)^T)$
ξ	design variables $\xi^T = (w^T, q^T, u^T(t))$
Ξ	design space
y^k	differential states of the k -th experiment

List of Acronyms

DAE	Algebraic Differential Equation
DoE	Design of optimal Experiments
KKT	Karush-Kuhn-Tucker
ODE	Ordinary Differential Equation
PDE	Partial Differential Equation
PE	Parameter Estimation
SQP	Sequential Quadratic Programming

Table of Contents

Abstract	IV
Zusammenfassung	VI
Acknowledgments	VIII
List of Symbols and List of Acronyms	IX
1 Introduction	1
1.1 Tasks in Parameter Estimation and Optimum Experimental Design	4
1.2 Basics of Nonlinear Optimization	5
1.3 Thesis Outline and Contributions	8
2 Parameter Estimation Problems	11
2.1 Multiple Experiment Parameter Estimation Problems	11
2.2 Discretization of the Dynamics	14
2.2.1 Single Shooting Approach	14
2.2.2 Multiple Shooting Approach	15
2.3 A Generalized Gauss-Newton Method	17
2.4 Solution of the Linearized Problem	19
2.5 Convergence Properties of Newton-Type Methods	22
2.6 Compatibility Analysis	25
2.6.1 Compatibility of the Model and the Measurements	26
2.6.2 An Estimate of the Lipschitz-Constant κ	30
3 Sensitivity Analysis	34
3.1 Parameter Representation	34
3.2 The Linear Covariance Matrix	42
3.3 Confidence Regions	44
3.3.1 Likelihood Ratio Confidence Regions	44
3.3.2 Linearized Confidence Regions	46
3.3.3 A Quadratic Approximation of Confidence Regions	49
3.4 A Quadratic Approximation of the Covariance Matrix	53
3.5 Examples of Confidence Regions	54
3.5.1 Biochemical Oxygen Demand	55
3.5.2 Energy Radiated from a Carbon Filament Lamp	56

4	The Design of Optimal Experiments	59
4.1	DoE Problem Formulation	59
4.2	The Underlying Parameter Estimation Problem	62
4.3	DoE Objective Functions	63
4.3.1	The Common Approach	63
4.3.2	The Q-Criterion	64
4.4	Solving the DoE Problem	72
4.4.1	Sequential Quadratic Programming	75
4.5	DoE Robustification	79
4.5.1	A Sequential Approach	79
4.5.2	A Worst-Case Formulation	81
4.5.3	Robustness of the Q-Criterion	84
4.5.4	Chance-Constrained Formulation	85
5	Numerical Treatment of Multiple Experiment Parameter Estimation Problems	87
5.1	Gauss-Newton Increments for Multiple Experiment Problems	87
5.1.1	Aspects of Parallelization	95
5.2	The Covariance Matrix with Multiple Experiments	97
5.2.1	Aspects of Parallelization	102
5.3	The Numerical and Parallel Computation of $\text{trace}(C)$	103
6	Derivatives	106
6.1	Derivatives of the Parameter Estimation Problem	106
6.1.1	The Structure of the Jacobi Matrices	107
6.1.2	The Structure of the Second Derivatives	110
6.2	Derivatives in the Design of Optimal Experiments	116
6.2.1	Derivative of the Q-criterion	117
6.2.2	Derivative of the Covariance Matrix	120
6.2.3	Derivatives with Respect to the Design Variables	122
6.3	Derivatives of the Generalized Inverses	126
6.3.1	Derivative of a Moore-Penrose Pseudo-Inverse	126
6.3.2	Derivative of the Generalized Inverse J^+	127
6.4	Computation of Derivatives	129
6.4.1	Automatic Differentiation	130
6.4.2	Finite Differences	130
6.4.3	Internal Numerical Differentiation	131
7	Numerical Examples	134
7.1	A Nonlinear Example	135
7.2	The Monod model	136
7.3	The Verhulst-Pear Equation	139
8	Conclusion	144

List of Figures	147
List of Tables	148
References	149

1 Introduction

The use of model-based simulations in order to gain knowledge of unknown phenomena and process behaviors is a challenging task in many natural sciences. They are used in a far-reaching field, for instance in biological and chemical applications, but also in economics or in aerospace. However, a growing interest in terms of numerical simulations of dynamic processes can be observed. By means of mathematical models and computerized simulations, process behavior can be considered under different experimental conditions and it can be optimized with respect to certain criteria. Thus, the identification of optimal process conditions can for example reduce costs, save time, improve products or even completely new methods can be developed. Furthermore, the obtained information can also be used to optimize existing plants or to design new ones.

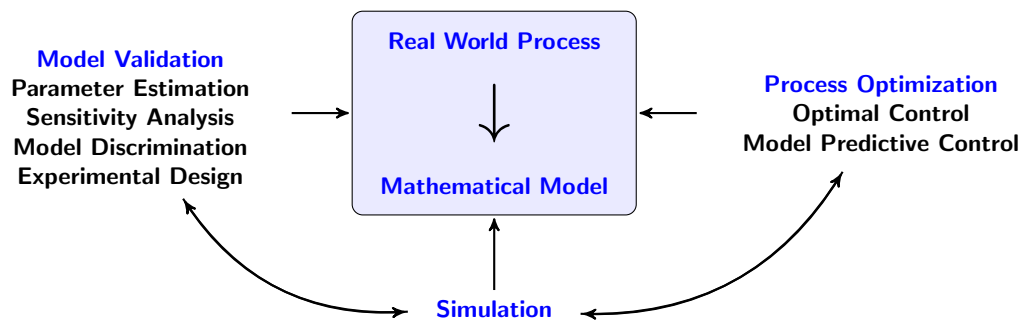


Figure 1.1: Modeling, simulation and optimization, Körkel [62].

A fundamental prerequisite for the successful application of model-based simulations and optimizations is that the mathematical model describes the real process behavior sufficiently well. Frequently, the mathematical model includes some unknown and nature given constants, the so-called parameters. Since the parameters cannot be measured or computed analytically, it is a basic problem to determine these values. Therefore, methods of model validation are required. These consist of parameter estimation, sensitivity analysis, model discrimination and the design of optimal experiments. Having a validated model, the process can be optimized by means of optimal control theory and model predictive control. The procedure of model validation, process optimization and simulation is illustrated in Figure 1.1.

In the following, we give a brief overview of the introduced methods and procedures.

Parameter Estimation

In order to be able to estimate the unknown model parameters, a common approach is to minimize the discrepancies between real measurements and a corresponding measuring function in a suitable norm with respect to the parameters. Thereby, the parameters have to satisfy the dynamics of the process and other potential constraints. After a numerical treatment of the underlying dynamic system, this results in a finite dimensional nonlinear constrained optimization problem. For a thorough treatment of nonlinear parameter estimation, see e.g. Bard [10], Beck and Arnold [15], Draper and Smith [43], and Seber and Wild [102].

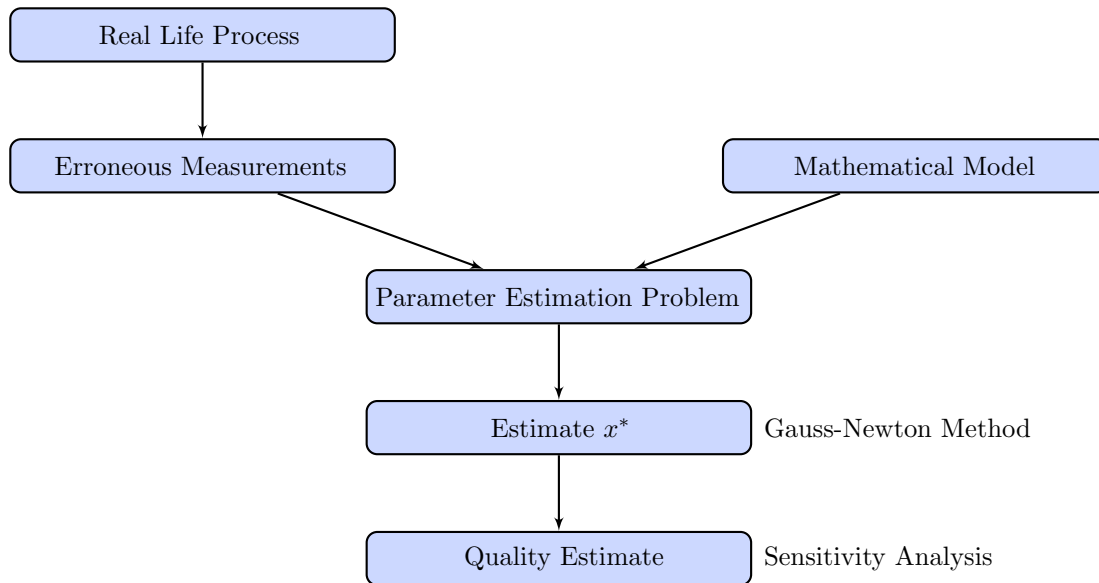


Figure 1.2: Parameter estimation and sensitivity analysis.

Sensitivity Analysis

Due to the fact that the measurements always contain measurement errors, the parameter estimation problem is affected by random events. Thus, the resulting parameter estimates are influenced by uncertainties so that we need to perform a sensitivity analysis in order to be able to make any quality statements of the estimate. An illustration of this situation can be found in Figure 1.2. A possible approach to quantify the quality of an estimated parameter vector is to use confidence regions. The idea of confidence regions is to define a domain surrounding the parameter estimates, in such a way, that the true parameters lie in this region with a certain probability. Obviously, it is preferable to obtain parameter estimates with comparatively small confidence regions. An overview of the sensitivity analy-

sis for parameter estimation problems and confidence regions can be found in e.g. Beale [14], Donaldson and Schnabel [41], Draper and Smith [43], Pázman [86], and Potocký and To Van Ban[89].

Model Discrimination

Frequently, we are confronted with the question whether a correct mathematical model describes the underlying real world process. If there is more than one mathematical model that possibly suits the process, we need a method to identify the correct model and to eliminate the incorrect ones. This is the subject of model discrimination. As we only have a limited number of erroneous measurements, it is never possible to verify a particular model. However, in some cases we can falsify a wrong model or decide which model is more likely among a set of alternatives. The topic of model discrimination is explained thoroughly in e.g. Atkinson and Cox [5], Horn [56], Kostina and Kriwet [66], Leamer [71], and Lehmann [72].

Design of Optimal Experiments

Next to the unknown quantities that are to be estimated, the experimental setup—and therefore the parameter estimation problem—consists of some influenceable components, which might have a crucial effect on the accuracy of the parameter estimate. Possible components are e.g. adjustable flow rates, temperature profiles and especially the choice of measurement times. In the model-based design of optimal experiments one tries to identify those system settings which allow an estimate with the maximum of statistical accuracy. This results in a further constrained optimization problem, whose objective function is a suitable quality criterion.

Following Franceschini and Macchietto [47], the basic problem formulation of the design of optimal experiments was first introduced by Fisher [46] in 1935. Common design methods are given in Box et al. [30], Box and Draper [29], Box and Lucas [31], and Atkinson and Donev [6], Kiefer [59], Draper and Hunter [42], Fedorov [44]. A detailed discussion of numerical methods of the design of optimal experiments can be found in Körkel [62], Körkel et al. [64], Bauer et al. [12, 13], Pukelsheim [92].

Optimal Control and Model Predictive Control

Optimal control and model predictive control are addressed to the task of examining future process behaviors with respect to different input quantities. Furthermore, they allow the identification of the optimal control components of the process and their corresponding state trajectories of the dynamic systems over a certain period of time with respect to a suitable cost function. Thus, next to the mathematical model describing the process behavior and a specification of all the variables and constraints, we particularly require the definition of an appropriate cost function. Whereas optimal control is used for an offline optimization of the process behavior, methods of model predictive control deliver a direct feedback and they can also be used for online optimization. Optimal control and model predictive control problems

are generally nonlinear constrained optimization problems. Their direct or indirect solution methods have been developed since the middle of the last century.

A thorough treatment of optimal control can be found in e.g. Althans and Falb [4], Betts [16], Brogan [32], Bryson [33], Kirk [60], Pontryagin and Boltyanskii [88]. For model predictive control we refer to Allgöwer and Zheng [1], Bock et al. [20], Camacho and Bordons [35], Findeisen and Allgöwer [45], Kwon et al. [70], Garcia et al. [79], and Mayne et al. [77].

1.1 Tasks in Nonlinear Parameter Estimation and Optimum Experimental Design

The growing interest in model-based simulation and optimization leads to a substantial increase of complexity of the underlying mathematical models. Frequently we have to deal with highly nonlinear model functions, which put high requirements on the employed numerical methods. To ensure a successful application of the model-based simulations and optimizations to the continually growing complexity of mathematical models, a continual adaption of the common methods and an innovative development of new mathematical methods is required.

In this thesis we attend to current challenging issues in parameter estimation and sensitivity analysis, as well as to the design of optimal experiments. Thereby, the main focus is addressed to the following tasks:

Common approaches to perform a sensitivity analysis for assessing the quality of a parameter estimate are based on linearized confidence regions and their corresponding linear approximation of the covariance matrix. These confidence techniques are based on the first order derivative, i.e. its generalized inverse of the model functions, respectively. The resulting confidence regions are shaped elliptically, and the algorithms have a low complexity as well as low computational effort. However, especially when dealing with highly nonlinear model functions the linearized confidence regions are often insufficient to quantify the statistical accuracy of the estimate. The fact that the linearized methods are insufficient in many situations is also a well known problem in literature:

“The results [...] show just how poor the linearization method can be in some cases.”
Rooney and Biegler [94].

“However, if this assumption is not appropriate for nonlinear estimation problems, a different mathematical description for the confidence region is needed.” Donaldson and Schnabel [41].

“The linearization technique usually applied for the computation of nonlinear confidence regions is shown to be inappropriate in the case of large exchange fluxes.”
Wiechert et al. [110].

In order to be able to counteract these deficiencies, we attend to the task of introducing

a new tool to quantify the statistical accuracy of a parameter estimate in difficult highly nonlinear situations. In particular, it is crucial to analyze and investigate the properties of the new confidence technique in view of the design of optimal experiments and the parameter estimation problem. Here, we particularly focus on bounds of the introduced confidence region as well as on its relation to the local convergence properties of the solution method of the parameter estimation problem.

A challenging task in the design of optimal experiments is to deal with uncertainties caused by the parameter values that are to be estimated. In the context of the design of optimal experiments these parameters are constant, but if at all they are only known to lie in a particular region. These circumstances may have critical effects on the resulting solutions which are the identified settings for the underlying parameter estimation problem. In some difficult situations, the defective system settings of the parameter estimation problem lead to unsatisfactory results and its solution methods may fail. In order to get more reliable and stable system settings in highly nonlinear situations, a new criterion for the design of optimal experiments is required. Therefore, it is our goal to define a new objective function for the design of optimal experiments, based on the introduced sensitivity analysis. A special requirement of the new criterion is to consider not only higher parameter sensitivities, but rather to have a favorable effect on the convergence properties of the solution method for the parameter estimation problem. Moreover, we pay special attention to an efficient numerical computation of the new design of experiments objective function and its derivative.

Another goal of this thesis is the development of efficient and numerically stable methods of parameter estimation and the design of optimal experiments for the treatment of multiple experiment parameter estimation problems. Therefore, we consider numerical and parallel computation procedures to compute the *Gauss-Newton* increments, the covariance matrix as well as parallel computation techniques for the trace of the covariance matrix and its derivative in the context of the design of optimal experiments.

1.2 Basics of Nonlinear Optimization

Solving a nonlinear constrained optimization problem is an essential part concerning parameter estimation and the design of optimal experiments. Therefore, we briefly present optimality conditions and basic properties of nonlinear constrained optimization problems, where the solution space is restricted by equality and inequality constraints.

Let us consider a nonlinear constrained optimization problem (NLP) of the general form

$$\begin{aligned} \min_x f(x) \\ \text{s.t. } g(x) = 0, \\ h(x) \geq 0, \end{aligned} \tag{1.2.1}$$

where all the functions $f : D \subseteq \mathbb{R}^n \rightarrow \mathbb{R}$, $g : D \subseteq \mathbb{R}^n \rightarrow \mathbb{R}^{n_g}$, and $h : D \subseteq \mathbb{R}^n \rightarrow \mathbb{R}^{n_h}$ are assumed to be sufficiently smooth.

In the following definition, we formalize the feasible set of the considered optimization problem.

Definition 1.2.1 (Feasible Set and Feasible Point). *The feasible set \mathcal{S} of problem (1.2.1) is the set which contains all the points satisfying the equality and the inequality conditions,*

$$\mathcal{S} := \{x \in D \subseteq \mathbb{R}^n \mid g(x) = 0 \text{ and } h(x) \geq 0\}.$$

A point $x \in \mathcal{S}$ is a feasible point.

The second definition characterizes local, global, and strict minima.

Definition 1.2.2 (Local, Global, and Strict Minima). *A vector $x^* \in \mathcal{S}$ is a local minimum of problem (1.2.1) if there exists a neighborhood $N \subset \mathcal{S}$ of x^* such that $f(x^*) \leq f(x)$ for all $x \in N$. If $f(x^*) < f(x)$ for all $x \in N \setminus \{x^*\}$, then x^* is called a strict local minimum. A vector $x^* \in \mathcal{S}$ satisfying $f(x^*) \leq f(x)$ for all $x \in \mathcal{S}$ is called a global minimum of problem (1.2.1). If it holds that $f(x^*) < f(x)$ for all feasible points $x \in \mathcal{S} \setminus \{x^*\}$, then x^* is called a strict global minimum.*

In order to formulate the necessary and sufficient optimality conditions for the introduced optimization problem, the following definitions are necessary.

Definition 1.2.3 (Active and Inactive Inequalities). *The set of active inequalities at a point $x \in \mathcal{S}$ is defined as $I(x) := \{i \in \mathbb{N} \mid h_i(x) = 0\}$, whereas the set of inactive inequalities is given by $I^+(x) := \{i \in \mathbb{N} \mid h_i(x) > 0\}$.*

By using the active inequalities we are able to define a regular point.

Definition 1.2.4 (Regular Points). *Let $x \in \mathcal{S}$ and suppose that the active inequalities are given by $I(x) = \{i_1, \dots, i_s\}$. Let a function $\tilde{g} : D \subseteq \mathbb{R}^{n_x} \rightarrow \mathbb{R}^{n_{\tilde{g}}}$ be given by*

$$\tilde{g}(x) = \begin{pmatrix} g(x) \\ \tilde{h}(x) \end{pmatrix},$$

where $\tilde{h}(x) = (h_{i_1}(x), \dots, h_{i_s}(x))^T$ includes the active inequalities. Then, $x \in \mathcal{S}$ is a regular point if the matrix $\nabla \tilde{g}(x)$ has full rank, i.e. $\text{rank}(\nabla \tilde{g}(x)) = n_g + s$.

A well known and important function in optimization theory is the Lagrange function as given in the following definition.

Definition 1.2.5 (The Lagrange Function). *The Lagrange function is defined by*

$$\mathcal{L}(x, \lambda, \mu) := f(x) - \lambda^T g(x) - \mu^T h(x). \tag{1.2.2}$$

The vectors $\lambda \in \mathbb{R}^{n_g}$, $\mu \in \mathbb{R}^{n_h}$ are called the Lagrange multipliers.

Remark 1.2.6 *If we consider an optimization problem where the solution space is only restricted by equality constraints, a feasible point $x \in \{x \mid g(x) = 0\}$ is regular if $\text{rank}(\nabla g(x)) = n_g$. In the equality constrained case the Lagrange function reduces to*

$$\mathcal{L}(x, \lambda) := f(x) - \lambda^T g(x). \quad (1.2.3)$$

The necessary optimality conditions for an equality and inequality constrained optimization problem are given in the following theorem.

Theorem 1.2.7 (Necessary Optimality Conditions)

Suppose that $x^ \in \mathcal{S}$ is regular and a local minimum of (1.2.1). Then there exist Lagrange multipliers $\lambda^* \in \mathbb{R}^{n_g}$ and $\mu^* \in \mathbb{R}^{n_h}$, such that*

1. *the first-order necessary optimality condition holds,*

$$\nabla_x \mathcal{L}(x^*, \lambda^*, \mu^*) = \nabla_x f(x^*) - \nabla g^T(x^*) \lambda^* - \nabla h^T(x^*) \mu^* = 0,$$

where it holds $\mu^ \geq 0$ and the complementarity $h^T(x^*) \mu^* = 0$;*

2. *the second-order necessary optimality condition holds,*

$$w^T \nabla_{xx}^2 \mathcal{L}(x^*, \lambda^*, \mu^*) w \geq 0,$$

for all elements $w \in T(x^) := \{w \in \mathbb{R}^n \mid \nabla \tilde{g}(x^*) w = 0\}$.*

Proof. A proof of this theorem can be found in Nocedal and Wright [81].

■

In the following definition we characterize the Karush-Kuhn-Tucker conditions as well as a Karush-Kuhn-Tucker point.

Definition 1.2.8 (Karush-Kuhn-Tucker Conditions). *The feasibility of a vector together with the first-order necessary optimality conditions are also known as the Karush-Kuhn-Tucker conditions (KKT conditions). A point (x^*, λ^*, μ^*) satisfying the KKT conditions is called a Karush-Kuhn-Tucker point (KKT point).*

The sufficient optimality conditions of problem (1.2.1) are given in the next theorem.

Theorem 1.2.9 (Sufficient Optimality Conditions)

Suppose that $x^ \in \mathcal{S}$ is a feasible point, which fulfills with λ^* and $\mu^* \geq 0$ the first-order necessary optimality conditions $\nabla_x \mathcal{L}(x^*, \lambda^*, \mu^*) = 0$, and the complementarity $h^T(x^*) \mu^* = 0$. Furthermore, if it holds that*

$$w^T \nabla_{xx}^2 \mathcal{L}(x^*, \lambda^*, \mu^*) w > 0$$

for all $w \in T^+(x^) \setminus 0$, where*

$$T^+(x^*) := \{w \in \mathbb{R}^n \mid \nabla g(x^*) w = 0, \nabla h_i(x^*) w = 0 \text{ and } \mu_i^* > 0, \forall i \in I(x^*)\},$$

then x^ is a strict local minimum.*

Proof. The proof of this theorem is explored thoroughly in Nocedal and Wright [81].

■

We conclude this section with a remark concerning the stability of the used numerical methods.

Remark 1.2.10 *For stability reasons of the used optimization methods, strict complementarity*

$$\begin{aligned}\mu_i^* = 0 &\iff h_i(x^*) > 0, \\ \mu_i^* > 0 &\iff h_i(x^*) = 0,\end{aligned}$$

is often required.

These basic principles of nonlinear optimization are a brief summary of what is necessary for this thesis. For a thorough treatment of nonlinear constrained optimization problems, we refer to Nocedal and Wright [81], Luenberger and Ye [74], and Geiger and Kanzow [51].

1.3 Thesis Outline and Contributions

The commonly used objective functions of the design of optimal experiments problems are based on a linear sensitivity analysis of the underlying parameter estimation problem. In this thesis, we mainly attend to the task of developing a sensitivity analysis based on quadratic approximations as well as of introducing a new objective function to robustify the design of optimal experiments procedure. Furthermore, we dwell on efficient and numerically stable methods for the treatment of multiple experiment parameter estimation problems in the context of parameter estimation and the design of optimal experiments.

The main contributions of this thesis are:

- a quadratic approximation of the parameter vector depending on the measurement errors,
- a definition and analysis of a quadratic approximation of confidence regions as well as a derivation of adequate bounds,
- a computation of a quadratic approximation of the covariance matrix,
- an introduction of a new objective function of the design of optimal experiments, the Q-criterion,
- a computation of suitable approximations of the Lipschitz constant κ in the context of the design of optimal experiments,
- an investigation of the robustness properties of the introduced Q-criterion,

- parallel and numerically stable computation techniques for multiple experiment parameter estimation problems in parameter estimation and the design of optimal experiments,
- a computation of the derivative of the Q-criterion and the generalized inverse of the Jacobians of the model functions of the parameter estimation problem.

This thesis contains the following chapters.

- In Chapter 2, fundamental results in multiple experiment parameter estimation problems are reviewed. Starting with a general problem formulation and definitions of the basic quantities, we provide numerical methods for obtaining a finite dimensional equality constrained parameter estimation problem. For solving the introduced problems, we propose a generalized *Gauss-Newton* method. The chapter further considers the convergence properties of Newton-type methods. In this context, we pay special attention to a Lipschitz constant κ , it having a crucial impact on the convergence properties and the condition of the underlying parameter estimation problem.
- Chapter 3 describes the sensitivity analysis for determining the statistical assessment of the resulting parameter estimates. Essential parts of this chapter are a first and a second order representation of the parameter vector, as well as the computation of a first and a second order approximation of the covariance matrix. Moreover, we consider confidence regions in order to quantify the statistical accuracy of an estimate. Especially, we define and analyze a quadratic approximation of confidence regions as a new tool to perform a sensitivity analysis. Finally, we present some illustrating examples of different confidence regions.
- Chapter 4 is addressed to the design of optimal experiments. After a general introduction, we present different objective functions for the upcoming optimization problem. Especially, we define a new objective function based on the bounds of the quadratically approximated confidence region as introduced in chapter 3. Furthermore, we describe numerical methods for the treatment of the design of optimal experiment problems and propose *Sequential Quadratic Programming* as a solution method. We continue with a robustification of the considered procedure, where we pay special attention to the robustness properties of the newly introduced objective function.
- Chapter 5 deals with the numerical treatment of multiple experiment parameter estimation problems. In particular, we focus on the numerical and parallel computation of the *Gauss-Newton* increments and a linear approximation of the covariance matrix, as well as a parallel computation technique of the A-criterion and its derivative for the design of optimal experiments.
- Chapter 6 discusses the computation of the derivatives, which are needed in order to be able to solve the parameter estimation and the design of optimal experiment

problems. More precisely, we regard the first and the second order derivatives of the parameter estimation functions, as well as the derivatives of the newly introduced objective function for the design of optimal experiments. This includes the derivative of the Jacobians of the parameter estimation functions with respect to the design variables, and the derivative of the covariance matrix. Furthermore, the derivatives of generalized inverses are considered, and we dwell on methods for the numerical computation of derivatives.

- In Chapter 7, we consider three numerical examples to investigate the properties of the introduced objective function of the design of optimal experiments. Here, we pay special attention to the impact of the results from the design of experiments on the *Gauss-Newton* convergence properties.
- We conclude this thesis with a summary in Chapter 8.

2 Parameter Estimation Problems

In this chapter, we consider multiple experiment parameter estimation problems for the identification of unknown model coefficients. Thereby, we concentrate on processes with dynamics that can be modeled by means of ordinary differential equations (ODE). For the treatment of parameter estimation problems based on systems of differential algebraic equations (DAE), see e.g. Körkel [62] and Bock et al. [25]. Parameter estimation problems with partial differential equations (PDE) are presented e.g. by Hinze et al. [55] and Tröltzsch [105].

The first part of this chapter provides basic definitions of the relevant quantities and variables. Furthermore, the constrained multiple experiment parameter estimation problem is formulated. For being able to solve this optimization problem by means of common optimization methods, we need to discretize the differential systems to obtain a finite dimensional solution space. For the discretization of the dynamics, we present the *Single Shooting* approach and the *Multiple Shooting* approach in Section 2.2. In order to solve the resulting finite dimensional nonlinear constrained multiple experiment parameter estimation problem, we consider a generalized *Gauss-Newton* method in Section 2.3. Its main computational effort is determined by solving a linearized system in each iteration. How to solve the linearized problems is discussed in Section 2.4. Subsequently, we consider the local convergence properties of Newton-type methods in Section 2.5. In Section 2.6 we regard the significant meaning of a Lipschitz constant κ and we present an estimate of κ for equality constrained parameter estimation problems.

2.1 Multiple Experiment Parameter Estimation Problems

Let us consider a dynamic real world process, which can be performed under $M \in \mathbb{N}$ different experimental conditions. Each experimental setup k may be given by its own dynamics in the general form of an ordinary differential equation (ODE) such as

$$\dot{y}^k(t) = f^k(t, y^k(t), p, \tilde{p}^k, q^k, u^k(t)).$$

The nonlinear model functions f^k describe the process behavior of the k -th experimental layout and they are the mathematical description of a natural process under certain conditions. The independent variable $t \in [t_a^k, t_e^k] \subset \mathbb{R}$ represents the time—not necessarily physical time—and the vector-valued variables $y^k : [t_a^k, t_e^k] \rightarrow \mathbb{R}^{n_y^k}$, $k = 1, \dots, M$, describe the states of the k -th experiment at time t . The constant control variables $q^k \in \mathbb{R}^{n_q^k}$, and the time-dependent control functions $u^k(t) : [t_a^k, t_e^k] \rightarrow \mathbb{R}^{n_u^k}$ determine the conditions of a particular experiment. The values of these components can be influenced by the

experimenter, and their sizes play an important role in the design of optimal experiments. The unknown and nature given constants of the system are denoted by $p \in \mathbb{R}^{n_p}$ and $\tilde{p}^k \in \mathbb{R}^{n_{\tilde{p}^k}}$. At this point, we distinguish between the global parameters p by which the ordinary differential equations are coupled and the local parameters \tilde{p}^k , which only occur in their corresponding experimental systems $k = 1, \dots, M$. The constant values of the global and local parameters are determined by nature and we are not able to measure them or to compute them in any analytical way. Therefore, it is our task in this chapter to estimate these components.

During the procedure of a parameter estimation the constant controls q^k and the control functions u^k can be ignored, since they remain unaffected by this optimization process. Thus, for simplicity of notation, we omit these control components in our representation. In Section 4 we will come back to them when dealing with the design of optimal experiments. At that point these quantities are crucial as a part of the so-called design variables.

A common approach to perform a parameter estimation is the use of experimental data and trying to adapt an observation function to these data. Suppose that there are erroneous measurements η_i^k available for points in time $t_i^k \in [t_a^k, t_e^k]$, where

$$t_a^k = t_1^k < t_1^k < \dots < t_{m^k}^k = t_e^k,$$

for each experimental layout $k = 1, \dots, M$. Obviously, we could consider several measurements at a certain point in time, but we neglect this in favor of a clearer notation. Moreover, we assume that the measurements are tainted with independent normally distributed measurement errors $\epsilon_i^k \sim \mathcal{N}(0, (\sigma_i^k)^2)$, $i = 1, \dots, m_k$.

By introducing nonlinear observation functions h_i^k , the following relations hold

$$\eta_i^k = h_i^k(\bar{y}^k(t_i^k), \bar{p}, \bar{\tilde{p}}^k) + \epsilon_i^k, \quad \begin{array}{l} k = 1, \dots, M, \text{ (experimental layouts)} \\ i = 1, \dots, m^k, \text{ (points in time)} \end{array}$$

where \bar{p} and $\bar{\tilde{p}}^k$ represent the true global and the true local parameter values, and \bar{y}^k represent the corresponding true state variables.

Due to the assumption that the measurement errors are independent and normally distributed, we get a maximum likelihood estimate of the wanted parameter values by minimizing the sum of the weighted least-squares functionals

$$\sum_{k=1}^M \|F_1^k(y^k(t_1^k), \dots, y^k(t_{m^k}^k), p, \tilde{p}^k)\|_2^2 := \sum_{k=1}^M \sum_{i=1}^{m^k} \left(\frac{\eta_i^k - h_i^k(y^k(t_i^k), p, \tilde{p}^k)}{\sigma_i^k} \right)^2,$$

where we introduced the functions

$$F_1^k \left(y^k(t_1^k), \dots, y^k(t_{m^k}^k), p, \tilde{p}^k \right) := \Sigma_k^{-1} \begin{pmatrix} \eta_1^k - h_1^k(y^k(t_1^k), p, \tilde{p}^k) \\ \vdots \\ \eta_{m^k}^k - h_{m^k}^k(y^k(t_{m^k}^k), p, \tilde{p}^k) \end{pmatrix} \in \mathbb{R}^{m^k}, \quad (2.1.1)$$

where the diagonal matrices

$$\Sigma_k = \begin{pmatrix} \sigma_1^k & & \\ & \ddots & \\ & & \sigma_{m^k}^k \end{pmatrix}$$

contain the standard deviations of the measurement errors. The well known least-squares approach was introduced by Gauss in 1809 [50], and a general introduction and basic properties can be found in e.g. Scholz [98], Bard [10], Beck and Arnold [15], and Gifi [52].

If the measurement errors are not normally distributed, we need to consider other objective functionals to get a maximum likelihood estimate of the parameters. If the measurement errors are assumed to be independent and Laplace-distributed, a l_1 -norm estimation leads to a maximum likelihood estimate, see Birkes and Dodge [18], Kostina [65], and Binder [17]. Another approach is given by using Huber estimation, which is a combination of a least-squares estimation and a l_1 -norm estimation. The Huber estimate is used in robust estimation and it reduces the effect of outliers. For a thorough treatment of the Huber estimate, see Binder [17].

Often, the parameter values that are to be estimated and their corresponding states of the system have to satisfy some additional constraints. Possible restrictions are e.g. that a certain parameter value needs to be non-negative because it is related to a growth rate, or that the states have to fulfill some initial value or boundary value conditions. Such potential restrictions to the parameter space or to the space of the states can be considered by equality conditions, such as

$$r^k(y^k(t_1^k), \dots, y^k(t_{m^k}^k), p, \tilde{p}^k) = 0, \quad k = 1, \dots, M,$$

where we assume that the functions $r^k : \mathbb{R}^{n_y^k} \times \dots \times \mathbb{R}^{n_y^k} \times \mathbb{R}^{n_p} \times \mathbb{R}^{n_{\tilde{p}}^k} \rightarrow \mathbb{R}^{m_r^k}$ are at least twice continuously differentiable. For simplicity of notations, at this point, we only consider restrictions at the measurement times. Obviously, we can also consider inequality restrictions to the parameters and the states, but in favor of a simplified notation we neglect this, and refer to e.g. Bock [19].

All in all, the nonlinear multiple experiment parameter estimation problem to identify the unknown parameter values and the corresponding states is composed of the single components of the experiment specific setups in the following way:

Find solutions y^k , $k = 1, \dots, M$, a global parameter vector p , and experiment specific parameter vectors \tilde{p}^k , in such a way, that the weighted differences between the observation functions and the measurements become minimal

$$\frac{1}{2} \sum_{k=1}^M \left\| F_1^k \left(y^k(t_1^k), \dots, y^k(t_{m^k}^k), p, \tilde{p}^k \right) \right\|_2^2 = \min_{y^1, \dots, y^M, p, \tilde{p}^1, \dots, \tilde{p}^M}.$$

Thereby, the optimization variables have to satisfy the equality constraints

$$r^k(y^k(t_1^k), \dots, y^k(t_{m^k}^k), p, \tilde{p}^k) = 0, \quad k = 1, \dots, M,$$

and all the experiment specific ordinary differential equations

$$\dot{y}^k(t) = f^k(t, y^k(t), p, \tilde{p}^k).$$

The times $t_i^k \in [t_a^k, t_e^k]$ are given explicitly or in an implicit form by switching functions

$$Z_i^k(t, y^k(t), p, \tilde{p}^k) = 0, \quad i = 1, \dots, m^k, \quad k = 1, \dots, M.$$

2.2 Discretization of the Dynamics

Due to the unknown states y^k , $k = 1, \dots, M$, of the ordinary differential equation systems, the introduced multiple experiment parameter estimation problem has an infinite solution space. In order to be able to solve this problem by means of common optimization methods, a discretization of the ordinary differential equations is required. This is especially essential for the exertion of computers. In the following subsections two discretization techniques are presented.

2.2.1 Single Shooting Approach

The first, and maybe the most intuitive approach of discretization, is the *Single Shooting* approach, as explained by e.g. Bock [19] and Stoer and Bulirsch [103]. According to this approach, we have to solve one initial value problem for each experimental setup

$$\begin{aligned} \dot{y}^k(t) &= f^k(t, y^k(t), p, \tilde{p}^k) \\ y(t_a^k) &= s^k, \end{aligned}$$

over the entire time intervals $[t_a^k, t_e^k]$, by introducing initial values $s^k \in \mathbb{R}^{n_y^k}$, $k = 1, \dots, M$. Thereby, the initial values are new optimization variables of the underlying parameter estimation problem. We assume that every initial value problem is solvable for all $(s^k, p, \tilde{p}^k) \in \mathbb{R}^{n_y^k} \times \mathbb{R}^{n_p} \times \mathbb{R}^{n_{\tilde{p}}^k}$, and hence we get solutions $y^k(t)$ for any time $t \in [t_a^k, t_e^k]$ by

$$y^k(t) = y^k(t; s^k, p, \tilde{p}^k),$$

for $k = 1, \dots, M$. One difficulty of the *Single Shooting* approach lies in the choice of *good* parametrization variables s^k . Bad choices of these variables may cause convergence problems of the *Gauss-Newton* method, which is discussed in Subsection 2.3. In some cases ordinary differential equations do not have a global solution, and consequently the *Single Shooting* approach is insufficient for the general case. However, an advantage of this approach is the relatively low computational effort. Basically, we have to solve M initial value problems and we introduce $\sum_{k=1}^M n_y^k$ new optimization variables.

The *Single Shooting* approach leads to the following nonlinear finite-dimensional parameter estimation problem:

$$\begin{aligned} \min_{s^1, \dots, s^M, p, \tilde{p}^1, \dots, \tilde{p}^M} & \frac{1}{2} \sum_{k=1}^M \left\| F_1^k(s^k, p, \tilde{p}^k) \right\|_2^2 \\ \text{s.t.} & r^k(s^k, p, \tilde{p}^k) = 0, \quad k = 1, \dots, M. \end{aligned} \quad (2.2.1)$$

2.2.2 Multiple Shooting Approach

In this subsection, we recommend the *Multiple Shooting* method, in order to counteract the convergence difficulties of the *Single Shooting* approach. Originally, the *Multiple Shooting* method was developed for the treatment of boundary value problems—see e.g. Bulirsch [34], and Stoer and Bulirsch [103]—and it was used for the discretization of the dynamics in the context of parameter estimation problems by Bock [19] and Bock and Plitt [26].

Following this approach, we divide each experiment specific time interval into several sub-intervals by introducing *Multiple Shooting* nodes $\tau_j^k \in [t_a^k, t_e^k]$, $j = 0, \dots, l_k$, $k = 1, \dots, M$. For the k -th experimental setup we get a grid of the form

$$t_a^k = \tau_0^k < \tau_1^k < \dots < \tau_{l_k}^k = t_e^k,$$

where the first shooting node corresponds to the corresponding first time point and the last shooting node corresponds to the last time point.

All in all, the ordinary differential equation systems are replaced by $\sum_{k=1}^M l_k$ initial value problems

$$\begin{aligned} \dot{y}^k(t) &= f^k(t, y^k(t), p, \tilde{p}^k), \quad t \in [\tau_j^k, \tau_{j+1}^k), \\ y^k(\tau_j^k) &= s_j^k, \end{aligned} \quad (2.2.2)$$

and we obtain the solutions

$$y^k(t) = y^k(t; s_j^k, p, \tilde{p}^k)$$

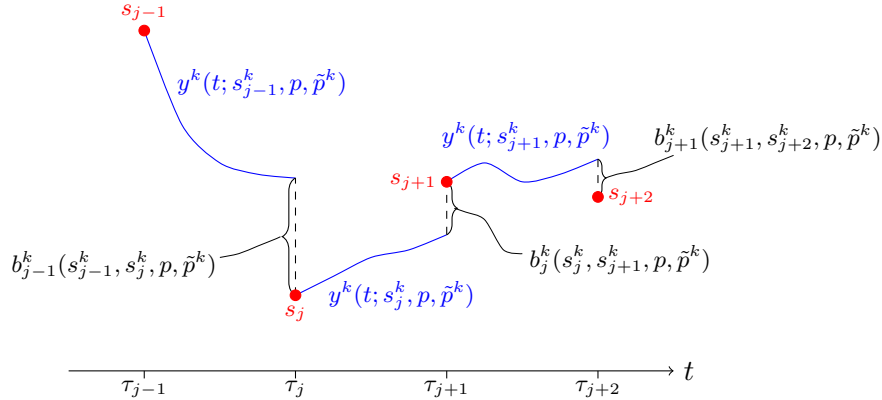
for each single sub-interval $[\tau_j^k, \tau_{j+1}^k)$, $j = 0, \dots, l_k - 1$, $k = 1, \dots, M$.

In order to ensure that we end up with a continuous solution, we have to add matching conditions to the parameter estimation problem. This can be done by considering the additional equality constraints

$$b_j^k(s_j^k, s_{j+1}^k, p, \tilde{p}^k) := y^k(\tau_{j+1}^k; s_j^k, p, \tilde{p}^k) - s_{j+1}^k \stackrel{!}{=} 0, \quad (2.2.3)$$

where $j = 0, \dots, l_k - 1$, $k = 1, \dots, M$.

An illustration of the *Multiple Shooting* approach is given in Figure 2.1.


 Figure 2.1: Illustration of the *Multiple Shooting* method

Using the *Multiple Shooting* method to discretize the dynamic systems, we have to introduce $\sum_{k=1}^M n_y^k \cdot (l_k + 1)$ new optimization variables and $\sum_{k=1}^M n_y^k \cdot l_k$ additional equality constraints. This leads to a drastic increase of the number of optimization variables and equality constraints. The additional computational effort can be counteracted by using adequate numerical techniques as given in e.g. Stoer and Bulirsch [103] and Bock [19]. The key benefit of the *Multiple Shooting* approach is, that we are able to insert every piece of available information about the system states into the parameter estimation problem, and that the *Multiple Shooting* grid can be chosen such that the solutions of the initial value problem always exist, see Bock [19]. Furthermore, all the initial value problems (2.2.2) are independent from one other, and therefore they can easily be solved in parallel. A parallelization of the *Multiple Shooting* method is especially favorable in the case of a parameter estimation problem with a single experiment structure, where it holds that $M = 1$. Otherwise we might have the problem that there are many more experiments than available processors. More information about parallelization techniques of the *Multiple Shooting* method can be found in Gallitzendörfer [49].

A discretization with the *Multiple Shooting* approach leads to the following nonlinear finite-dimensional parameter estimation problem:

$$\begin{aligned}
 \min_{s^1, \dots, s^M, p, \tilde{p}^1, \dots, \tilde{p}^M} & \frac{1}{2} \sum_{k=1}^M \left\| F_1^k(s^k, p, \tilde{p}^k) \right\|_2^2 \\
 \text{s.t.} & \quad r^k(s^k, p, \tilde{p}^k) = 0, \quad k = 1, \dots, M, \\
 & \quad b_j^k(s_j^k, s_{j+1}^k, p, \tilde{p}^k) = 0, \quad j = 0, \dots, l_k - 1, \quad k = 1, \dots, M,
 \end{aligned} \tag{2.2.4}$$

where $s^{1T} := (s_0^{1T}, \dots, s_{l_1}^{1T})$, \dots , $s^{MT} := (s_0^{MT}, \dots, s_{l_M}^{MT})$.

Remark 2.2.1 Another discretization technique can be defined by replacing the matching conditions of *Multiple Shooting* by collocation conditions, see Ascher [2], Bär [9],

Schulz [99, 100], and Cervantes and Biegler [36]. This approach also leads to an equality constrained parameter estimation problem, typically of much higher dimension.

2.3 A Generalized Gauss-Newton Method

Both, the *Single Shooting* and the *Multiple Shooting* approach lead to a finite dimensional equality constrained parameter estimation problem in the form of a standard optimization problem, such as

$$\begin{aligned} \min_{x_1, \dots, x_M, p} \frac{1}{2} \sum_{k=1}^M \left\| F_1^k(x_k, p) \right\|_2^2 \\ \text{s.t. } F_2^k(x_k, p) = 0, \quad k = 1, \dots, M. \end{aligned} \quad (2.3.1)$$

Using the *Multiple Shooting* method, the experiment specific optimization variables are given by $x_k^T = (s^{kT}, \tilde{p}^{kT}) \in \mathbb{R}^{n_x^k}$, where $n_x^k = n_y^k \cdot l_k + n_{\tilde{p}}^k$, and the at least twice continuously differentiable equality constraint functions are given by

$$F_2^k(x_k, p) := \begin{pmatrix} r^k(s^k, p, \tilde{p}^k) \\ b_0^k(s_0^k, s_1^k, p, \tilde{p}^k) \\ \vdots \\ b_{l_k-1}^k(s_{l_k-1}^k, s_{l_k}^k, p, \tilde{p}^k) \end{pmatrix} \in \mathbb{R}^{m_2^k}, \quad (2.3.2)$$

where $m_2^k = m_r^k + n_y^k \cdot l_k$.

In order to solve the constrained parameter estimation problem (2.3.1), we recommend a generalized *Gauss-Newton* method. Originally, the *Gauss-Newton* method was only established for unconstrained *least-squares* problems. A generalization for the treatment of constrained parameter estimation problems with ordinary differential equations was introduced by Bock [19] in 1987. For parallelization techniques of the algorithm, we refer to Gallitzendörfer [49] and Zieße et al. [112].

The following algorithm as developed by Bock [19], describes a generalized *Gauss-Newton* method to solve a multiple experiment parameter estimation problem.

Algorithm 1 (A generalized Gauss-Newton method)

1. Start with initial guesses $(x_1^{(0)T}, \dots, x_M^{(0)T}, p^{(0)T})$ and set $i = 0$.
2. Solve the linearized problem

$$\begin{aligned} \min_{\Delta x_1, \dots, \Delta x_M, \Delta p} \frac{1}{2} \sum_{k=1}^M \left\| F_1^k(x_k^{(i)}, p^{(i)}) + \frac{\partial F_1^k}{\partial x_k}(x_k^{(i)}, p^{(i)}) \Delta x_k + \frac{\partial F_1^k}{\partial p}(x_k^{(i)}, p^{(i)}) \Delta p \right\|_2^2 \\ \text{s.t. } F_2^k(x_k^{(i)}, p^{(i)}) + \frac{\partial F_2^k}{\partial x_k}(x_k^{(i)}, p^{(i)}) \Delta x_k + \frac{\partial F_2^k}{\partial p}(x_k^{(i)}, p^{(i)}) \Delta p = 0, \quad k = 1, \dots, M, \end{aligned}$$

and obtain a solution $(\Delta x_1^{(i)T}, \dots, \Delta x_M^{(i)T}, \Delta p^{(i)T})$.

3. Compute a new iterate according to

$$\begin{pmatrix} x_1^{(i+1)} \\ \vdots \\ x_M^{(i+1)} \\ p^{(i+1)} \end{pmatrix} = \begin{pmatrix} x_1^{(i)} \\ \vdots \\ x_M^{(i)} \\ p^{(i)} \end{pmatrix} + t^{(i)} \begin{pmatrix} \Delta x_1^{(i)} \\ \vdots \\ \Delta x_M^{(i)} \\ \Delta p^{(i)} \end{pmatrix} \quad (2.3.3)$$

by means of a step size $t^{(i)} \in (0, 1]$.

4. If a suitable termination criterion is fulfilled:

Stop and the solution is

$$x^{*T} := (x_1^{(i+1)T}, \dots, x_M^{(i+1)T}, p^{(i+1)T}).$$

Otherwise

Set $i = i + 1$ and go to step 2.

We continue with some comments and remarks to the generalized *Gauss-Newton* method.

Remark 2.3.1

- A suitable termination criterion is, for instance, that the weighted norm of the increments is less than some tolerance, e.g.

$$\frac{1}{n} \left\| \left(\Delta x_1^{(i)T}, \dots, \Delta x_M^{(i)T}, \Delta p^{(i)T} \right) \right\|_2 \leq \text{tolerance}.$$

The weight $\frac{1}{n}$ is basically determined by the number of optimization variables.

- The step size $t^{(i)} \in (0, 1]$ is a damping factor for the globalization of the convergence of the iterative process. For the computation of a suitable step size $t^{(i)} \in (0, 1]$ common strategies, as the Armijo-rule, the Goldstein-rule, or the Powell-Wolfe-strategy, can be used. For a detailed discussion we refer to Nocedal and Wright [81], Luenberger and Ye [74], or Bonnans et al. [27]. An empirical and very effective approach for the choice of the step length $t^{(i)}$ of a new Gauss-Newton iterate is the restrictive monotonicity test, which is based on a quadratic upper bound of the natural level function. For a thorough treatment of the restrictive monotonicity test see Bock [19] and Bock et al. [24].
- The local convergence speed of the generalized Gauss-Newton method is linear. A full description of the convergence properties is given in Section 2.5.
- The basic computational effort of the generalized Gauss-Newton method is determined by solving linearized optimization problems and by computing the required derivatives. For the computation of the derivatives we refer to Section 6. The solution of the linearized problem by means of a generalized inverse is discussed in the following Section 2.4. An efficient approach to solve the linearized problem in the case of a multiple experiment parameter estimation problem is given in Section 5.1.

2.4 Solution of the Linearized Problem

Regarding the generalized *Gauss-Newton* method for solving equality constrained parameter estimation problems, the main computational effort is determined by solving a linearized problem in each iteration. This section deals with the solution of the linearized problem and its properties. In particular, we show that the increment can be determined by using a generalized inverse of the Jacobians of the underlying model functions. This generalized inverse plays also an important role in our further considerations.

Let us consider a slightly rewritten parameter estimation problem. If we introduce the functions

$$F_1(x) := \begin{pmatrix} F_1^1(x_1, p) \\ \vdots \\ F_1^M(x_k, p) \end{pmatrix} \in \mathbb{R}^{m_1} \text{ and } F_2(x) := \begin{pmatrix} F_2^1(x_1, p) \\ \vdots \\ F_2^M(x_k, p) \end{pmatrix} \in \mathbb{R}^{m_2},$$

where the optimization variables are combined to $x^T := (x_1^T, \dots, x_M^T, p^T) \in \mathbb{R}^{n_x}$, the multiple experiment parameter estimation problem (2.3.1) can be expressed by

$$\begin{aligned} \min_x \quad & \frac{1}{2} \|F_1(x)\|_2^2 \\ \text{s.t.} \quad & F_2(x) = 0. \end{aligned} \tag{2.4.1}$$

Consequently, the linearized parameter estimation problem of step 2 of Algorithm 1 is equal to

$$\begin{aligned} \min_{\Delta x} \quad & \|J_1(x)\Delta x + F_1(x)\|_2^2 \\ \text{s.t.} \quad & J_2(x)\Delta x + F_2(x) = 0, \end{aligned} \tag{2.4.2}$$

where the Jacobians are defined by

$$J_1(x) := \frac{\partial F_1(x)}{\partial x} \in \mathbb{R}^{m_1 \times n_x} \text{ and } J_2(x) := \frac{\partial F_2(x)}{\partial x} \in \mathbb{R}^{m_2 \times n_x}.$$

For our further considerations we always assume that the Jacobians J_1 and J_2 satisfy the following two regularity assumptions:

- Given a feasible point $x \in \mathbb{R}^{n_x}$, the regularity assumption *Constraint Qualification* (CQ) holds if matrix $J_2(x)$ has full rank

$$\text{rank } J_2(x) = m_2. \tag{2.4.3}$$

A feasible vector $x \in \mathbb{R}^{n_x}$ is a *regular* point, if the condition (CQ) is fulfilled.

- If x is a feasible point, the regularity assumption *Positive Definiteness* (PD) is fulfilled if

$$\text{rank } J(x) = n_x, \tag{2.4.4}$$

where $J(x) = \begin{pmatrix} J_1(x) \\ J_2(x) \end{pmatrix}$.

In connection with the introduced parameter estimation problem, the two regularity assumptions play an important role. By assuming the *Constraint Qualification*, we ensure that there are no contractions and no redundancies in the constraints. The *Positive Definiteness* assures us that we have enough information—which means enough measurements—to estimate all unknown parameter values.

The following lemma is important for our further investigations and its proof can be found in almost every book on optimization e.g. Nocedal and Wright [81] and Luenberger and Ye [74].

Lemma 2.4.1 *Let us assume that the regularity assumptions (CQ) and (PD) are fulfilled. Then it holds that*

1. the matrix product $J_1^T(x)J_1(x)$ is positive definite on the kernel of $J_2(x)$.
2. the matrix

$$\begin{pmatrix} J_1^T(x)J_1(x) & J_2^T(x) \\ J_2(x) & 0 \end{pmatrix} \quad (2.4.5)$$

is regular.

Proof.

1. Let $0 \neq v \in \mathbb{R}^{n_x}$, with $J_2(x)v = 0$. Because of the regularity condition (PD) it holds that $\text{rank } J(x) = n_x$ and therefore $\ker \begin{pmatrix} J_1(x) \\ J_2(x) \end{pmatrix} = \{0\}$. Since $J_2(x)v = 0$ it must hold that $J_1(x)v \neq 0$. This means $v^T J_1^T(x)J_1(x)v > 0$.
2. If we assume that there exists a vector $\begin{pmatrix} v \\ w \end{pmatrix} \neq 0$, such that

$$\begin{pmatrix} J_1^T(x)J_1(x) & J_2^T(x) \\ J_2(x) & 0 \end{pmatrix} \begin{pmatrix} v \\ w \end{pmatrix} = 0,$$

it follows $v^T J_1^T(x)J_1(x)v + v^T J_2^T(x)w = v^T J_1^T(x)J_1(x)v = 0$. Due to 1. this results in $v = 0$. If we take $v = 0$ into account, it also follows that $J_2^T(x)w = 0$ and because of the regularity condition (CQ) we obtain that $w = 0$. ζ

■

The matrix (2.4.5) is also known as the *Karush-Kuhn-Tucker* matrix, or KKT-matrix in short.

The following theorem shows that the increment of a new *Gauss-Newton* iterate can basically be determined by solving a linear system, see Bock [19].

Theorem 2.4.2 *Let us assume that the Jacobi matrices satisfy the regularity assumptions (CQ) and (PD) and let us denote*

$$F(x) := \begin{pmatrix} F_1(x) \\ F_2(x) \end{pmatrix} \in \mathbb{R}^{m_1+m_2} \text{ and } J(x) := \begin{pmatrix} J_1(x) \\ J_2(x) \end{pmatrix} \in \mathbb{R}^{(m_1+m_2) \times n_x}.$$

Then it holds that:

1. There exists a unique KKT-point $(\Delta x, \lambda)$ of the linearized problem (2.4.2) and Δx is a strict minimum.
2. There exists a linear map $J^+ : \mathbb{R}^{m_1+m_2} \rightarrow \mathbb{R}^{n_x}$, such that the solution of the linearized problem (2.4.2) is given by a matrix-vector product

$$\Delta x = -J^+(x)F(x). \quad (2.4.6)$$

3. The operator J^+ is a generalized inverse and it fulfills $J^+JJ^+ = J^+$.
4. The generalized inverse has the explicit representation

$$J^+(x) := (\mathbb{I} \ 0) \begin{pmatrix} J_1^T(x)J_1(x) & J_2^T(x) \\ J_2(x) & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T(x) & 0 \\ 0 & \mathbb{I} \end{pmatrix}. \quad (2.4.7)$$

Proof. The Lagrange function of the linearized problem is

$$\mathcal{L}(\Delta x, \lambda) = \frac{1}{2} \|J_1(x)\Delta x + F_1(x)\|_2^2 - \lambda^T (J_2(x)\Delta x + F_2(x))$$

and the optimality conditions are given by the linear system

$$\begin{pmatrix} J_1^T(x)J_1(x) & J_2^T(x) \\ J_2(x) & 0 \end{pmatrix} \begin{pmatrix} \Delta x \\ -\lambda \end{pmatrix} + \begin{pmatrix} J_1^T(x)F_1(x) \\ F_2(x) \end{pmatrix} = 0^{n_x+m_2}.$$

According to Lemma 2.4.1 the KKT-matrix is regular and we get a unique solution

$$\begin{pmatrix} \Delta x \\ -\lambda \end{pmatrix} = - \begin{pmatrix} J_1^T(x)J_1(x) & J_2^T(x) \\ J_2(x) & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T(x) & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} F_1(x) \\ F_2(x) \end{pmatrix}. \quad (2.4.8)$$

Due to the regularity assumptions (CQ) and (PD), Δx is a strict local minimum. Thus, we verified the first assumption of the theorem. The second and the fourth assumption follow from Formula (2.4.8) by denoting

$$J^+(x) := (\mathbb{I} \ 0) \begin{pmatrix} J_1^T(x)J_1(x) & J_2^T(x) \\ J_2(x) & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T(x) & 0 \\ 0 & \mathbb{I} \end{pmatrix}.$$

In order to proof the third assumption, we note that $v^* := J^+JJ^+y$ is the solution of

$$\begin{aligned} & \min_v \|J_1v - J_1J^+y\|_2^2 \\ & \text{s.t. } J_2v - J_2J^+y = 0, \end{aligned}$$

for an arbitrary vector $y \in \mathbb{R}^{m_1+m_2}$. Obviously, $v = J^+y$ is also a solution and therefore the third assumption holds. ■

We continue with some remarks.

Remark 2.4.3

a) In the general case of a constrained parameter estimation problem, the introduced generalized inverse J^+ is **not** a Moore-Penrose pseudo-inverse which is characterized by the four axioms

$$\begin{array}{ll} i) & JJ^+J = J \\ ii) & (JJ^+)^T = JJ^+ \\ iii) & J^+JJ^+ = J^+ \\ iv) & (J^+J)^T = J^+J, \end{array}$$

see e.g. Schmidt and Trenkler [97]. However, it satisfies the property $J^+J = \mathbb{I}$.

b) In the case of an unconstrained parameter estimation problem as

$$\min_x \frac{1}{2} \|F_1(x)\|_2^2,$$

the iteration matrix for a new Gauss-Newton iterate is given by

$$J^+(x) = (J_1^T(x)J_1(x))^{-1} J_1^T(x), \tag{2.4.9}$$

and it can easily be shown that it is a Moore-Penrose pseudo-inverse.

Remark 2.4.4 In Section 5.1, we discuss an efficient and numerically stable algorithm for solving the linearized problem in the case of a multiple experiment parameter estimation problem. Furthermore, we look at its aspects of parallelization in Subsection 5.1.1.

2.5 Convergence Properties of Newton-Type Methods

In this section, we consider the local convergence properties of Newton-type methods for equality constrained parameter estimation problems,

$$\begin{array}{l} \min_x \frac{1}{2} \|F_1(x)\|_2^2 \\ \text{s.t. } F_2(x) = 0, \end{array}$$

as given in Formula (2.4.1). The following theorem characterizes the local convergence properties of Newton-type methods, where a new iterate is basically determined by an update of the prior iterate,

$$x^{(i+1)} = x^{(i)} + \Delta x^{(i)},$$

and the increment is given by

$$\Delta x^{(i)} = -M(x^{(i)})F(x^{(i)}), \quad (2.5.1)$$

with a suitable iteration matrix $M(x^{(i)})$. We use the function $F : D \subseteq \mathbb{R}^{n_x} \rightarrow \mathbb{R}^m$ and its Jacobian $J : D \subseteq \mathbb{R}^{n_x} \rightarrow \mathbb{R}^{m \times n_x}$, with

$$F(x) := \begin{pmatrix} F_1(x) \\ F_2(x) \end{pmatrix} \text{ and } J(x) := \begin{pmatrix} J_1(x) \\ J_2(x) \end{pmatrix},$$

where $J_1(x) = \partial F_1(x)/\partial x$ and $J_2(x) = \partial F_2(x)/\partial x$.

Theorem 2.5.1 (Local Contraction Theorem, Bock [19])

Let $D \subseteq \mathbb{R}^{n_x}$, $F \in C(D, \mathbb{R}^m)$ and $J := \partial F/\partial x$ be the Jacobi matrix of the nonlinear function F . For all $x, y \in D$ with $\Delta x := y - x = -M(x)F(x)$ and $t \in (0, 1]$ it holds that:

- There exists an $\omega < \infty$, such that

$$\|M(y)(J(x + t\Delta x) - J(x))\Delta x\| \leq \omega t \|\Delta x\|^2. \quad (2.5.2)$$

- There exists an $\kappa(x) \leq \kappa < 1$, such that

$$\|M(y)R(x)\| \leq \kappa(x) \|\Delta x\| \quad (2.5.3)$$

with the residual $R(x) := F(x) + J(x)\Delta x = (\mathbb{I} - J(x)M(x))F(x)$.

Furthermore, let a given initial guess $x^{(0)} \in D$ fulfill

$$\delta_0 := \kappa + \frac{\omega}{2} \|\Delta x^{(0)}\| < 1,$$

and the ball

$$D_0 := \left\{ z \in \mathbb{R}^n \mid \|z - x^{(0)}\| \leq \frac{\|\Delta x^{(0)}\|}{1 - \delta_0} \right\} \subseteq D$$

be a subset of D . Then it holds that:

1. The iteration $x^{(i+1)} = x^{(i)} + \Delta x^{(i)}$ is well-defined and $x^{(i)} \in D_0$ for all $i \in \mathbb{N}$.
2. There exists a point $x^* \in D_0$, such that $x^{(i)} \rightarrow x^*$ for $i \rightarrow \infty$.
3. It holds the a-priori estimate

$$\|x^{(i+j)} - x^*\| \leq \delta_i^j \frac{\|\Delta x^{(i)}\|}{1 - \delta_i},$$

where

$$\delta_i := \kappa + \frac{\omega}{2} \|\Delta x^{(i)}\|, \text{ with } \Delta x^{(i)} := -M(x^{(i)})F(x^{(i)}).$$

4. It holds that

$$\|\Delta x^{(i+1)}\| \leq \delta_i \|\Delta x^{(i)}\| = \kappa \|\Delta x^{(i)}\| + \frac{\omega}{2} \|\Delta x^{(i)}\|^2.$$

Proof. This proof is explored thoroughly in Bock [19].

■

The convergence properties of Theorem 2.5.1 are valid for the whole class of Newton-type methods where the increment of a new iterate is determined according to (2.5.1). In the special case of the *Gauss-Newton* method the iteration matrix M is given by the generalized inverse J^+ as introduced in (2.4.7), which is the solution operator of the linearized problem (2.4.2). Following Bock [19] and Bock et al. [22] the satisfiability of the conditions of Theorem 2.5.1 in case of the *Gauss-Newton* method can be construed as follows.

Satisfiability of $\omega < \infty$

Suppose that $F \in C^2(D, \mathbb{R}^m)$ and $\mathcal{U}_{x^*} \subseteq D$ is an adequate neighborhood of the solution x^* . For the existence and the uniqueness of the generalized inverse J^+ , we assume that the regularity conditions (CQ) and (PD) are fulfilled for all $y \in \mathcal{U}_{x^*}$ and that $\|J^+(y)\| \leq c_1$, with a positive constant $c_1 \in \mathbb{R}_{>0}$. Furthermore, we assume that the Jacobian $J = \partial F / \partial x$ satisfies the Lipschitz condition $\|(J(x + t\Delta x) - J(x)) \Delta x\| \leq c_2 \cdot t \|\Delta x\|^2$ with a Lipschitz constant $\|dJ\| \leq c_2 \in \mathbb{R}_{>0}$. Then it holds that

$$\begin{aligned} \|J^+(y) (J(x + t\Delta x) - J(x)) \Delta x\| &\leq \|J^+(y)\| \cdot \|(J(x + t\Delta x) - J(x)) \Delta x\| \\ &\leq c_1 \cdot c_2 \cdot t \|\Delta x\|^2. \end{aligned}$$

Hence, with $\omega := c_1 \cdot c_2$, assumption (2.5.2) depends on the constants c_1 and c_2 . Therefore, ω is large if the norm of the second derivative $\|dJ\|$ is large, which means that F is very nonlinear, and if the norm of the generalized inverse $\|J^+(y)\|$ is large, which means that the KKT-matrix—as given in (2.4.5)—is almost rank deficient. The Lipschitz constant ω is basically determined by $\|dJ\|$ in any norm and can be seen as a measure of the curvature of the nonlinear function F .

Satisfiability of $\kappa < 1$

Suppose again that $F \in C^2(D, \mathbb{R}^m)$ and that $\mathcal{U}_{x^*} \subseteq D$ is an adequate neighborhood of the solution x^* . For the satisfiability of assumption (2.5.3), we consider the Lipschitz condition

$$\begin{aligned} \|J^+(y) - J^+(x)\| &\leq \|dJ^+(x)\| \cdot \|y - x\| \\ &\leq L \cdot \|y - x\|, \end{aligned}$$

for all $x, y \in \mathcal{U}_{x^*}$, with the Lipschitz constant $\|dJ^+(x)\| \leq L \in \mathbb{R}_{>0}$. Due to $J^+(x)R(x) = 0$ - where the residual is given by $R(x) = F(x) + J(x)\Delta x$, it follows that

$$\begin{aligned} \|J^+(y)R(x)\| &= \|(J^+(y) - J^+(x))R(x)\| \\ &\leq L \cdot \|R(x)\| \cdot \|\Delta x\|. \end{aligned}$$

If the residual is bounded according to $\|R(x)\| \leq c_3$, the assumption $\kappa := L \cdot c_3 < 1$ is satisfiable if c_3 is small enough and $\|dJ^+(x)\| \leq L$ has only moderate size. Thus, κ depends not only on a deterministic part $\|dJ^+(x)\|$, but also on a random part c_3 describing the size of the residual. Considering the residual at the solution point x^* , we obtain

$$R(x^*) = F(x^*) + J(x^*)\Delta x^* = \begin{pmatrix} F_1(x^*) + J_1(x^*)\Delta x^* \\ F_2(x^*) + J_2(x^*)\Delta x^* \end{pmatrix} = \begin{pmatrix} F_1(x^*) \\ 0 \end{pmatrix}.$$

Hence, $R(x^*)$ consists of those least-squares components, which are non-zero evaluated at the solution x^* . Here, the model does not exactly match the data and therefore, κ can be seen as a measure of the compatibility between the model and the measurements. The significant meaning of κ is discussed in detail in the following section 2.6.

Remark 2.5.2 *One main result of Chapter 3 will be that these Lipschitz constants κ and ω are also useful to determine the statistical accuracy of the estimate x^* . We will show that bounds of a quadratic approximation of confidence regions can be characterized by means of the constants ω and κ . In Chapter 4 we will introduce and analyze a new objective function for the design of optimal experiments based on κ and ω .*

2.6 Compatibility Analysis

As discussed in the last section, the local convergence properties of the generalized *Gauss-Newton* method are basically determined by the two Lipschitz constants κ and ω . More precisely, we have asymptotic linear convergence with rate κ if the initial value $x^{(0)}$ satisfies

$$\kappa + \frac{\omega}{2} \left\| J^+(x^{(0)})F(x^{(0)}) \right\| < 1.$$

The significant meaning of the constant κ in connection with a parameter estimation problem was investigated by Bock in his fundamental work *Randwertproblemmethoden zur Parameteridentifizierung in Systemen nichtlinearer Differentialgleichungen*, [19]. In this section we summarize the two main results R1 and R2.

R1: If $\kappa < 1$, the generalized *Gauss-Newton* method converges to a strict local minimum x^* , which is stable against small perturbations.

R2: If $\kappa > 1$, perturbations exist such that x^* is still a stationary point, but not a minimum.

In Subsection 2.6.2, we present an estimate of κ for a constrained parameter estimation problem.

2.6.1 Compatibility of the Model and the Measurements

In this section, we consider the fundamental properties of the Lipschitz constant κ , related to the convergence properties of the *Gauss-Newton* method. Following Bock et al. [22], we consider an unconstrained optimization problem for simplicity of notation

$$\min_x \frac{1}{2} \|F_1(x)\|_2^2 =: \phi(x). \quad (2.6.1)$$

The function $F_1 : \mathbb{R}^{n_x} \rightarrow \mathbb{R}^{m_1}$ is assumed to be at least twice continuously differentiable and to consist of the differences between measurements $\eta := (\eta_1, \dots, \eta_{m_1})^T$ and their corresponding observation functions $h(x) := (h_1(x), \dots, h_{m_1}(x))^T$, e.g.

$$F_1(x) = \eta - h(x). \quad (2.6.2)$$

The Jacobian and the Hessian of problem (2.6.1) are given by

$$\begin{aligned} \nabla_x \phi(x) &= J_1^T(x) F_1(x), \\ H(x) &:= \nabla_x^2 \phi(x) = J_1^T(x) J_1(x) + \sum_{i=1}^{m_1} \frac{\partial^2 F_{1i}}{\partial x^2} F_{1i} \\ &= J_1^T(x) J_1(x) + \frac{\partial J_1^T(x)}{\partial x} (\mathbb{I}_{n_x} \otimes F_1(x)). \end{aligned} \quad (2.6.3)$$

Considering the Hessian, we see that it is composed of a deterministic part $B(x) := J_1^T(x) J_1(x)$ and a random part $E(x) := \frac{\partial J_1^T(x)}{\partial x} (\mathbb{I}_{n_x} \otimes F_1(x))$, where the randomness is determined by the function F_1 . As given in Formula (2.4.4) for the constrained case, we also assume here that the regularity condition (PD) is fulfilled, which means that $\text{rank}(J_1(x)) = n < m_1$.

In our further considerations, we need the spectral radius of a matrix.

Definition 2.6.1 *Suppose that $\lambda_1, \dots, \lambda_n$ are the real or complex eigenvalues of a squared $n \times n$ matrix A . Then its spectral radius $\rho(A)$ is defined as*

$$\rho(A) = \max_{i=1}^n \{|\lambda_i|\}.$$

R1: Small Residual Problems, where $\kappa < 1$

The following lemma provides an equivalent condition to the assumption

$$\|J^+(y)R(x)\| \leq \kappa(x) \|y - x\|$$

of the *Local Contraction Theorem* 2.5.1, see Bock et al. [22]. Moreover, it shows that for small residuals the random part E of the Hessian is—with respect to a multiplication with the inverse of the deterministic part B^{-1} —bonded by 1. In other words, for a small residual, the deterministic part B dominates the random part E .

Theorem 2.6.2 *Suppose that $x^* \in D$ is a stationary point of the Gauss-Newton method. Considering the Lipschitz constant κ of Theorem 2.5.1, it holds that*

$$\kappa < 1 \iff \rho(B(x^*)^{-1}E(x^*)) < 1.$$

Proof. This proof follows Bock et al. [22]. Regarding the first order Taylor series of $J^+(y)R(x)$ around the point x , we get

$$J^+(y)R(x) = B(x)^{-1}E(x)(y-x) + \mathcal{O}(\|y-x\|^2).$$

Note that we are in the unconstrained case where $m_2 = 0$ with $J^+(x) = (J_1^T J_1)^{-1} J_1^T$ and

$$\begin{aligned} J^+(x)R(x) &= J^+(x)F_1(x) - \overbrace{J^+(x)J_1(x)J^+(x)}^{=J^+(x)} F_1(x) \\ &= 0. \end{aligned}$$

“ \Leftarrow ” : Suppose that $\rho(B(x^*)^{-1}E(x^*)) =: \kappa_1 < 1$ and choose a neighborhood \mathcal{U}_{x^*} of x^* and a norm such that $\|B(x)^{-1}E(x)\| \leq \kappa_2 < 1$ for all x in \mathcal{U}_{x^*} . If we reduce \mathcal{U}_{x^*} in such a way that $\mathcal{O}(\|y-x\|^2) \leq \frac{1-\kappa_2}{2}\|y-x\|$ for all x, y , then by taking the first order Taylor series into account, we get that

$$\begin{aligned} \|J^+(y)R(x)\| &\leq \|B(x)^{-1}E(x)\| \cdot \|y-x\| + \mathcal{O}(\|y-x\|^2) \\ &\leq \kappa_2\|y-x\| + \frac{1-\kappa_2}{2}\|y-x\| \\ &= \frac{1+\kappa_2}{2}\|y-x\| \\ &=: \kappa_3\|y-x\|, \end{aligned}$$

where $\kappa_3 < 1$.

“ \Rightarrow ” : Suppose that

$$\begin{aligned} \|J^+(y)R(x)\| &= \|B(x)^{-1}E(x)(y-x) + \mathcal{O}(\|y-x\|^2)\| \\ &\leq \kappa\|y-x\|, \end{aligned}$$

with $\kappa < 1$. Then it follows that

$$\begin{aligned} \|B(x^*)^{-1}E(x^*)(y-x)\| - \mathcal{O}(\|y-x\|^2) &\leq \kappa\|y-x\| \\ \iff \|B(x^*)^{-1}E(x^*)(y-x)\| &\leq \kappa\|y-x\| + \mathcal{O}(\|y-x\|^2). \end{aligned}$$

If we choose x, y from a neighborhood of x^* , such that $\mathcal{O}(\|y-x\|^2) \leq \frac{1-\kappa}{2}\|y-x\|$, the inequality may be rewritten as

$$\begin{aligned} \|B(x^*)^{-1}E(x^*)(y-x)\| &\leq \frac{1+\kappa}{2}\|y-x\| \\ &=: \kappa_1\|y-x\|, \end{aligned}$$

where $\kappa_1 < 1$. Therefore, we get $\|B(x^*)^{-1}E(x^*)\| \leq \kappa_1 < 1$ and $\rho(B(x^*)^{-1}E(x^*)) < 1$. ■

The next fundamental theorem verifies the first main result R1.

Theorem 2.6.3 *Suppose that $x^* \in D$ is a stationary point of the Gauss-Newton method and*

$$\rho(B(x^*)^{-1}E(x^*)) < 1.$$

Then it holds that x^ is already a minimizer of the underlying parameter estimation problem and it is stable against perturbations.*

Proof. The assertion follows if the Hessian $H(x^*)$ is positive definite. Considering (2.6.3), it follows that

$$\begin{aligned} H(x^*) \text{ positive definite} &\iff B(x^*) + E(x^*) \text{ positive definite} \\ &\iff \mathbb{I} + B(x^*)^{-\frac{1}{2}}E(x^*)B(x^*)^{-\frac{1}{2}} \text{ positive definite.} \end{aligned}$$

Note that the square root $B(x^*)^{-\frac{1}{2}}$ exists since the Jacobian $J_1(x^*)$ has full rank and consequently $B(x^*)$ is positive definite. Hence, the Hessian is positive definite if the eigenvalues of $B(x^*)^{-\frac{1}{2}}E(x^*)B(x^*)^{-\frac{1}{2}}$ are within the interval $[0, 1)$. Because of the similarity transformation

$$B(x^*)^{-1}E(x^*) = B(x^*)^{-\frac{1}{2}} \left(B(x^*)^{-\frac{1}{2}}E(x^*)B(x^*)^{-\frac{1}{2}} \right) B(x^*)^{\frac{1}{2}},$$

the matrices $B(x^*)^{-1}E(x^*)$ and $B(x^*)^{-\frac{1}{2}}E(x^*)B(x^*)^{-\frac{1}{2}}$ have the same eigenvalues and the assumption of Theorem 2.6.3 follows from $\rho(B(x^*)^{-1}E(x^*)) < 1$. ■

R2: Large Residual Problems, where $\kappa > 1$

In order to investigate the large residual situation, we consider a reformulation of the underlying parameter estimation problem by introducing a homotopy constant $\tau \in [-1, 1]$. Suppose again that the vector x^* denotes the solution of problem (2.6.1). We define $\tilde{F}_1(x, \tau) := F_1(x) + (\tau - 1)F_1(x^*)$ and consider the modified optimization problem

$$\min_x \frac{1}{2} \|\tilde{F}_1(x, \tau)\|_2^2, \tag{2.6.4}$$

where F_1 consists of the differences between measurements and corresponding observation functions as given in (2.6.2). Especially, for $\tau = 1$ and $\tau = -1$ it holds that

$$\tilde{F}_1(x, 1) = F_1(x) = \eta - h(x),$$

and

$$\begin{aligned} \tilde{F}_1(x, -1) &= F_1(x) - 2\tilde{F}_1(x^*) = h(x^*) + (h(x^*) - \eta) - h(x) \\ &= h(x^*) - F_1(x^*) - h(x) =: \tilde{\eta} - h(x), \end{aligned}$$

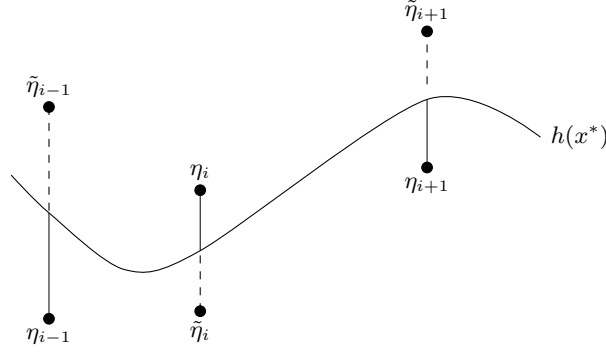


Figure 2.2: Illustration of the reflected measurements $\tilde{\eta}$, Bock et al. [22].

where $\tilde{\eta} := h(x^*) - F_1(x^*)$. Note that $\tilde{\eta}$ arises from η by reflecting the measurement errors at the estimated trajectory. The measurement reflection is illustrated in Figure 2.2. Furthermore, it follows, that for any $\tau \in [-1, 1]$, it holds that $\tilde{J}_1(x, \tau) = J_1(x)$ and therefore

$$\begin{aligned} \frac{\partial}{\partial x} \|\tilde{F}_1(x, \tau)\|_2^2 \Big|_{x=x^*} &= J_1^T(x) \tilde{F}_1(x, \tau) \Big|_{x=x^*} \\ &= \tau \underbrace{J_1^T(x^*) F_1(x^*)}_{=0} = 0. \end{aligned}$$

Hence, x^* is a stationary point of the modified problem for any choice of $\tau \in [-1, 1]$. The Hessian of the modified problem is given by

$$\tilde{H}(x, \tau) := B(x) + \tau E(x),$$

where $B(x) = J_1^T(x) J_1(x)$ and $E(x) = \frac{\partial J_1^T(x)}{\partial x} (\mathbb{I}_{n_x} \otimes F_1(x))$.

The following theorem shows that the solution of the modified problem (2.6.4) is not statistically stable for large residual problems where $\rho(B^{-1}(x^*)E(x^*)) > 1$. Therefore, an advantage of the *Gauss-Newton* method is that it does not converge to solutions which may become a saddle point or maximizer, see Bock et al. [22].

Theorem 2.6.4 *Suppose that x^* is a stationary point of problem (2.6.1), with $\hat{\kappa} := \rho(B^{-1}(x^*)E(x^*)) > 1$. Then, x^* is a stationary point of (2.6.4) for any $\tau \in [-1, 1]$ and the Hessian $\tilde{H}(x^*, \tau)$ is not positive for all $\tau < -\frac{1}{\hat{\kappa}}$.*

Proof. If we define $\hat{E}(x^*) := B^{-\frac{1}{2}}(x^*)E(x^*)B^{-\frac{1}{2}}(x^*)$, it holds that

$$\begin{aligned} 1 < \hat{\kappa} &= \rho(B^{-1}(x^*)E(x^*)) \\ &= \rho\left(B^{-\frac{1}{2}}(x^*)\left(B^{-\frac{1}{2}}(x^*)E(x^*)B^{-\frac{1}{2}}(x^*)\right)B^{\frac{1}{2}}(x^*)\right) \\ &= \rho(\hat{E}(x^*)). \end{aligned}$$

Considering the eigenvalues of the modified Hessian, we obtain

$$\begin{aligned}
 \tilde{H}(x^*, \tau) \text{ pos. def.} &\iff B(x^*) + \tau E(x^*) \text{ pos. def.} \\
 &\iff B^{\frac{1}{2}}(x^*) \left(\mathbb{I} + \tau B^{-\frac{1}{2}}(x^*) E(x^*) B^{-\frac{1}{2}}(x^*) \right) B^{\frac{1}{2}}(x^*) \text{ pos. def.} \\
 &\iff \mathbb{I} + \tau B^{-\frac{1}{2}}(x^*) E(x^*) B^{-\frac{1}{2}}(x^*) \text{ pos. def.} \\
 &\iff \mathbb{I} + \tau \hat{E}(x^*) \text{ pos. def.}
 \end{aligned}$$

Since $\rho\left(\mathbb{I} + \tau \hat{E}(x^*)\right) = 1 + \tau \hat{\kappa}$ for all $\tau < -\frac{1}{\hat{\kappa}}$ it holds that $\rho\left(\tilde{H}(x^*, \tau)\right) < 0$ and the modified Hessian is not positive definite. ■

2.6.2 An Estimate of the Lipschitz-Constant κ

In this subsection, we present an estimate for the Lipschitz constant κ for constrained parameter estimation problems of the form

$$\begin{aligned}
 \min_x \frac{1}{2} \|F_1(x)\|_2^2 \\
 \text{s.t. } F_2(x) = 0,
 \end{aligned} \tag{2.6.5}$$

as introduced in (2.4.1). For the next lemma it is useful to denote

$$F(x) := \begin{pmatrix} F_1(x) \\ F_2(x) \end{pmatrix} \text{ and its Jacobian } J(x) := \frac{\partial F(x)}{\partial x} = \begin{pmatrix} \frac{\partial F_1(x)}{\partial x} \\ \frac{\partial F_2(x)}{\partial x} \end{pmatrix} =: \begin{pmatrix} J_1(x) \\ J_2(x) \end{pmatrix}.$$

Lemma 2.6.5 *Let us assume that x is a feasible point of the equality constrained parameter estimation problem (2.4.1) and that the Jacobians J_1 and J_2 satisfy the regularity assumptions (CQ) and (PD) as defined in (2.4.3) and (2.4.4), respectively. Furthermore, we introduce the following notations*

$$\begin{aligned}
 \lambda(x) &:= - \begin{pmatrix} 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} J_1^T(x) J_1(x) & J_2^T(x) \\ J_2(x) & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T(x) & 0 \\ 0 & \mathbb{I} \end{pmatrix} F(x) \\
 v(x) &:= F_1(x) - J_1(x) \mathcal{C}(x) J_1^T(x) F_1(x), \\
 R(x) &:= F(x) - J(x) J^+(x) F(x), \\
 \mathcal{C}(x) &:= J^+(x) \begin{pmatrix} \mathbb{I} & 0 \\ 0 & 0 \end{pmatrix} J^{+T}(x), \\
 E(x) &:= \frac{\partial J_1^T(x)}{\partial x} (\mathbb{I} \otimes v(x)) + \frac{\partial J_2^T(x)}{\partial x} (\mathbb{I} \otimes \lambda(x)),
 \end{aligned}$$

where

$$\frac{\partial J_1^T(x)}{\partial x} (\mathbb{I} \otimes v(x)) := \left(\frac{\partial J_1^T(x)}{\partial x_1}, \dots, \frac{\partial J_1^T(x)}{\partial x_{n_x}} \right) \begin{pmatrix} v(x) & & 0 \\ & \ddots & \\ 0 & & v(x) \end{pmatrix} \in \mathbb{R}^{m_1 \times n_x}$$

and

$$\frac{\partial J_2^T(x)}{\partial x} (\mathbb{I} \otimes \lambda(x)) := \left(\frac{\partial J_2^T(x)}{\partial x_1}, \dots, \frac{\partial J_2^T(x)}{\partial x_{n_x}} \right) \begin{pmatrix} \lambda(x) & & 0 \\ & \ddots & \\ 0 & & \lambda(x) \end{pmatrix} \in \mathbb{R}^{m_2 \times n_x}.$$

Furthermore, we define

$$\tilde{\kappa}(x) := \|\mathcal{C}(x)E(x)\|.$$

1. Then it holds that

$$\begin{aligned} \|J^+(y)R(x)\| &= \|dJ^+(x)R(x)\| + \mathcal{O}(\|\Delta x\|^2) \\ &\leq \tilde{\kappa} \|\Delta x\| + \mathcal{O}(\|\Delta x\|^2), \end{aligned}$$

where $\Delta x := y - x = -J^+(x)F(x)$, with $x, y \in D \subseteq \mathbb{R}^{n_x}$ and the total derivative $dJ^+(x) := \sum_{i=1}^{n_x} \frac{\partial J^+(x)}{\partial x_i} \Delta x_i$.

2. In terms of κ as defined in Theorem 2.5.1 it holds that

$$\tilde{\kappa} < 1 \implies \kappa < 1.$$

3. If x^* is an arbitrary point satisfying the KKT conditions of the equality constrained parameter estimation problem (2.4.1), $E(x^*)$ reduces to

$$E(x^*) = \frac{\partial J_1^T(x^*)}{\partial x} (\mathbb{I} \otimes F_1(x^*)).$$

Proof.

1. A first order Taylor series of $J^+(y)$ around x yields

$$J^+(y) = J^+(x) + \sum_{i=1}^{n_x} \frac{\partial J^+(x)}{\partial x_i} \Delta x_i + \mathcal{O}(\|\Delta x\|^2),$$

and because of $J^+(x)R(x) = 0$ we get

$$\|J^+(y)R(x)\| = \|dJ^+(x)R(x)\| + \mathcal{O}(\|\Delta x\|^2),$$

where $dJ^+(x) := \sum_{i=1}^{n_x} \frac{\partial J^+(x)}{\partial x_i} \Delta x_i$. Recognizing Lemma 6.3.5, where the derivative of the generalized inverse is given, we obtain the following equation

$$\begin{aligned} dJ^+(x)R(x) &= \left(\mathcal{C}(x) dJ^T(x) \left(\begin{pmatrix} \mathbb{I} & 0 \\ 0 & 0 \end{pmatrix} - (J(x)J^+(x))^T \right) - J^+(x)(dJ(x))J^+(x) \right) R(x) \\ &= \mathcal{C}(x) dJ^T(x) \left(\begin{pmatrix} \mathbb{I} & 0 \\ 0 & 0 \end{pmatrix} - (J(x)J^+(x))^T \right) (\mathbb{I} - J(x)J^+(x)) \begin{pmatrix} F_1(x) \\ 0 \end{pmatrix} \\ &= \mathcal{C}(x) dJ^T(x) (\mathbb{I} - (J(x)J^+(x))^T) \begin{pmatrix} F_1(x) \\ 0 \end{pmatrix}, \end{aligned}$$

where we used

$$\left(\begin{pmatrix} \mathbb{I} & 0 \\ 0 & 0 \end{pmatrix} - (J(x)J^+(x))^T \right) (\mathbb{I} - J(x)J^+(x)) \begin{pmatrix} F_1(x) \\ 0 \end{pmatrix} = (\mathbb{I} - (J(x)J^+(x))^T) \begin{pmatrix} F_1(x) \\ 0 \end{pmatrix}.$$

Furthermore, with

$$\mathcal{J}^{-1}(x) := \begin{pmatrix} \mathcal{C}(x) & Z^T(x) \\ Z(x) & T(x) \end{pmatrix} := \begin{pmatrix} J_1^T(x)J_1(x) & J_2^T(x) \\ J_2(x) & 0 \end{pmatrix}^{-1}$$

and $dJ^T = (dJ_1^T, dJ_2^T)$ it holds that

$$\begin{aligned} &dJ^T(x) (\mathbb{I} - (J(x)J^+(x))^T) \begin{pmatrix} F_1(x) \\ 0 \end{pmatrix} \\ &= dJ_1^T(x) \left(F_1(x) - (\mathbb{I} \ 0) \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1}(x) \begin{pmatrix} J_1^T(x)F_1(x) \\ 0 \end{pmatrix} \right) \\ &\quad + dJ_2^T(x) \left(- (0 \ \mathbb{I}) \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1}(x) \begin{pmatrix} J_1^T(x)F_1(x) \\ 0 \end{pmatrix} \right) \\ &= dJ_1^T(x) (F_1(x) - J_1(x)\mathcal{C}(x)J_1^T(x)F_1(x)) + dJ_2^T(x)\lambda(x) \\ &= dJ_1^T(x)v(x) + dJ_2^T(x)\lambda(x) \\ &= \left(\frac{\partial J_1^T(x)}{\partial x} (\mathbb{I} \otimes v(x)) + \frac{\partial J_2^T(x)}{\partial x} (\mathbb{I} \otimes \lambda(x)) \right) \Delta x. \end{aligned}$$

Therefore, we get

$$\begin{aligned} \|dJ^+(x)R(x)\| &= \|\mathcal{C}(x)E(x)\Delta x\| \\ &\leq \|\mathcal{C}(x)E(x)\| \|\Delta x\| \\ &= \tilde{\kappa} \|\Delta x\|. \end{aligned}$$

2. If we reduce D in such a way that $\mathcal{O}(\|y - x\|^2) \leq \frac{1-\tilde{\kappa}}{2}\|y - x\|$ for all x, y , it holds that

$$\begin{aligned} \|J^+(y)R(x)\| &= \tilde{\kappa} \|\Delta x\| + \mathcal{O}(\|y - x\|^2) \\ &\leq \tilde{\kappa} \|\Delta x\| + \frac{1-\tilde{\kappa}}{2} \|y - x\| \\ &= \frac{1+\tilde{\kappa}}{2} \|y - x\| \\ &=: \bar{\kappa} \|\Delta x\|, \end{aligned}$$

where $\bar{\kappa} < 1$.

3. This follows since it holds that $J_1^T(x^*)F_1(x^*) = 0$, if x^* satisfies the KKT conditions of the equality constrained parameter estimation problem (2.4.1)

■

Remark 2.6.6 *The matrix $\mathcal{C}(x)$ is a linear approximation of the covariance matrix of the parameter vector x . We define and discuss the covariance matrix in detail in Section 3.2.*

Considering the introduced κ approximation, it also depends on a deterministic part $\mathcal{C}(x^*)$ and a random part $E(x^*)$. Therefore, even in the constrained case the assumption $\kappa < 1$ holds true if the deterministic part is moderate and the random part is relatively small.

3 Sensitivity Analysis

As presented in Chapter 2, erroneous measurements are an essential part of the input data of the introduced parameter estimation problem. Thus, the whole system is affected by random events, and the resulting estimate cannot be seen as an ultimate solution. In order to be able to make any quality statements of the estimate, we have to perform a sensitivity analysis. A powerful tool to quantify the effect of the measurement errors on the estimate are confidence regions. As already mentioned in the introduction, confidence regions are regions surrounding the parameter estimate in such a way that the true parameter values lie in this region with a certain probability. In particular, in this chapter we define and analyze a new quadratic approximation of confidence regions. Most results of this chapter are also presented in Kostina and Nattermann [68].

In the first Section 3.1, we establish a first and a second order representation of the parameter vector depending on the measurement errors. Based on these representations, we compute a first and a second order approximation of the covariance matrix of the parameters in Sections 3.2 and 3.4, respectively. In Section 3.3, we deal with the theory of confidence regions. After having discussed the common approach of likelihood ratio confidence regions and linearization techniques, we define and analyze a new quadratic approximation of confidence region. Finally, we consider the shapes and approximation properties of different confidence regions by showing some comparative illustrations in Section 3.5.

3.1 Parameter Representation

First and foremost, we consider an equality constrained multiple experiment parameter estimation problem as introduced in Formula (2.4.1)

$$\begin{aligned} \min_x \quad & \frac{1}{2} \|F_1(x)\|_2^2 \\ \text{s.t.} \quad & F_2(x) = 0. \end{aligned} \tag{3.1.1}$$

The functions $F_1 : \mathbb{R}^{n_x} \rightarrow \mathbb{R}^{m_1}$ and $F_2 : \mathbb{R}^{n_x} \rightarrow \mathbb{R}^{m_2}$ consist of the experiment specific model functions,

$$F_1(x) := \begin{pmatrix} F_1^1(x_1, p) \\ \vdots \\ F_1^M(x_M, p) \end{pmatrix} \in \mathbb{R}^{m_1} \quad \text{and} \quad F_2(x) := \begin{pmatrix} F_2^1(x_1, p) \\ \vdots \\ F_2^M(x_M, p) \end{pmatrix} \in \mathbb{R}^{m_2}, \tag{3.1.2}$$

and they are assumed to be at least twice continuously differentiable with the Jacobians

$$J_1(x) = \frac{\partial F_1(x)}{\partial x} \in \mathbb{R}^{m_1 \times n_x} \text{ and } J_2(x) = \frac{\partial F_2(x)}{\partial x} \in \mathbb{R}^{m_2 \times n_x}.$$

In this section, we investigate the parameter sensitivities related to the measurement errors by computing a first and a second order representation of the unknown parameter vector as a function of an error weight $\tau \in [0, 1]$. To this end, we consider the modified problem

$$\begin{aligned} \min_{x \in \mathbb{R}^{n_x}} \quad & \frac{1}{2} \|F_1(x, \tau)\|_2^2 \\ \text{s.t.} \quad & F_2(x) = 0, \end{aligned} \tag{3.1.3}$$

where the objective function additionally depends on the weight τ . Taking (2.1.1) and (3.1.2) into account, the modified function F_1 is given block-wise by

$$F_1^k(x_k, p, \tau) := \Sigma_k^{-1} \begin{pmatrix} (h_1^k(\bar{x}_k, \bar{p}) + \tau \cdot \varepsilon_1^k) - h_1^k(x_k, p) \\ \vdots \\ (h_{m^k}^k(\bar{x}_k, \bar{p}) + \tau \cdot \varepsilon_{m^k}^k) - h_{m^k}^k(x_k, p) \end{pmatrix} \in \mathbb{R}^{m^k},$$

where \bar{x}_k denotes the true experiment specific parameter and discretization variables, and \bar{p} denotes the vector of the true global parameter values. Note that if $\tau = 0$, the solution of problem (3.1.3) corresponds to the true values $\bar{x}^T := (\bar{x}_1^T, \dots, \bar{x}_M^T, \bar{p}^T)$, and in the situation of $\tau = 1$, the initial problem (3.1.1) and the modified problem (3.1.3) have the same solution x^* . In practice we are obviously unable to use the rewritten parameter estimation problem for any value $\tau \neq 1$, and the following considerations are primarily of theoretical nature. However, through this modification we have some theoretical control over the measurement errors $\varepsilon^T := ((\varepsilon^1)^T, \dots, (\varepsilon^M)^T)$.

The first order necessary optimality conditions, combined with the constraints of problem (3.1.3) can be expressed by the condition $\mathcal{F}(x, \lambda, \tau) = 0$, where we introduced a function $\mathcal{F} : \mathbb{R}^{n_x} \times \mathbb{R}^{m_2} \times [0, 1] \rightarrow \mathbb{R}^{n_x+m_2}$ by

$$\mathcal{F}(x, \lambda, \tau) := \begin{pmatrix} J_1^T(x, \tau)F_1(x, \tau) + J_2^T(x)\lambda \\ F_2(x) \end{pmatrix}. \tag{3.1.4}$$

Thereby, the vector $\lambda \in \mathbb{R}^{m_2}$ denotes the Lagrange multiplier. Let the Jacobian of $\mathcal{F}(x, \lambda, \tau)$ with respect to x and λ be given by

$$\mathcal{J}(x, \lambda, \tau) := \partial \mathcal{F} / \partial (x, \lambda) \in \mathbb{R}^{(n_x+m_2) \times (n_x+m_2)}.$$

For simplification of notation, we introduce the following notations for our further considerations:

$$\begin{aligned} \mathcal{F}[\tau] &:= \mathcal{F}(x(\tau), \lambda(\tau), \tau), & F_1[\tau] &:= F_1(x(\tau), \tau), & F_2[\tau] &:= F_2(x(\tau)), \\ \mathcal{J}[\tau] &:= \mathcal{J}(x(\tau), \lambda(\tau), \tau), & J_1[\tau] &:= J_1(x(\tau), \tau), & J_2[\tau] &:= J_2(x(\tau)). \end{aligned}$$

Furthermore, it is also useful to introduce the diagonal matrix

$$\Sigma := \begin{pmatrix} \Sigma_1 & & \\ & \ddots & \\ & & \Sigma_M \end{pmatrix},$$

including all the experiment specific standard deviations of the measurement errors.

The following lemma gives a representation of the first derivative of the parameter vector as a function of τ . Using this derivative, we get a first order Taylor approximation of the vector x , see Bock et al. [23].

Lemma 3.1.1 (First Order Representation)

Let $x(0) = \bar{x}$ be the vector of the true parameters and assume that the Jacobians J_1 and J_2 satisfy the regularity assumptions (CQ) and (PD) in a neighborhood of \bar{x} . Then, for $\tau \in U_{\tau_0=0}$ the derivatives $\dot{x}(\tau)$ and $\dot{\lambda}(\tau)$ are uniquely defined by the system

$$\mathcal{J}[\tau] \begin{pmatrix} \dot{x}(\tau) \\ \dot{\lambda}(\tau) \end{pmatrix} = - \begin{pmatrix} J_1^T[\tau](\Sigma^{-1}\varepsilon) \\ 0 \end{pmatrix},$$

and a first order representation of the parameter vector is given by

$$\begin{aligned} x(\tau) &= x(0) + \tau \dot{x}(0) + \mathcal{O}(\tau^2) \\ &= \bar{x} + \tau J^+(\bar{x}) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} + \mathcal{O}(\tau^2). \end{aligned}$$

Proof. Let $x(\tau)$ be a solution of the modified problem with $x(\tau) \rightarrow x(0) = \bar{x}$ if $\tau \rightarrow 0$. In the case of $\tau = 0$, the true parameter vector $x(0) = \bar{x}$ is the solution of (3.1.3) and $F_1(\bar{x}, 0) = 0$. Trivially, the vector \bar{x} is a feasible point, and thus, the constraints $F_2(\bar{x}) = 0$ are fulfilled. Furthermore, it holds that $\lambda(0) = 0$, because of the regularity assumption (CQ). The Jacobian $\mathcal{J}(x, \lambda, \tau) := \partial \mathcal{F} / \partial (x, \lambda)$ of the vector-valued function $\mathcal{F}(x, \lambda, \tau)$ is explicitly given by

$$\mathcal{J}[\tau] = \begin{pmatrix} J_1^T[\tau]J_1[\tau] + \frac{\partial J_1^T}{\partial x}[\tau](\mathbb{I} \otimes F_1[\tau]) + \frac{\partial J_2^T}{\partial x}[\tau](\mathbb{I} \otimes \lambda) & J_2^T[\tau] \\ J_2[\tau] & 0 \end{pmatrix}.$$

Evaluated at $\tau = 0$, the Jacobian reduces to

$$\mathcal{J}[0] = \begin{pmatrix} J_1^T[0]J_1[0] & J_2^T[0] \\ J_2[0] & 0 \end{pmatrix},$$

and according to the regularity conditions (CQ) and (PD) it is non-singular. Thus, at $\tau_0 = 0$ the assumptions of the implicit function theorem are fulfilled, and therefore there exist a τ_0 -neighborhood U_{τ_0} , unique functions $x(\tau) : U_{\tau_0} \rightarrow \mathbb{R}^{n_x}$ and $\lambda(\tau) : U_{\tau_0} \rightarrow \mathbb{R}^{m_2}$ that satisfy the optimality condition $\mathcal{F}(x, \lambda, \tau) = 0$ and the initial conditions $x(0) = \bar{x}$ and $\lambda(0) = 0$. Moreover, a neighborhood of $\tau_0 = 0$ exists such that for all τ in this

neighborhood the derivatives $\dot{x}(\tau) := \partial x(\tau)/\partial\tau$ and $\dot{\lambda}(\tau) := \partial\lambda(\tau)/\partial\tau$ are the unique solution of the linear system

$$\mathcal{J}[\tau] \begin{pmatrix} \dot{x}(\tau) \\ \dot{\lambda}(\tau) \end{pmatrix} = -\frac{\partial\mathcal{F}[\tau]}{\partial\tau}, \text{ where } \frac{\partial\mathcal{F}[\tau]}{\partial\tau} = \begin{pmatrix} J_1^T[\tau]\Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}.$$

In particular, for $\tau = 0$ the derivative of the parameter vector is given by

$$\frac{\partial x(0)}{\partial\tau} = -J^+(\bar{x}) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}.$$

The first order representation results directly from a Taylor expansion. ■

Before we define the second order representation of the parameter vector, let us consider some useful lemmata. In the first lemma, the derivative of \mathcal{J} is given with respect to the error weight τ .

Lemma 3.1.2 *The derivative of $\mathcal{J} = \partial\mathcal{F}/\partial(x, \lambda)$ with respect to the weight τ is given by*

$$\frac{\partial\mathcal{J}[0]}{\partial\tau} = \begin{pmatrix} (dJ_1^T)J_1 + J_1^T(dJ_1) + \frac{\partial J_1^T}{\partial x}(\mathbb{I} \otimes (J_1\dot{x} + \Sigma^{-1}\varepsilon)) + \frac{\partial J_2^T}{\partial x}(\mathbb{I} \otimes \dot{\lambda}) & dJ_2^T \\ 0 & 0 \end{pmatrix},$$

where all the functions are evaluated at $\tau = 0$ and \bar{x} , respectively. The total derivatives are given by the weighted sum of the partial derivatives as

$$dJ_j(x(\tau)) = \sum_{i=1}^{n_x} \frac{\partial J_j(x(\tau))}{\partial x_i} \dot{x}_i(\tau), \quad j = 1, 2.$$

Furthermore it holds that

$$(\mathbb{I} \otimes (J_1\dot{x} + \Sigma^{-1}\varepsilon)) := \begin{pmatrix} (J_1\dot{x} + \Sigma^{-1}\varepsilon) & & 0 \\ & \ddots & \\ 0 & & (J_1\dot{x} + \Sigma^{-1}\varepsilon) \end{pmatrix} \in \mathbb{R}^{(m_1 \cdot n_x) \times n_x}$$

and

$$(\mathbb{I} \otimes \lambda) := \begin{pmatrix} \lambda & & 0 \\ & \ddots & \\ 0 & & \lambda \end{pmatrix} \in \mathbb{R}^{(m_2 \cdot n_x) \times n_x}.$$

Proof. The representation of the Jacobian follows from standard derivative rules and the relations $\mathcal{F}[0] = 0$ and $\lambda(0) = 0$. ■

The second technical lemma is used in the ongoing considerations.

Lemma 3.1.3 *Let $x(0) = \bar{x}$ be the true parameter vector and assume that the Jacobians J_1 and J_2 satisfy the regularity assumptions (CQ) and (PD) in a neighborhood of \bar{x} . Then the following relation holds for $\tau = 0$,*

$$\begin{aligned} & -(\mathbb{I} \ 0) \mathcal{J}^{-1} \frac{\partial \mathcal{J}}{\partial \tau} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1} \varepsilon \\ 0 \end{pmatrix} \\ & = \mathcal{C} (dJ^T) (\mathbb{I} - 2(JJ^+)^T) \begin{pmatrix} \Sigma^{-1} \varepsilon \\ 0 \end{pmatrix} + J^+ (dJ) (-J^+) \begin{pmatrix} \Sigma^{-1} \varepsilon \\ 0 \end{pmatrix}. \end{aligned}$$

All the functions are assumed to be evaluated at $\tau = 0$ and \bar{x} , respectively, and the total derivatives are given by the weighted sum of the partial derivatives as

$$dJ_j(x(\tau)) = \sum_{i=1}^{n_x} \frac{\partial J_j(x(\tau))}{\partial x_i} \dot{x}_i(\tau), \quad j = 1, 2,$$

and

$$\mathcal{C} := (\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix}.$$

Proof. In the following, we neglect the function arguments and all the functions are assumed to be evaluated at $\tau = 0$ and \bar{x} , respectively. By definition of J^+ we get

$$\begin{aligned} (JJ^+)^T \begin{pmatrix} \Sigma^{-1} \varepsilon \\ 0 \end{pmatrix} &= \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \begin{pmatrix} J_1^T & J_2^T \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \Sigma^{-1} \varepsilon \\ 0 \end{pmatrix} \\ &= \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & J_2^T \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \Sigma^{-1} \varepsilon \\ 0 \end{pmatrix} \\ &= \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1} \varepsilon \\ 0 \end{pmatrix}, \end{aligned} \tag{3.1.5}$$

where the last equation holds because of the multiplication with $(\varepsilon^T \Sigma^{-1}, 0^T)^T$. Now, the lemma follows after an appropriate partition of the derivative $\partial \mathcal{J} / \partial \tau$, which is given in Lemma 3.1.2. By considering that $\partial \mathcal{J} / \partial \tau$ consists of the following sum

$$\underbrace{\begin{pmatrix} (dJ_1^T) J_1 & dJ_2^T \\ 0 & 0 \end{pmatrix}}_{a)} + \underbrace{\begin{pmatrix} J_1^T (dJ_1) & 0 \\ dJ_2 & 0 \end{pmatrix}}_{b)} + \underbrace{\begin{pmatrix} \frac{\partial J_1^T}{\partial x} (\mathbb{I} \otimes (J_1 \dot{x} + \Sigma^{-1} \varepsilon)) & 0 \\ 0 & 0 \end{pmatrix}}_{c)} + \underbrace{\begin{pmatrix} \frac{\partial J_2^T}{\partial x} (\mathbb{I} \otimes \lambda) & 0 \\ 0 & 0 \end{pmatrix}}_{d)}$$

the lemma follows from the sub-items:

$$\begin{aligned} \text{a)} \quad & -(\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} (dJ_1^T) J_1 & dJ_2^T \\ 0 & 0 \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1} \varepsilon \\ 0 \end{pmatrix} \\ & = -(\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} (dJ_1^T \ dJ_2^T) \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1} \varepsilon \\ 0 \end{pmatrix} \\ & \stackrel{(3.1.5)}{=} -\mathcal{C} (dJ^T) (JJ^+)^T \begin{pmatrix} \Sigma^{-1} \varepsilon \\ 0 \end{pmatrix} \end{aligned}$$

$$\begin{aligned}
 \text{b) } & -(\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} J_1^T(dJ_1) & 0 \\ dJ_2 & 0 \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \\
 & = -(\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} dJ_1 \\ dJ_2 \end{pmatrix} (\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \\
 & = J^+(dJ)(-J^+) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}
 \end{aligned}$$

c) With $w := J_1\dot{x} + \Sigma^{-1}\varepsilon$, we have

$$\begin{aligned}
 & -(\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} \frac{\partial J_1^T}{\partial x}(\mathbb{I} \otimes (J_1\dot{x} + \Sigma^{-1}\varepsilon)) & 0 \\ 0 & 0 \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \\
 & = -(\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \underbrace{\left(\frac{\partial J_1^T}{\partial x_1}w, \dots, \frac{\partial J_1^T}{\partial x_n}w \right)}_{=-\dot{x}} (\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \\
 & = \mathcal{C} \sum_{i=1}^n \frac{\partial J_1^T}{\partial x_i} \dot{x}_i w \\
 & = \mathcal{C} dJ_1^T \left(\Sigma^{-1}\varepsilon - J_1 J^+ \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \right) \\
 & = \mathcal{C} (dJ_1^T \ 0) (\mathbb{I} - (JJ^+)^T) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \\
 \text{d) } & -(\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} \frac{\partial J_2^T}{\partial x}(\mathbb{I} \otimes \dot{\lambda}) & 0 \\ 0 & 0 \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \\
 & = -(\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \underbrace{\left(\frac{\partial J_2^T}{\partial x_1}\dot{\lambda}, \dots, \frac{\partial J_2^T}{\partial x_n}\dot{\lambda} \right)}_{=-\dot{x}} (\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \\
 & = \mathcal{C} \sum_{i=1}^n \frac{\partial J_2^T}{\partial x_i} \dot{x}_i \dot{\lambda} \stackrel{\text{Lemma 3.1.1}}{=} -\mathcal{C} (0 \ dJ_2^T) (JJ^+)^T \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}
 \end{aligned}$$

■

Remark 3.1.4 *The introduced matrix \mathcal{C} corresponds to a linear approximation of the covariance matrix of the parameters. A detailed discussion of the covariance matrix can be found in the next section.*

The following lemma gives a representation of the second derivative of the parameter vector as a function of τ . Using this derivative, we get a second order Taylor approximation of the vector x .

Lemma 3.1.5 (Second Order Representation)

Let $x(0) = \bar{x}$ be the vector of the true parameters and assume that the Jacobians J_1 and J_2 satisfy the regularity assumptions (CQ) and (PD) in a neighborhood of \bar{x} . Then, for $\tau \in U_{\tau_0=0}$ it holds that a second order Taylor expansion is given by

$$x(\tau) = x(0) + \tau \dot{x}(0) + \frac{\tau^2}{2} \ddot{x}(0) + \mathcal{O}(\tau^3),$$

where the first and the second derivatives are

$$\dot{x}(0) = - \begin{pmatrix} \mathbb{I} & 0 \end{pmatrix} \mathcal{J}^{-1}[0] \begin{pmatrix} J_1^T[0] & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} = -J^+(\bar{x}) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix},$$

and

$$\ddot{x}(0) = -2 \left(dJ^+(\bar{x}) \begin{pmatrix} \mathbb{I} - J(\bar{x})J^+(\bar{x}) \\ 0 \end{pmatrix} + \frac{1}{2} J^+(\bar{x}) (dJ(\bar{x})) (-J^+(\bar{x})) \right) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix},$$

with the total derivatives

$$dJ^+(\bar{x}) = \sum_{i=0}^n \frac{\partial J^+(\bar{x})}{\partial x_i} \dot{x}_i(0) \quad \text{and} \quad dJ(\bar{x}) = \sum_{i=0}^n \frac{\partial J(\bar{x})}{\partial x_i} \dot{x}_i(0).$$

Proof. For simplicity of notation, we omit the function arguments in this proof. In particular the functions without an argument are assumed to be evaluated at $\tau = 0$ and \bar{x} , respectively. In the proof of Lemma 3.1.1, we obtained that due to the implicit function theorem, the derivatives $\dot{x}(\tau)$ and $\dot{\lambda}(\tau)$ are defined on a domain U_{τ_0} and that they are continuously differentiable. Hence, we are able to compute the second derivative of x with respect to τ . For $\tau \in U_{\tau_0}$ we get

$$\begin{aligned} \frac{\partial^2 x(\tau)}{\partial \tau^2} &= - \frac{\partial}{\partial \tau} \left(\begin{pmatrix} \mathbb{I} & 0 \end{pmatrix} \mathcal{J}^{-1}[\tau] \begin{pmatrix} J_1^T[\tau] (\Sigma^{-1}\varepsilon) \\ 0 \end{pmatrix} \right) \\ &= \underbrace{\begin{pmatrix} \mathbb{I} & 0 \end{pmatrix} \mathcal{J}^{-1}[\tau] \frac{\partial \mathcal{J}[\tau]}{\partial \tau} \mathcal{J}^{-1}[\tau] \begin{pmatrix} J_1^T[\tau] (\Sigma^{-1}\varepsilon) \\ 0 \end{pmatrix}}_{(i)} - \underbrace{\begin{pmatrix} \mathbb{I} & 0 \end{pmatrix} \mathcal{J}^{-1}[\tau] \begin{pmatrix} \frac{\partial J_1^T[\tau]}{\partial \tau} (\Sigma^{-1}\varepsilon) \\ 0 \end{pmatrix}}_{(ii)}. \end{aligned}$$

If we restrict our considerations to $\tau = 0$ the expression (ii) may be rewritten as

$$\begin{aligned} \begin{pmatrix} \mathbb{I} & 0 \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} \frac{\partial}{\partial \tau} J_1^T (\Sigma^{-1}\varepsilon) \\ 0 \end{pmatrix} &= \begin{pmatrix} \mathbb{I} & 0 \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} dJ_1^T (\Sigma^{-1}\varepsilon) \\ 0 \end{pmatrix} \\ &= \mathcal{C}(dJ^T) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \end{aligned}$$

and correspondingly the expression (i) may be rewritten as

$$\mathcal{C}(dJ^T) \begin{pmatrix} \mathbb{I} - 2(JJ^+)^T \\ 0 \end{pmatrix} \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} + J^+(dJ)(-J^+) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}$$

according to Lemma 3.1.3. Altogether we obtain

$$\frac{\partial^2 x(\tau)}{\partial \tau^2} = 2 \left(\mathcal{C}(dJ^T) (\mathbb{I} - (JJ^+)^T) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} + \frac{1}{2} J^+ (dJ) (-J^+) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \right).$$

Recognizing Lemma 6.3.5 where the derivative of the generalized inverse J^+ is discussed, and since

$$(\mathbb{I} - (JJ^+)^T) (\mathbb{I} - JJ^+) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} = (\mathbb{I} - (JJ^+)^T) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}$$

and $J^+(\mathbb{I} - JJ^+) = 0$, we get that

$$\ddot{x}(0) = -2 \left((dJ^+(\bar{x})) (\mathbb{I} - J(\bar{x})J^+(\bar{x})) + \frac{1}{2} J^+(\bar{x}) (dJ(\bar{x})) (-J^+(\bar{x})) \right) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}.$$

The second order representation follows directly from a Taylor expansion. ■

Thus, a second order representation of the parameter vector depends on the Jacobian J , the generalized inverse J^+ , the second derivative dJ and the weighted measurement errors. Note that as a result of Lemma 6.3.5 dJ is the only second derivative that is needed. Especially in the context of the design of optimal experiments, where we also need the second derivative dJ , every matrix function of the second order representation from Lemma 3.1.5 is already known.

The Second Order Representation and the Lipschitz Constants κ and ω

There exists a remarkable relation between the introduced second order parameter representation and the Lipschitz constants κ and ω , which are widely discussed in Section 2.6. Considering the second order representation in any arbitrary norm, the triangular inequality yields

$$\begin{aligned} \frac{1}{2} \|\ddot{x}(0)\| &\leq \left\| dJ^+(\bar{x}) (\mathbb{I} - J(\bar{x})J^+(\bar{x})) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \right\| \\ &\quad + \frac{1}{2} \left\| J^+(\bar{x}) (dJ(\bar{x})) (-J^+(\bar{x})) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \right\|. \end{aligned} \tag{3.1.6}$$

Obviously, we do not know the true parameter vector \bar{x} in practice. If we take the estimate x^* instead, assuming that it is a good approximation of the true values, the first expression of the right hand side can be interpreted by using Lemma 2.6.5. According to this lemma, it holds that

$$\begin{aligned} \left\| dJ^+(\bar{x}) (\mathbb{I} - J(\bar{x})J^+(\bar{x})) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \right\| &= \|dJ^+(\bar{x})R(\bar{x})\| \\ &\leq \tilde{\kappa}(\bar{x}) \|\Delta x\| \\ &\approx \tilde{\kappa}(x^*) \|\Delta x\|, \end{aligned}$$

where

$$R(\bar{x}) := (\mathbb{I} - J(\bar{x})J^+(\bar{x})) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}.$$

Note that $\Sigma^{-1}\varepsilon = F_1(\bar{x})$. The second expression of (3.1.6) can be estimated by

$$\begin{aligned} \frac{1}{2} \left\| J^+(\bar{x})(dJ(\bar{x}))(-J^+(\bar{x})) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \right\| &\leq \frac{1}{2} \left\| J^+(\bar{x})(dJ(\bar{x})) \right\| \|\Delta x\| \\ &\leq \frac{1}{2} \left\| J^+(\bar{x}) \frac{\partial J(\bar{x})}{\partial x} \right\| \|\Delta x\|^2 \\ &=: \tilde{\omega}(\bar{x}) \|\Delta x\|^2 \\ &\approx \tilde{\omega}(x^*) \|\Delta x\|^2, \end{aligned}$$

where we defined $\tilde{\omega}(x^*)$ in a similar way to ω of the *Local Contraction Theorem* 2.5.1 by

$$\tilde{\omega}(x^*) := \left\| J^+(x^*) \frac{\partial J(x)}{\partial x} \right\|.$$

Thus, we get the following bound for the second derivative of the parameter values:

$$\frac{1}{2} \|\ddot{x}(0)\| \lesssim \left(\tilde{\kappa}(x^*) + \frac{\tilde{\omega}(x^*)}{2} \|\Delta x\| \right) \|\Delta x\|.$$

The bound depends on $\tilde{\kappa}$ as well as on $\tilde{\omega}$ with a squared weight $\|\Delta x\|^2$. Basically $\tilde{\omega}$ consists of the second derivative of the problem functions and can be seen as a measure of the nonlinearity of the problem. Hence, the second derivative is bounded by a combination of the nonlinearity and the prior input error.

Considering once again Theorem 2.5.1, we observe that the second derivative is bounded by the convergence rate of the *Gauss-Newton* method. We take a closer look to this in Chapter 4 in which we deal with the design of optimal experiments.

3.2 The Linear Covariance Matrix

In this section, we consider the distribution of the parameter estimate x^* related to the measurement errors. Furthermore, we investigate a linear approximation of the covariance matrix.

In Lemma 3.1.1 of the previous section, we deduced a first-order Taylor series of x as a function of the error weight by

$$x(\tau) = \bar{x} + \tau \frac{\partial x(0)}{\partial \tau} + \mathcal{O}(\tau^2) = \bar{x} - \tau J^+(\bar{x}) \begin{pmatrix} -\Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} + \mathcal{O}(\tau^2). \quad (3.2.1)$$

Bearing in mind that the measurement errors are assumed to be independent and normally distributed with zero mean and the standard deviations σ_i^k , $i = 1, \dots, m^k$, for all experiments $k = 1, \dots, M$, the first-order approximation of $x(\tau)$ is also normally distributed and for full measurement errors ($\tau = 1$) we obtain the expected value

$$\begin{aligned} \mathbb{E}(x(\tau)) \Big|_{\tau=1} &= \bar{x} + \mathbb{E} \left(\frac{\partial x(0)}{\partial \tau} \right) \\ &= \bar{x} - J^+(\bar{x}) \begin{pmatrix} -\Sigma^{-1} \mathbb{E}(\varepsilon) \\ 0 \end{pmatrix} = \bar{x} \end{aligned}$$

Hence, the variance-covariance matrix is given by

$$\begin{aligned} \bar{\mathcal{C}}(\tau) \Big|_{\tau=1} &= \mathbb{E} \left[\left(x(\tau) - \mathbb{E}(x(\tau)) \right) \left(x(\tau) - \mathbb{E}(x(\tau)) \right)^T \right] \Big|_{\tau=1} \\ &= \mathbb{E} \left[J^+(\bar{x}) \begin{pmatrix} \Sigma^{-1} \varepsilon \\ 0 \end{pmatrix} \left(\varepsilon^T \Sigma^{-1} \quad 0 \right) J^{+T}(\bar{x}) \right] \\ &= J^+(\bar{x}) \begin{pmatrix} \mathbb{I}_{m_1} & 0 \\ 0 & 0_{m_2} \end{pmatrix} J^{+T}(\bar{x}). \end{aligned}$$

For simplicity we will abbreviate variance-covariance matrix to covariance matrix in our further considerations. In practice we use the estimate x^* for the computation of the covariance matrix instead of the unknown parameter vector \bar{x} . This is justified by the expectation that the solution of the generalized *Gauss-Newton* method is a suitable approximation of the true values \bar{x} . Thus, in our further considerations we use the covariance matrix

$$\mathcal{C} := J^+(x^*) \begin{pmatrix} \mathbb{I}_{m_1} & 0 \\ 0 & 0_{m_2} \end{pmatrix} J^{+T}(x^*). \quad (3.2.2)$$

This matrix is symmetric, positive semi-definite, and its rank is given by $\text{rank}(\mathcal{C}) = \bar{m} := n_x - m_2$.

Remark 3.2.1 *So far, we rely on the assumption of independent and normally distributed measurement errors ε_i^k with a zero mean and variances $(\sigma_i^k)^2$, $i = 1, \dots, m^k$, for $k = 1, \dots, M$. In many cases, the exact variances are unknown, but rather up to a common factor β^2 , e.g. $\sigma^2 = \beta^2 \bar{\sigma}^2$. This circumstance has no effect on the estimate x^* . Nevertheless, for the covariance matrix it holds that*

$$\mathcal{C} := \beta^2 J^+(x^*) \begin{pmatrix} \mathbb{I}_{m_1} & 0 \\ 0 & 0_{m_2} \end{pmatrix} J^{+T}(x^*).$$

As developed by Bard [10],

$$\beta^2 = \frac{\|F_1(x^*)\|_2^2}{m_1 - (n_x - m_2)}$$

is a general-purpose estimate of the common factor.

In our further considerations we neglect the common factor and we use the representation (3.2.2).

Remark 3.2.2 *The covariance matrix of an unconstrained parameter estimation problem*

$$\min_x \frac{1}{2} \|F_1(x)\|_2^2,$$

is given by

$$\mathcal{C} = J^+(x^*)J^{+T}(x^*) = (J_1^T(x^*)J_1(x^*))^{-1} \quad (3.2.3)$$

and it is the inverse of the so called Fisher information matrix, see e.g. van Trees [106].

3.3 Confidence Regions

In this section, we consider confidence regions to investigate the statistical accuracy of an estimate x^* . As already mentioned, the idea of confidence regions is to define a region around the nominal parameters x^* , in such a way that the true parameter values \bar{x} lie in this region with a certain probability level $1 - \alpha$, where $0 \leq \alpha \leq 1$. However, as explained by Pázman [86], $\mathcal{D}(\eta, \alpha)$ denotes a confidence region, if the equality

$$\mathbb{P}(\bar{x} \in \mathcal{D}(\eta, \alpha)) = 1 - \alpha, \quad (3.3.1)$$

or at least the inequality

$$\mathbb{P}(\bar{x} \in \mathcal{D}(\eta, \alpha)) \geq 1 - \alpha \quad (3.3.2)$$

holds, for given measurements η . Basically, there are several possibilities to construct a confidence region, but some further requirements are favorable. On the one hand, confidence regions should be numerically well tractable. This means that the computation should be easy, fast and especially not error-prone. On the other hand, the confidence region should be as accurate as possible, which means as small as possible in regard of (3.3.1) or at least (3.3.2).

First of all, we consider common techniques to define and approximate confidence regions as well as their advantages and disadvantages. Subsequently, we define and analyze a new quadratic approximation of confidence regions.

3.3.1 Likelihood Ratio Confidence Regions

Considering an unconstrained parameter estimation problem, where we are confronted with the task

$$\min_{x \in \mathbb{R}^n} \frac{1}{2} \|F_1(x)\|_2^2, \quad (3.3.3)$$

a nonlinear likelihood ratio confidence region for an estimate x^* is given by the following definition, see e.g. Beale [14], Draper and Smith [43], and Pázman [86].

Definition 3.3.1 Suppose that x^* is a solution of problem (3.3.3). Then

$$\mathcal{DU}_{lr}(\alpha) = \left\{ x \in D \mid \|F_1(x)\|_2^2 - \|F_1(x^*)\|_2^2 \leq \gamma_{n_x}^2(\alpha) \right\}, \quad (3.3.4)$$

defines a nonlinear confidence region, where $\gamma_{n_x}^2(\alpha)$ is defined by

- the $(1 - \alpha)$ -quantile of the χ^2 -distribution if the standard deviations σ_i^k of the measurement errors are known;
- the $(1 - \alpha)$ -quantile of the F -distribution $F_{n_x, m_1 - n_x}$ if the standard deviations σ_i^k of the measurement errors are unknown. More precisely, it holds that $\gamma_{n_x}^2(\alpha) := s^2 \cdot n_x \cdot F_{n_x, m_1 - n_x}$, where

$$s^2 := \frac{\|F_1(x^2)\|_2^2}{m_1 - n_x}. \quad (3.3.5)$$

An asymptotic justification of the confidence region (3.3.4) can be derived by a simple likelihood ratio test, by testing a hypothesis x^* against another hypothesis $x \neq x^*$. This test results in a log-proportional expression like $\|F_1(x)\|_2^2 - \|F_1(x^*)\|_2^2$. Taking into account that the measurement errors are independent and normally distributed, we asymptotically get (3.3.4), see Pázman [86].

As explained by Seber and Wild [102] and Bates and Watts [11], the introduced confidence region may be unbounded or disjoint. The latter can occur if multiple local minima are present in the nonlinear parameter estimation, and the same contour value of the likelihood function occurs around the local minima.

The definition of the nonlinear confidence region can be adapted to constrained parameter estimation problems (3.1.1), see Bock [19].

Definition 3.3.2 Suppose that x^* is a solution of the equality constrained parameter estimation problem (3.1.1). Then, the nonlinear likelihood ratio confidence region is defined by

$$\mathcal{D}_{lr}(\alpha) := \left\{ x \in D \mid F_2(x) = 0, \|F_1(x)\|_2^2 - \|F_1(x^*)\|_2^2 \leq \gamma_{\bar{m}}^2(\alpha) \right\}, \quad (3.3.6)$$

where $\gamma_{\bar{m}}^2(\alpha)$ is defined as in Definition 3.3.1, and $\bar{m} := n_x - m_2$ denotes the number of degrees of freedom.

However, the introduced likelihood ratio confidence regions can—even in the unconstrained case—be accepted as the true confidence region. The adequate approximation properties of the likelihood ratio confidence regions must be paid by a huge complexity and a very high computational effort, especially in highly nonlinear cases. The computation of (3.3.6), or at least of some appropriate bounds, requires the solution of a nonlinear equation with \bar{m} degrees of freedom. Due to this fact likelihood ratio confidence regions are impracticable for many applications, see e.g. Vanrolleghem and Keesman [108].

3.3.2 Linearized Confidence Regions

To counteract the high computational effort of likelihood ratio confidence regions, a common approach of quantifying the statistical accuracy of an estimate x^* is to apply linearization techniques, see e.g. Bock [19], Draper and Smith [43], Pázmán [86], and Seber and Wild [102]. The following linearized confidence region results from a first order Taylor expansion on the nonlinear region $\mathcal{D}_{lr}(\alpha)$.

Definition 3.3.3 *Suppose that x^* is a solution of the equality constrained parameter estimation problem (3.1.1). Then, a linearized confidence region is given by*

$$\begin{aligned} \mathcal{D}_{lin}(\alpha) := \{x \in D \mid F_2(x^*) + J_2(x^*)(x - x^*) = 0, \\ \|F_1(x^*) + J_1(x^*)(x - x^*)\|_2^2 - \|F_1(x^*)\|_2^2 \leq \gamma_{\bar{m}}^2(\alpha)\}, \end{aligned}$$

where $\gamma_{\bar{m}}^2(\alpha)$ is defined as in Definition 3.3.1 and \bar{m} as in Definition 3.3.2.

If we take into account that x^* is a feasible point—and therefore $F_2(x^*) = 0$ —as well as $J_1^T(x^*)F_1(x^*) = 0$ due to the optimality conditions of x^* , we can rewrite $\mathcal{D}_{lin}(\alpha)$ as

$$\mathcal{D}_{lin}(\alpha) := \{x \in D \mid J_2(x^*)(x - x^*) = 0, \|J_1(x^*)(x - x^*)\|_2^2 \leq \gamma_{\bar{m}}^2(\alpha)\}. \quad (3.3.7)$$

By means of a linearization of the likelihood ratio confidence region in the unconstrained case we get

$$\mathcal{DU}_{lin}(\alpha) := \{x \in D \mid \|J_1(x^*)(x - x^*)\|_2^2 \leq \gamma_{n_x}^2(\alpha)\}, \quad (3.3.8)$$

and the meaning of $\gamma_{n_x}^2(\alpha)$ remains unaffected.

As it can be found in Bock [19], another approach to perform a linear sensitivity analysis is based on the *Gauss-Newton* solution operator J^+ , by using the first-order, error-depending representation of x , as given in Lemma 3.1.1.

Definition 3.3.4 *Suppose that x^* is the solution of the equality constrained parameter estimation problem (3.1.1), and the Jacobians J_1 and J_2 satisfy the regularity assumptions (CQ) and (PD) in x^* . Then, a linear confidence region is given by*

$$\bar{\mathcal{D}}_{lin}(\alpha) := \left\{ x^* + \Delta x \mid \Delta x = -J^+(x^*) \begin{pmatrix} \eta \\ 0 \end{pmatrix}, \|\eta\|_2^2 \leq \gamma_{\bar{m}}^2(\alpha) \right\}, \quad (3.3.9)$$

where $\gamma_{\bar{m}}^2(\alpha)$ is defined as in Definition 3.3.1 and \bar{m} as in Definition 3.3.2.

In the next lemma we show that both linear confidence regions $\mathcal{D}_{lin}(\alpha)$ and $\bar{\mathcal{D}}_{lin}(\alpha)$ are equal, see Bock et al. [23].

Lemma 3.3.5 *Under the assumptions of Definition 3.3.4, it holds that*

$$\mathcal{D}_{lin}(\alpha) = \bar{\mathcal{D}}_{lin}(\alpha).$$

Proof. First of all we show the inclusion $\mathcal{D}_{lin}(\alpha) \subseteq \overline{\mathcal{D}}_{lin}(\alpha)$:

Suppose that $x \in \mathcal{D}_{lin}(\alpha)$, and $\Delta x := x - x^*$ and let $\eta = -J_1(x^*)\Delta x$. Thus, it holds that $\|\eta\|_2^2 \leq \gamma_{\overline{m}}^2(\alpha)$, because of

$$\|\eta\|_2^2 = \|-J_1(x^*)\Delta x\|_2^2 = \|-J_1(x^*)(x - x^*)\|_2^2 \stackrel{(3.3.7)}{\leq} \gamma_{\overline{m}}^2(\alpha).$$

Since the regularity conditions (CQ) and (PD) are fulfilled, the generalized inverse J^+ exists and we obtain

$$\begin{aligned} \Delta x &= J^+(x^*) \begin{pmatrix} J_1(x^*) \\ J_2(x^*) \end{pmatrix} \Delta x \\ &= J^+(x^*) \begin{pmatrix} J_1(x^*)\Delta x \\ 0 \end{pmatrix} \\ &= -J^+(x^*) \begin{pmatrix} \eta \\ 0 \end{pmatrix}. \end{aligned}$$

Thus, $x \in \overline{\mathcal{D}}_{lin}(\alpha)$ and therefore $\mathcal{D}_{lin}(\alpha) \subseteq \overline{\mathcal{D}}_{lin}(\alpha)$.

In order to verify the other inclusion $\overline{\mathcal{D}}_{lin}(\alpha) \subseteq \mathcal{D}_{lin}(\alpha)$, let $x \in \overline{\mathcal{D}}_{lin}(\alpha)$. Per definition of J^+ , the vector Δx solves the linear system

$$\begin{aligned} J_1^T(x^*)J_1(x^*)\Delta x + J_2^T(x^*)\lambda &= -J_1^T(x^*)\eta \\ J_2(x^*)\Delta x &= 0 \end{aligned}$$

for a certain vector λ . Then we get

$$\begin{aligned} (\eta + J_1(x^*)\Delta x)^T J_1(x^*)\Delta x &= \eta^T J_1(x^*)\Delta x + \Delta x^T J_1^T(x^*)J_1(x^*)\Delta x \\ &= -\lambda^T J_2(x^*)\Delta x \\ &= 0, \end{aligned}$$

and for $\|\eta + J_1(x^*)\Delta x\|_2^2$ it follows that

$$\begin{aligned} 0 &\leq \|\eta + J_1(x^*)\Delta x\|_2^2 \\ &= \|\eta\|_2^2 + 2\eta^T J_1(x^*)\Delta x + \Delta x^T J_1(x^*)^T J_1(x^*)\Delta x \\ &= \|\eta\|_2^2 - 2\Delta x^T J_1(x^*)^T J_1(x^*)\Delta x + \Delta x^T J_1(x^*)^T J_1(x^*)\Delta x \\ &= \|\eta\|_2^2 - \|J_1(x^*)(x - x^*)\|_2^2. \end{aligned}$$

Hence, it holds that $\|J_1(x^*)(x - x^*)\|_2^2 \leq \|\eta\|_2^2 \leq \gamma_{\overline{m}}^2(\alpha)$, which means that $x \in \mathcal{D}_{lin}(\alpha)$. ■

Thus, the properties of confidence region (3.3.7) can be adapted to the region (3.3.9). The following lemma can be found in Bock et al. [23], and it shows that the exact bounds on the region (3.3.9) are related to the diagonal elements of the covariance matrix (3.2.2).

Lemma 3.3.6 *Let x^* be a solution of the equality constrained parameter estimation problem (3.1.1) and assume that the Jacobians J_1 and J_2 satisfy the regularity assumptions (CQ) and (PD) in x^* . Then $\mathcal{D}_{lin}(\alpha)$ is contained in a minimal box defined by the cross product of the confidence intervals*

$$\mathcal{D}_{lin}(\alpha) \subset \prod_{i=1}^{n_x} [x_i^* - \theta_i, x_i^* + \theta_i], \quad (3.3.10)$$

where $\theta_i = \sqrt{C_{ii}\gamma_m^2(\alpha)}$. The constants C_{ii} denote the diagonal elements of the covariance matrix \mathcal{C} . Furthermore, it holds that

$$\max_{x \in \mathcal{D}_{lin}(\alpha)} |x_i - x_i^*| = \theta_i, \quad i = 1, \dots, n_x.$$

Proof. Each component $x \in \mathcal{D}_{lin}(\alpha)$ satisfies the estimate

$$|\Delta x_i|^2 = \left| e_i^T J^+(x^*) \begin{pmatrix} \eta \\ 0 \end{pmatrix} \right|^2 \leq \|e_i^T J^+(x^*) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix}\|_2^2 \cdot \|\eta\|_2^2 \leq C_{ii}^2 \cdot \gamma_m^2(\alpha). \quad (3.3.11)$$

In order to show that this bound is exact, we determine the maximum value of $|\Delta x_i|^2$. Therefore, we consider the optimization problem

$$\begin{aligned} \max_{\eta} & \left| e_i^T J^+(x^*) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \eta \right|^2 \\ \text{s.t.} & \|\eta\|_2^2 \leq \gamma_m^2(\alpha). \end{aligned}$$

The solution of this problem is

$$\eta^{*T} = \frac{\gamma_m(\alpha) e_i^T J^+(x^*) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix}}{\|e_i^T J^+(x^*) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix}\|_2},$$

and the corresponding value of the objective function is

$$\gamma_m^2(\alpha) \|e_i^T J^+(x^*) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix}\|_2^2 = C_{ii}^2 \gamma_m^2(\alpha),$$

where C_{ii} denotes the i -th diagonal element of the linear approximation of the covariance matrix. Consequently the equality in (3.3.11) is shown. ■

As a result of Lemma 3.3.6, it suffices to compute the diagonal elements of the covariance matrix to perform a first-order sensitivity analysis.

The shape of the linearized confidence region is characterized by an ellipsoid and its computation is very cheap. In the case of linear observation functions h^k , these regions are

optimal in the sense that they have a minimal volume with a confidence level exactly equal to $(1 - \alpha)$. However, this holds only for the linear case, and in literature many nonlinear applications can be found in which the elliptical regions are poor approximations, see e.g. Donaldson and Schnabel [41], Rooney and Biegler [94], Schwaab et al. [101], and Wiechert et al. [110].

3.3.3 A Quadratic Approximation of Confidence Regions

To pursue the idea of the linearized region (3.3.9), we introduce a quadratic approximation of confidence regions based on the second order representation of the parameter vector depending on the measurement errors. Considering Lemma 3.1.5, a quadratic approximation of confidence regions is defined as follows.

Definition 3.3.7 *Let x^* be the solution of the equality constrained parameter estimation problem (3.1.1) and assume that the Jacobians J_1 and J_2 satisfy the regularity assumptions (CQ) and (PD) in x^* . Then, a quadratic approximation of a confidence region is defined by*

$$\begin{aligned} \overline{\mathcal{D}}_{quad}(\alpha) &:= \left\{ x^* + \Delta x + \frac{1}{2} \overline{\Delta x} \mid \Delta x = -J^+ \begin{pmatrix} \eta \\ 0 \end{pmatrix}, \right. \\ &\quad \left. \overline{\Delta x} = -2 \left(dJ^+(\mathbb{I} - JJ^+) - \frac{1}{2} J^+(dJ)J^+ \right) \begin{pmatrix} \eta \\ 0 \end{pmatrix}, \|\eta\|_2^2 \leq \gamma_{\overline{m}}^2(\alpha) \right\}, \end{aligned}$$

where all the functions are evaluated at x^* , and the total derivatives are given by the sum of the weighted partial derivatives

$$\begin{aligned} dJ(x^*) &= \frac{\partial J(x^*)}{\partial x} (\Delta x \otimes \mathbb{I}) = \sum_{i=1}^{n_x} \frac{\partial J(x^*)}{\partial x_i} (e_i^T \Delta x), \\ dJ^+(x^*) &= \frac{\partial J^+(x^*)}{\partial x} (\Delta x \otimes \mathbb{I}) = \sum_{i=1}^{n_x} \frac{\partial J^+(x^*)}{\partial x_i} (e_i^T \Delta x). \end{aligned}$$

If the standard deviations σ_i^k are known, $\gamma_{\overline{m}}^2(\alpha)$ is the $(1 - \alpha)$ -quantile of the χ^2 -distribution, and if the values σ_i^k are unknown, it holds that $\gamma_{\overline{m}}^2(\alpha) := s^2 \cdot n_x \cdot F_{n_x, m_1 - n_x}$, where $F_{n_x, m_1 - n_x}$ is the $(1 - \alpha)$ -quantile of the F-distribution and

$$s^2 := \frac{\|F_1(x^2)\|_2^2}{m_1 - n_x}. \quad (3.3.12)$$

We want to remark that the derivative of the Jacobian J is the only second derivative, that is needed to compute the quadratic approximation of confidence regions. The derivative of the generalized inverse J^+ is explicitly given in Lemma 6.3.5 and it basically consists of J , J^+ and dJ .

For the sake of completeness, we want to note that the new confidence region is also suitable for the case of an unconstrained parameter estimation problem, as given in (3.3.3). Here, a quadratic approximation of confidence regions is given by

$$\begin{aligned} \overline{\mathcal{D}\mathcal{U}}_{quad}(\alpha) := & \left\{ x^* + \Delta x + \frac{1}{2} \overline{\Delta x} \mid \Delta x = -J^+ \eta, \right. \\ & \left. \overline{\Delta x} = -2 \left(dJ^+ (\mathbb{I} - J_1 J^+) - \frac{1}{2} J^+ (dJ_1) J^+ \right) \eta, \|\eta\|_2^2 \leq \gamma_{n_x}^2(\alpha) \right\}, \end{aligned} \quad (3.3.13)$$

where $J^+ = (J_1^T J_1)^{-1} J_1^T$ is a Moore-Penrose pseudo-inverse and all the functions are assumed to be evaluated at the estimate x^* .

In the following, we investigate and analyze the properties of the confidence region introduced above. The first lemma yields exact bounds for each component of the quadratic part of the quadratically approximated confidence region.

Lemma 3.3.8 *Let x^* be a solution of the equality constrained parameter estimation problem (3.1.1) and assume that the Jacobians J_1 and J_2 satisfy the regularity assumptions (CQ) and (PD) in x^* . Then for $j = 1, \dots, n_x$ it holds that*

$$\max_{\|\eta\|_2^2 \leq \gamma_m^2(\alpha)} \frac{1}{2} \overline{\Delta x}_j = \mu^* \gamma_m^2(\alpha),$$

where μ^* is the maximum eigenvalue of the symmetric matrix $-\frac{1}{2} \sum_{i=1}^{n_x} (r_{j,i} c_i^T + c_i r_{j,i}^T)$ with

$$\begin{aligned} c_i^T &:= e_i^T (-J^+) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \\ r_{j,i}^T &:= -e_j^T \left(\frac{\partial J^+}{\partial x_i} (\mathbb{I} - J J^+) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} + \frac{1}{2} J^+ \frac{\partial J}{\partial x_i} (-J^+) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \right), \end{aligned}$$

and all the functions are assumed to be evaluated at x^* .

Proof. It holds that

$$\begin{aligned} \frac{1}{2} \overline{\Delta x} &= - \left(dJ^+ (\mathbb{I} - J J^+) \begin{pmatrix} \eta \\ 0 \end{pmatrix} + \frac{1}{2} J^+ (dJ) (-J^+) \begin{pmatrix} \eta \\ 0 \end{pmatrix} \right) \\ &= - \sum_{i=1}^{n_x} \left(\frac{\partial J^+}{\partial x_i} \dot{x}_i (\mathbb{I} - J J^+) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} + \frac{1}{2} J^+ \frac{\partial J}{\partial x_i} \dot{x}_i (-J^+) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \right) \eta \\ &= - \sum_{i=1}^{n_x} \left(\frac{\partial J^+}{\partial x_i} (\mathbb{I} - J J^+) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} + \frac{1}{2} J^+ \frac{\partial J}{\partial x_i} (-J^+) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \right) (c_i^T \eta) \eta, \end{aligned}$$

where we used that $\dot{x}_i = -e_i^T J^+ \begin{pmatrix} \eta \\ 0 \end{pmatrix} = c_i^T \eta$. Hence, it follows

$$\begin{aligned} \frac{1}{2} \overline{\Delta x}_j &= \sum_{i=1}^{n_x} -e_j^T \left(\frac{\partial J^+}{\partial x_i} (\mathbb{I} - J J^+) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} + \frac{1}{2} J^+ \frac{\partial J}{\partial x_i} (-J^+) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \right) (c_i^T \eta) \eta \\ &= \sum_{i=1}^{n_x} (r_{j,i}^T \eta) (c_i^T \eta). \end{aligned}$$

In order to find the maximum $\max_{\|\eta\|_2^2 \leq \gamma_m^2(\alpha)} \frac{1}{2} \overline{\Delta x}_j$, we consider the Lagrangian

$$\mathcal{L}(\eta, \mu) = - \sum_{i=1}^{n_x} (r_{j,i}^T \eta)(c_i^T \eta) - \mu(\gamma_m^2(\alpha) - \eta^T \eta)$$

and the necessary optimality condition

$$0 = \frac{\partial \mathcal{L}(\eta, \mu)}{\partial \eta} = \left(- \sum_{i=1}^{n_x} (r_{j,i} c_i^T + c_i r_{j,i}^T) + 2\mu \mathbb{I} \right) \eta.$$

Thus, we obtain that the matrix $- \sum_{i=1}^{n_x} (r_{j,i} c_i^T + c_i r_{j,i}^T)$ has an eigenvalue 2μ with the corresponding eigenvector η . Furthermore, the necessary optimality condition yields

$$\begin{aligned} 0 &= \left(- \sum_{i=1}^{n_x} (r_{j,i} c_i^T + c_i r_{j,i}^T) + 2\mu \mathbb{I} \right) \eta \\ \iff 0 &= - \sum_{i=1}^{n_x} \left((\eta^T r_{j,i})(c_i^T \eta) + (\eta^T c_i)(r_{j,i}^T \eta) \right) + 2\mu \eta^T \eta \\ \iff 2\mu \gamma_m^2(\alpha) &= 2 \sum_{i=1}^{n_x} (\eta^T r_{j,i})(c_i^T \eta) \end{aligned}$$

and we have

$$\max_{\|\eta\|_2^2 \leq \gamma_m^2(\alpha)} \frac{1}{2} \overline{\Delta x}_j = \mu^* \gamma_m^2(\alpha),$$

where μ^* is the maximum eigenvalue of the matrix

$$- \sum_{i=1}^{n_x} (r_{j,i} c_i^T + c_i r_{j,i}^T).$$

■

In the following lemma we introduce bounds for each component of the elements of the quadratically approximated confidence region.

Lemma 3.3.9 *Let x^* be a solution of the equality constrained parameter estimation problem (3.1.1) and assume that the Jacobians J_1 and J_2 satisfy the regularity assumptions (CQ) and (PD) in x^* . Then $\overline{\mathcal{D}}_{quad}(\alpha)$ is contained in a box defined by the cross product of the confidence intervals*

$$\overline{\mathcal{D}}_{quad}(\alpha) \subset \bigtimes_{i=1}^{n_x} [x_i^* - \theta_i, x_i^* + \theta_i],$$

where

$$\theta_i = \sqrt{\mathcal{C}_{ii}}\gamma_{\bar{m}}(\alpha) + \sum_{k=1}^{n_x} \sqrt{\left(\tilde{J}_k \tilde{J}_k^T\right)_{ii}} \cdot \sqrt{\mathcal{C}_{kk}}\gamma_{\bar{m}}^2(\alpha),$$

with

$$\tilde{J}_k := \frac{\partial J^+(x^*)}{\partial x_k} (\mathbb{I} - J(x^*)J^+(x^*)) - \frac{1}{2} J^+(x^*) \frac{\partial J(x^*)}{\partial x_k} J^+(x^*).$$

The value \mathcal{C}_{ii} denotes the i -th the diagonal element of the covariance matrix \mathcal{C} , $i = 1, \dots, n_x$. Here, all the matrix functions are assumed to be evaluated at the solution x^* .

Proof. The lemma follows from the following relations

$$\begin{aligned} \left| \Delta x_i + \frac{1}{2} \overline{\Delta x}_i \right| &= \left| e_i^T J^+ \begin{pmatrix} \eta \\ 0 \end{pmatrix} + e_i^T \left(dJ^+(\mathbb{I} - JJ^+) - \frac{1}{2} J^+ dJJ^+ \right) \begin{pmatrix} \eta \\ 0 \end{pmatrix} \right| \\ &\leq \left| e_i^T J^+ \begin{pmatrix} \eta \\ 0 \end{pmatrix} \right| + \left| e_i^T \left(dJ^+(\mathbb{I} - JJ^+) - \frac{1}{2} J^+ dJJ^+ \right) \begin{pmatrix} \eta \\ 0 \end{pmatrix} \right| \\ &\leq \|e_i^T J^+\|_2 \|\eta\|_2 + \left\| e_i^T \left(dJ^+(\mathbb{I} - JJ^+) - \frac{1}{2} J^+ dJJ^+ \right) \right\|_2 \|\eta\|_2 \\ &\leq \sqrt{\mathcal{C}_{ii}} \cdot \gamma_{\bar{m}}(\alpha) + \left\| e_i^T \sum_{k=1}^{n_x} \left(\frac{\partial J^+}{\partial x_k} (\mathbb{I} - JJ^+) - \frac{1}{2} J^+ \frac{\partial J}{\partial x_k} J^+ \right) \dot{x}_k \right\|_2 \|\eta\|_2 \\ &\leq \sqrt{\mathcal{C}_{ii}} \cdot \gamma_{\bar{m}}(\alpha) + \sum_{k=1}^{n_x} \left\| e_i^T \tilde{J}_k \right\|_2 \left| e_k^T J^+ \begin{pmatrix} \eta \\ 0 \end{pmatrix} \right| \cdot \gamma_{\bar{m}}(\alpha) \\ &\leq \sqrt{\mathcal{C}_{ii}} \cdot \gamma_{\bar{m}}(\alpha) + \sum_{k=1}^{n_x} \sqrt{\left(\tilde{J}_k \tilde{J}_k^T\right)_{ii}} \sqrt{\mathcal{C}_{kk}} \cdot \gamma_{\bar{m}}^2(\alpha), \end{aligned}$$

where all the functions are assumed to be evaluated at x^* . ■

The next lemma provides a further estimation of the new confidence region by using the introduced components $\tilde{\omega}$ and $\tilde{\kappa}$.

Lemma 3.3.10 *Under the assumptions of Lemma 3.3.9 the following inequality holds*

$$\left\| \Delta x + \frac{1}{2} \overline{\Delta x} \right\|_2 \leq \theta + (\tilde{\kappa}(x^*) + \frac{1}{2} \tilde{\omega}(x^*)\theta)\theta.$$

The value of θ is defined by $\theta := \sqrt{\text{trace}(\mathcal{C}(x^*))\gamma_{\bar{m}}^2(\alpha)}$, where $\mathcal{C}(x^*)$ denotes the linear approximation of the covariance matrix, and $\tilde{\kappa}(x^*)$ and $\tilde{\omega}(x^*)$ are given by

$$\begin{aligned} \tilde{\kappa}(x^*) &:= \|\mathcal{C}(x^*)E(x^*)\|, \\ \tilde{\omega}(x^*) &:= \left\| J^+(x^*) \frac{\partial J(x^*)}{\partial x} \right\|, \end{aligned}$$

where $E(x^*) = \frac{\partial J_1^T(x^*)}{\partial x} (\mathbb{I} \otimes F_1(x^*))$.

Proof. The lemma follows directly from Lemma 2.6.5 and (3.1.6). ■

Let us again consider the interpretations of the Lipschitz constants κ and ω , following the *Local Contraction Theorem* 2.5.1. According to Lemma 3.3.10 we may conclude that the new confidence regions depend on ω , the nonlinearity of the model function, as well as on κ , i.e. on the compatibility between the model and the real observations. A discussion of the superior properties of the quadratically approximated confidence region can be found in Section 4, when dealing with the design of optimal experiment problems.

3.4 A Quadratic Approximation of the Covariance Matrix

In Lemma 3.3.9 we have seen that the linear confidence regions are directly related to the diagonal elements of the linear approximation of the covariance matrix. In particular, if C_{ii} denotes the i -th diagonal element of the covariance matrix (3.2.2), we obtain linear approximations of the confidence intervals by

$$[x_i^* - \sqrt{C_{ii}\gamma^2(\alpha)}, x_i^* + \sqrt{C_{ii}\gamma^2(\alpha)}], \quad (3.4.1)$$

for $i = 1, \dots, n_x$.

In this section, we compute a quadratic approximation of the covariance matrix, to get another tool for a higher order sensitivity analysis. For this we replace in Formula (3.4.1) the diagonal elements of the linear approximation of the covariance matrix with the diagonal elements of a quadratic approximation of the covariance matrix.

Based on Lemma 3.1.5, in combination with the assumption that the estimate x^* is a reliable approximation of the true parameter vector \bar{x} , we get

$$\begin{aligned} x(\varepsilon) &:= x(\tau = 1) \\ &= x^* - J^+ \begin{pmatrix} -\Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} - \left[(dJ^+) (\mathbb{I} - JJ^+) - \frac{1}{2} J^+ (dJ) J^+ \right] \begin{pmatrix} -\Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}, \end{aligned}$$

up to the second order, where all the functions are assumed to be evaluated at x^* . For our further considerations, let the inverse of the KKT-matrix be explicitly given by

$$\begin{pmatrix} C(x^*) & Z^T(x^*) \\ Z(x^*) & T(x^*) \end{pmatrix} := \begin{pmatrix} J_1^T(x^*) J_1(x^*) & J_2^T(x^*) \\ J_2(x^*) & 0 \end{pmatrix}^{-1}. \quad (3.4.2)$$

If we take into account that the expected value is linear and that the measurement errors ε_i^k are normally distributed with the zero mean and variances $(\sigma_i^k)^2$, the expected value

of $x(\varepsilon)$ is given by

$$\begin{aligned}
 \mathbb{E}(x(\varepsilon)) &= \mathbb{E}(x^*) + J^+(x^*)\mathbb{E}\begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} + \sum_{i=1}^{n_x} \tilde{J}_i(x^*)\mathbb{E}\left[\left(e_i^T J^+(x^*)\begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}\right)\begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}\right] \\
 &= x^* + \frac{1}{\sigma^2} \sum_{i=1}^{n_x} \tilde{J}_i(x^*) \mathbb{E}\left[\left(e_i^T C(x^*) J_1^T(x^*) \Sigma^{-1}\varepsilon\right)\begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix}\right] \\
 &= x^* + \sum_{i=1}^{n_x} \tilde{J}_i(x^*) \begin{pmatrix} J_1(x^*)C(x^*) \\ 0 \end{pmatrix} e_i,
 \end{aligned} \tag{3.4.3}$$

with

$$\tilde{J}_i(x^*) := \frac{\partial J^+(x^*)}{\partial x_i} \left(\mathbb{I} - J(x^*)J^+(x^*) \right) - \frac{1}{2} J^+(x^*) \frac{\partial J(x^*)}{\partial x_i} J^+(x^*).$$

For the computation of (3.4.3) we also used that

$$\begin{aligned}
 J^+(x^*) \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} &= \begin{pmatrix} \mathbb{I} & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} C(x^*) & Z^T(x^*) \\ Z(x^*) & T(x^*) \end{pmatrix} \begin{pmatrix} J_1^T(x^*) & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} \\
 &= C(x^*) J_1^T(x^*) \Sigma^{-1}\varepsilon.
 \end{aligned}$$

Next, we compute a quadratic approximation of the covariance matrix.

$$\begin{aligned}
 \mathcal{C}_2 &:= \mathbb{E}\left[\left(x(\varepsilon) - \mathbb{E}(x(\varepsilon))\right)\left(x(\varepsilon) - \mathbb{E}(x(\varepsilon))\right)^T\right] \\
 &= \mathbb{E}\left(x(\varepsilon)x(\varepsilon)^T\right) + \mathbb{E}(x(\varepsilon))\mathbb{E}(x(\varepsilon))^T \\
 &= C + \sum_{i=1}^{n_x} \sum_{k=1}^{n_x} \tilde{J}_i \mathbb{E}\left[\left(e_i^T C J_1^T \Sigma^{-1}\varepsilon\right)\begin{pmatrix} \Sigma^{-1}\varepsilon \\ 0 \end{pmatrix} (\Sigma^{-1}\varepsilon^T, 0^T) \left(e_k^T C J_1^T \Sigma^{-1}\varepsilon\right)\tilde{J}_k^T\right] \\
 &\quad - \sum_{i=1}^{n_x} \sum_{k=1}^{n_x} \tilde{J}_i \begin{pmatrix} J_1 C e_i \\ 0 \end{pmatrix} \left(e_k^T C J_1^T, 0^T\right) \tilde{J}_k^T \\
 &= C + \sum_{i=1}^{n_x} \sum_{k=1}^{n_x} \left(\tilde{J}_i c_{ik} \tilde{J}_k^T + \tilde{J}_i \begin{pmatrix} J_1 C e_i e_k^T C J_1^T & 0 \\ 0 & 0 \end{pmatrix} \tilde{J}_k^T\right).
 \end{aligned} \tag{3.4.4}$$

All the functions are assumed to be evaluated at x^* and $c_{ik} := e_i^T C e_k$. Here some important results are taken from probability theory. For instance, the n -th power of an independent random variable is also independent and the moment of order 4 of a normally distributed random variable with zero mean and variance σ^2 is $3\sigma^4$. Note that the matrix C from (3.4.2) is also equal to the linear approximation of the covariance matrix (3.2.2).

3.5 Examples of Confidence Regions

In this section, we want to show some comparative illustrations of the different confidence regions to get an idea of their shapes and their approximation accuracies.

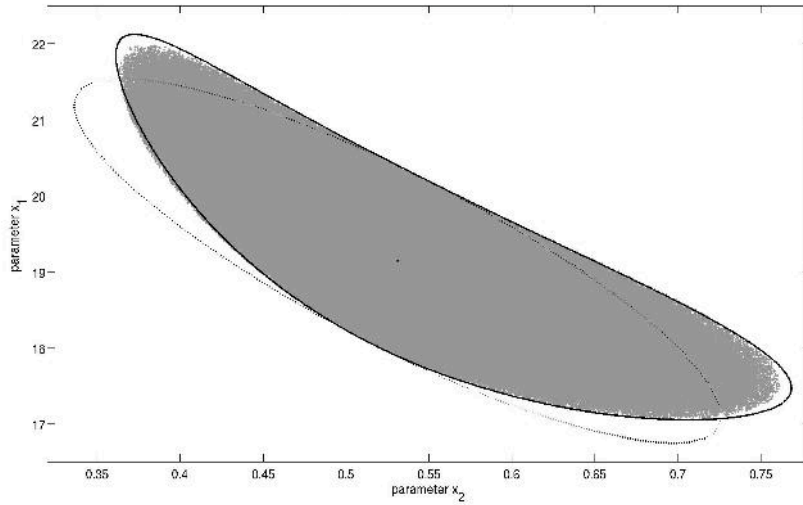


Figure 3.1: Confidence regions of example 3.5.1 with probability level $1 - \alpha = 0.95$.

3.5.1 Biochemical Oxygen Demand

As a first example, we consider the biochemical oxygen demand (BOD) of stream water. The experimental data are taken from Marske [76], where also the setup of the experiments is described. According to Bates and Watts [11] the corresponding observation function is

$$h(t; x_1, x_2) = x_1 \cdot (1 - \exp(-t \cdot x_2)).$$

The variable t denotes the time (in days) and the two unknown model parameters x_1 and x_2 have to be estimated. An application of the *Gauss-Newton* method yields the optimal parameter values $x_1 = 19.1426$ and $x_2 = 0.5311$ with the corresponding linear covariance matrix

$$C = \begin{pmatrix} 0.95876 & -0.066527 \\ -0.066527 & 0.0063474 \end{pmatrix}.$$

A comparison of the different confidence regions is given in Figures 3.1 and 3.2. The solid lines illustrate the likelihood ratio confidence regions (3.3.4), the dotted lines illustrate the linear confidence regions (3.3.8), and the gray areas illustrate the quadratic approximations of the confidence regions (3.3.13). Obviously, the quadratic approximations of the confidence regions are more precise approximations of the likelihood ratio confidence regions than the linearized regions.

In Table 3.1 a comparison of different confidence intervals with the probability levels $1 - \alpha = 0.995$ and $1 - \alpha = 0.95$ is illustrated. The intervals below the columns $\mathcal{D}_{lin}(\alpha)$, $\mathcal{D}_{quad}(\alpha)$ and $\mathcal{D}_{lr}(\alpha)$ are the exact bounds of the corresponding confidence regions. The values of $x_i^* - \tilde{\theta}_i$ and $x_i^* + \tilde{\theta}_i$, belonging to the confidence intervals of the last column, are computed by using the second order approximation of the covariance matrix. More

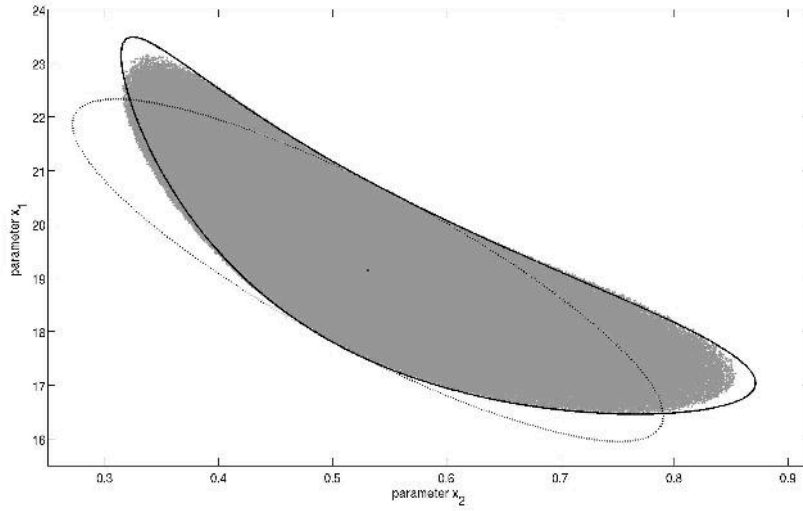

 Figure 3.2: Confidence regions of example 3.5.1 with probability level $1 - \alpha = 0.995$.

 Table 3.1: Confidence intervals of example 3.5.1 for $1 - \alpha = 0.95$ and $1 - \alpha = 0.995$.

$1 - \alpha$		$\mathcal{D}_{lin}(\alpha)$	$\mathcal{D}_{quad}(\alpha)$	$\mathcal{D}_{lr}(\alpha)$	$[x_i^* - \tilde{\theta}_i, x_i^* + \tilde{\theta}_i]$
0.95	x_1	[16.746, 21.539]	[17.062, 21.983]	[17.053, 22.121]	[16.589, 21.695]
	x_2	[0.3360, 0.7261]	[0.3632, 0.7621]	[0.3613, 0.7683]	[0.3262, 0.7358]
0.995	x_1	[15.955, 22.330]	[16.475, 23.149]	[16.466, 23.484]	[15.595, 22.689]
	x_2	[0.2717, 0.7904]	[0.3153, 0.8544]	[0.3145, 0.8712]	[0.2491, 0.8130]

precisely, it holds $\tilde{\theta}_i = \sqrt{\mathcal{C}_{2,ii}\gamma_2^2(\alpha)}$, where $\mathcal{C}_{2,ii}$ is the i -th diagonal element of the quadratic approximation of the covariance matrix (3.4.4). Here, it is remarkable that there is a strong similarity between the intervals of the likelihood ratio regions and the quadratic approximations of confidence regions. In particular, only these intervals are not symmetric around the estimate x^* .

3.5.2 Energy Radiated from a Carbon Filament Lamp

The second example deals with the energy y which is radiated from a carbon filament lamp per cm^2 , depending on the temperature t in Kelvin. It is taken from Daniel and Wood [38] and Keeping [58], where you can find a more thorough treatment of the matter. The observation function is given by

$$h(t; x_1, x_2) = x_1 t^{x_2}$$

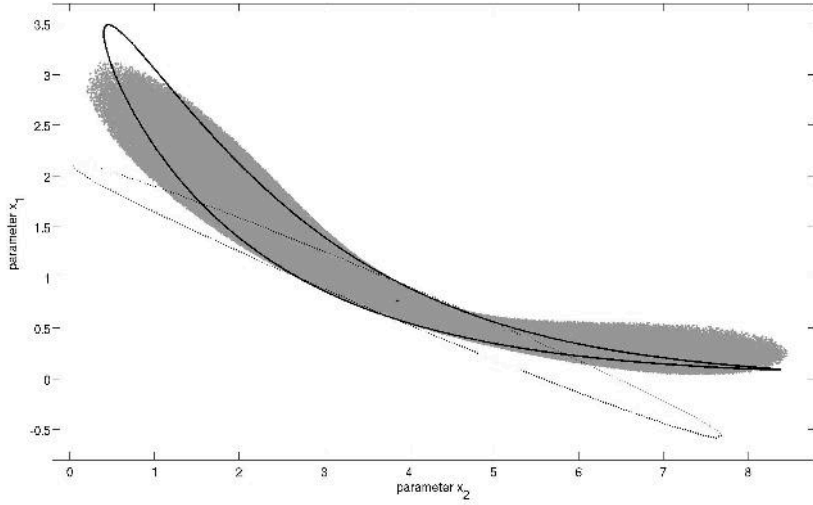


Figure 3.3: Confidence regions of example 3.5.2 with probability level $1 - \alpha = 0.95$.

with the two unknown constants x_1 and x_2 . The optimal parameter vector is $x^* = (0.7689, 3.86)^T$ with the linear approximation of the covariance matrix

$$C = \begin{pmatrix} 0.30967 & -0.86808 \\ -0.86808 & 2.479 \end{pmatrix}.$$

A comparison of the different confidence regions is given in Figures 3.3 and 3.4. As in example 3.5.1, the solid lines illustrate the likelihood ratio confidence regions (3.3.4), the dotted lines illustrate the linear confidence regions (3.3.8), and the gray areas illustrate the quadratic approximations of the confidence regions (3.3.13). Here it can also be seen that the quadratic approximations of the confidence regions are more precise approximations of the likelihood ratio confidence regions than the linearized regions.

Table 3.2: Confidence intervals of example 3.5.2 for $1 - \alpha = 0.95$ and $1 - \alpha = 0.995$.

$1 - \alpha$		$\mathcal{D}_{lin}(\alpha)$	$\mathcal{D}_{quad}(\alpha)$	$\mathcal{D}_{lr}(\alpha)$	$[x^* - \tilde{\theta}_i, x^* + \tilde{\theta}_i]$
0.95	x_1	[-0.5932, 2.130]	[0.045, 3.124]	[0.089, 3.488]	[-1.226, 2.764]
	x_2	[0.0066, 7.714]	[0.207, 8.453]	[0.404, 8.384]	[-0.373, 8.094]
0.995	x_1	[-1.0426, 2.580]	[-0.116, 4.348]	[0.039, 5.302]	[-2.382, 3.920]
	x_2	[-1.2649, 8.985]	[-1.095, 10.36]	[-0.638, 10.11]	[-2.129, 9.850]

A comparison of different confidence intervals with the probability levels $1 - \alpha = 0.995$ and $1 - \alpha = 0.95$ is illustrated in Table 3.2. The intervals below the columns $\mathcal{D}_{lin}(\alpha)$, $\mathcal{D}_{quad}(\alpha)$ and $\mathcal{D}_{lr}(\alpha)$ are the exact bounds of the corresponding confidence regions, and $\tilde{\theta}_i = \sqrt{\mathcal{C}_{2,ii}\gamma_2^2(\alpha)}$, where $\mathcal{C}_{2,ii}$ are the diagonal elements of the second order approximation

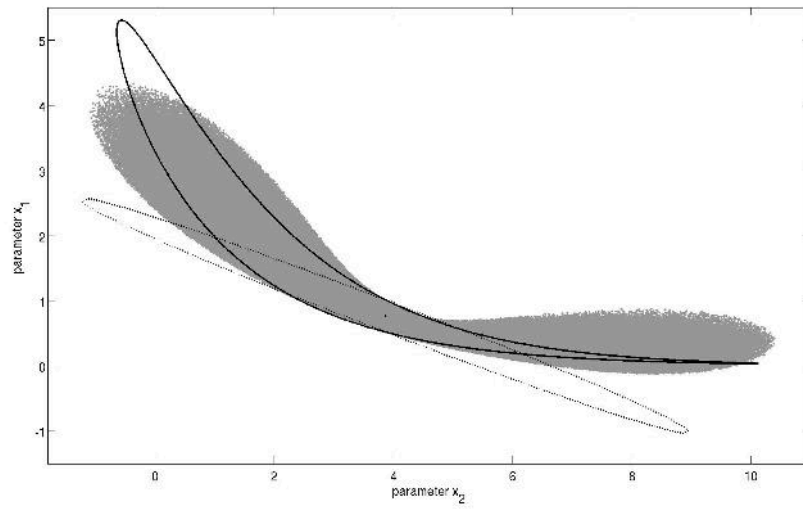


Figure 3.4: Confidence regions of example 3.5.2 with probability level $1 - \alpha = 0.995$.

of the covariance matrix (3.4.4). Again, the non-symmetric intervals of the quadratic confidence regions are more precise approximations of the intervals belonging to the likelihood ratio regions.

4 The Design of Optimal Experiments

In Chapter 2, we introduced nonlinear and constrained parameter estimation problems to identify unknown model coefficients. Due to the existence of erroneous measurements, the resulting estimate cannot be seen as an ultimate solution and we provided tools for quantifying the statistical accuracy in Chapter 3. Common approaches to perform a sensitivity analysis are based on linearization techniques and a powerful assessment criterion is given by the covariance matrix as introduced in Section 3.2. Since the linearizations are unsatisfactory in the case of highly nonlinear model functions, we introduced and analyzed a new approach based on a quadratic approximation in Subsection 3.3.3. The challenging task in the design of optimal experiments (DoE) is the maximization of the statistical accuracy of the parameter estimates by identifying optimal system settings and suitable measuring times. In this chapter, we formulate the design of optimal experiment problem and dwell on its solution procedure. In particular, we introduce and analyze a new objective function based on a bound of the quadratically approximated confidence region. Furthermore, we focus on methods of DoE robustification in view of the newly introduced objective function.

First of all, we formulate the design of optimal experiment problem and define all the relevant quantities in Section 4.1. In Section 4.2 we consider a slightly adapted parameter estimation problem. Subsequently, we discuss adequate objective functions of the design of optimal experiments problems in Section 4.3. We start by considering common approaches and then we define a new objective, the Q-criterion. Numerical treatments of the design of optimal experiment problems as well as *Sequential Quadratic Programming* as a solution method are discussed in Section 4.4. In order to take the parameter uncertainties into account, we amplify methods of robustification in Section 4.5. Here we particularly consider the robustness properties of the introduced Q-criterion.

4.1 DoE Problem Formulation

When aiming at the target of maximizing the statistical accuracy of a parameter estimate, we need to consider possibilities of influencing the design and the measurement properties of the experiments.

The most intuitive and usually also the most influential factor is the question of which measurement times are to be taken. Since the number of available measurements is often restricted due to cost reasons or a limited capacity, we have to figure out to which degree each measurement contributes to the estimate. Therefore, we consider an adequate discretization of the time line, while assuming that there are K^k possible measurement

times

$$t_a^k = t_1^k \leq t_2^k \leq \dots \leq t_{K^k}^k = t_e^k,$$

for each single experiment $k = 1, \dots, M$. Note that we do not suppose that all measurement times are necessarily different from one another. At each time point t_i^k measurements can be taken and the corresponding model response is given by

$$h_i^k(t_i^k, y^k(t_i^k), p, \tilde{p}^k, q^k, u^k(t^k)), \quad \begin{array}{l} k = 1, \dots, M, \\ i = 1, \dots, K^k. \end{array}$$

In contrast to Section 2.1, where the observation functions are defined, the functions h_i^k also depend on the constant controls q^k and the control functions $u^k(t)$. The control components have crucial effects on the system properties and their contribution to the design of optimal experiments is discussed below. For only considering an adequate selection of measuring time points, we add a weight $w_i^k \in \{0, 1\}$ to each measurement, $k = 1, \dots, M$, $i = 1, \dots, K^k$. If a certain measurement η_i^k is supposed to be considered during the procedure of parameter estimation, the corresponding weight is set to $w_i^k = 1$. Otherwise if a measurement should not be considered, it is set to $w_i^k = 0$. Often the minimum and maximum number of used measurements is prescribed, which leads to equality constraints for the introduced decision variables. If m_w^k denotes the minimum and M_w^k the maximum allowed number of measurements in each experimental layout, it should be satisfied that

$$m_w^k \leq \sum_{i=1}^{K^k} w_i^k \leq M_w^k, \quad k = 1, \dots, M. \quad (4.1.1)$$

Furthermore, for the measurement acquisition we often have only a limited budget or certain requirements that have to be fulfilled. Therefore, it should also be taken into account that the ascertainment of different measurements may have a different complexity and cause different costs. This can be considered by introducing a cost function $Cost^k(w^k) := \sum_{i=1}^{K^k} c_i^k w_i^k$, with appropriate coefficients c_i^k and the requirement

$$Cost^k(w^k) \leq C^k, \quad (4.1.2)$$

where C^k are adequate restriction constants. Following Körkel [62], we consider only linear cost functions in this thesis. Obviously, also nonlinear and more complex cost functions can be used. The procedure of identifying a suitable set of measurement times is also known as *Sampling Design*, where the weights $w^T := (w^{1T}, \dots, w^{MT})$, with their single components $w^k := (w_1^k, \dots, w_{K^k}^k)^T$ are called *sampling variables*.

As already mentioned above, the control components are also part of the design variables. Let us once again consider the dynamics describing the underlying processes,

$$\dot{y}^k(t) = f^k(t, y^k(t), p, \tilde{p}^k, q^k, u^k(t)),$$

where $t \in [t_a^k, t_e^k]$ and $k = 1, \dots, M$. In Section 2.1 we concluded that the constant control variables $q^k \in \mathbb{R}^{n_q^k}$ and the time-dependent control functions $u^k(t) : [t_a^k, t_e^k] \rightarrow \mathbb{R}^{n_u^k}$ can be determined by the experimenter. Since the control components specify the test conditions of an experiment, they also have a substantial influence on the measurements and therefore on the estimates. Often the controls have to satisfy certain constraints, e.g. temperature profiles or flow rates. We assume that all the constraints are given by the inequalities

$$m_{q_i}^k \leq q_i^k \leq M_{q_i}^k, \quad i = 1, \dots, n_q^k, \quad (4.1.3)$$

$$m_{u_i}^k \leq u_i^k(t) \leq M_{u_i}^k, \quad i = 1, \dots, n_u^k. \quad (4.1.4)$$

After having identified and characterized the quantities that determine the settings of the underlying parameter estimation, we can formalize the design variables in the following definition.

Definition 4.1.1 *The design variables are defined by the constant control components $q^T := (q^{1T}, \dots, q^{MT})$, the control functions $u^T(t) := (u(t)^{1T}, \dots, u(t)^{MT})$, as well as by the sampling variables $w^T := ((w^1)^T, \dots, (w^M)^T)$. We denote the design variables as*

$$\xi^T := (w^T, q^T, u^T(t)), \quad (4.1.5)$$

and we denote the set of all feasible realizations of design variables by $\Xi \subseteq \mathbb{R}^{n_\xi}$ and name it design space. A certain realization $\xi \in \Xi$ is called a design.

Having identified the adjustable and influenceable quantities of the parameter estimation problem, we are able to formulate an optimization problem which maximizes the accuracy of a parameter estimate, by minimizing a suitable real-valued objective function $\phi : \Xi \rightarrow \mathbb{R}$. Suitable objective functions and their properties are discussed in Section 4.3. So far, the design of optimal experiment problem is formulated as follows:

Minimize a suitable objective function $\phi : \Xi \rightarrow \mathbb{R}$ as defined in Section 4.3, with respect to the design variables $\xi \in \Xi$ and the states y^1, \dots, y^M

$$\min_{\substack{\xi \in \Xi \\ y^1, \dots, y^M}} \phi(\xi, y^1, \dots, y^M, p, \tilde{p}). \quad (4.1.6)$$

Furthermore, the design of optimal experiments optimization variables have to satisfy potential constraints, which we summarized by

$$m_\psi^k \leq \psi^k(t, y^k, p, \tilde{p}^k, q^k, u^k(t), w^k) \leq M_\psi^k, \quad k = 1, \dots, M, \quad (4.1.7)$$

$$0 = \chi^k(t, y^k, p, \tilde{p}^k, q^k, u^k(t), w^k), \quad k = 1, \dots, M, \quad (4.1.8)$$

$$w^k \in \{0, 1\}^{K^k}, \quad k = 1, \dots, M. \quad (4.1.9)$$

The global parameter values $p \in \mathbb{R}^{n_p}$ and the local parameters $\tilde{p}^T := (\tilde{p}^{1T}, \dots, \tilde{p}^{MT})$ are (initial) guesses of the true parameter values and they are assumed to satisfy the

corresponding dynamics as well as the experiment specific constraints,

$$\begin{aligned} \dot{y}^k(t) &= f^k(t, y^k(t), p, \tilde{p}^k, q^k, u^k(t)), \\ 0 &= r^k(y^k(t), p, \tilde{p}^k, q^k, u^k(t)), \end{aligned}$$

as defined in Section 2.1. Some remarks to the properties of the introduced optimization problem are stated below.

Remark 4.1.2

1. *The introduced optimization problem is an infinite mixed-integer nonlinear constrained optimization problem. In order to use standard optimization methods to solve this problem, numerical treatments are required, see Section 4.4.*
2. *The restrictions (4.1.7) and (4.1.8) are basically determined by the minimum and maximum number of used measurements in (4.1.1), the limited budget (4.1.2), and by the restrictions to the control components defined in (4.1.3) and (4.1.4). Obviously, we can consider many further restrictions to the solution space of the design variables, if necessary. Hereby, the exact definitions of the restrictions strongly depend on the underlying process and the prevailing circumstances.*
3. *In the context of the design of optimal experiments the global parameters p and the local parameters \tilde{p}^k are constant and they are not part of the optimization variables.*

4.2 The Underlying Parameter Estimation Problem

Basically, we consider a parameter estimation problem as introduced in (2.4.1), which is given in the form

$$\begin{aligned} \min_x \quad & \frac{1}{2} \|F_1(x)\|_2^2 \\ \text{s.t.} \quad & F_2(x) = 0, \end{aligned} \tag{4.2.1}$$

and we just have to add the decision variables w . Therefore, the objective function F_1 is weighted by a diagonal matrix \sqrt{W} given by

$$W := \begin{pmatrix} W_1 & & 0 \\ & \ddots & \\ 0 & & W_M \end{pmatrix}, \text{ where } W_k := \begin{pmatrix} w_1^k & & 0 \\ & \ddots & \\ 0 & & w_{K^k}^k \end{pmatrix},$$

for $k = 1, \dots, M$. While the restriction function F_2 remains unchanged, the objective function changes to

$$F_1(x) = \sqrt{W} \begin{pmatrix} F_1^1(x_1, p) \\ \vdots \\ F_1^M(x_M, p) \end{pmatrix} = \begin{pmatrix} \sqrt{W_1} F_1^1(x_1, p) \\ \vdots \\ \sqrt{W_M} F_1^M(x_M, p) \end{pmatrix} \in \mathbb{R}^{m_1},$$

where $x^T = (x_1^T, \dots, x_M^T, p^T)$. In particular, all the functions, namely the observation functions and the restriction functions, depend on the constant controls q^k and the control functions $u^k(t)$. Consequently, the Jacobians

$$J_1(x) = \frac{\partial F_1(x)}{\partial x} = \sqrt{W} \begin{pmatrix} \frac{\partial F_1^1(x_1, p)}{\partial x} \\ \vdots \\ \frac{\partial F_1^M(x_M, p)}{\partial x} \end{pmatrix} \text{ and } J_2(x) = \frac{\partial F_2(x)}{\partial x},$$

are also functions of the design variables.

4.3 DoE Objective Functions

In this section, we discuss suitable objective functions for the introduced design of optimal experiments problems. In order to be able to compare different designs, the used objective functions have to satisfy an ordering relation. In general, the function ϕ maps onto the real axis, and we can use the \leq -relation.

In the first subsection, we consider commonly used objective functions, whereas in the second subsection we define and investigate a new objective function.

4.3.1 The Common Approach

The commonly used objective functions are based on the linearized sensitivity analysis as introduced in Sections 3.2 and Subsection 3.3.2, see Pukelsheim [92]. In particular, we concluded that a linear sensitivity analysis can be performed by basically using the covariance matrix at the solution point x^* , which is given by

$$\mathcal{C}(x^*, \xi) = J^+(x^*, \xi) \begin{pmatrix} \mathbb{I} & 0 \\ 0 & 0 \end{pmatrix} J^{+T}(x^*, \xi). \quad (4.3.1)$$

In the following, we omit the arguments of the covariance matrix for simplicity of notation. Some well known DoE objective functions, which are widely used, are described below.

A-Criterion

By using the A-criterion as DoE objective function, we minimize the weighted trace of the covariance matrix,

$$\phi_A(\mathcal{C}) = \frac{1}{n_x} \text{trace}(\mathcal{C}).$$

The diagonal elements of the covariance matrix are the variances of the corresponding components of the estimate x^* . Hence, with the A-criterion the average variance is minimized. In connection with the linearized confidence ellipsoid from Subsection 3.3.2, the A-criterion minimizes the average length of the half-axes.

D-Criterion

By using the D-criterion as DoE objective function, we minimize the determinant of an adequate projection of the covariance matrix,

$$\phi_D(\mathcal{C}) = \det(\mathcal{K}^T \mathcal{C} \mathcal{K}).$$

The projection matrix $\mathcal{K} \in \mathbb{R}^{n_x \times n_\kappa}$ causes a projection on an n_κ -dimensional subspace of the parameter space, to ensure that the considered covariance matrix is non-singular. The D-criterion minimizes the volume of the linearized confidence ellipsoid (3.3.7).

E-Criterion

By using the E-criterion as DoE objective function, we minimize the maximum eigenvalue of the covariance matrix,

$$\phi_E(\mathcal{C}) = \max \{ \lambda \mid \lambda \text{ is an eigenvalue of } \mathcal{C} \}.$$

The E-criterion minimizes the maximum variance of the estimated parameters and this corresponds to the half-axes of the linearized confidence region.

M-Criterion

By using the M-criterion as DoE objective function, we minimize the square root of the maximum diagonal element of the covariance matrix,

$$\phi_M(\mathcal{C}) = \max \{ \sqrt{c_{ii}} \mid c_{ii} \text{ is diagonal element of } \mathcal{C}, i = 1, \dots, n_x \}.$$

Hence, the M-criterion minimizes the largest standard deviation of the parameters. This corresponds to the largest side length of the box defined in Formula (3.3.10). An application of the M-criterion requires further numerical methods. For a thorough treatment.

Figure 4.1 illustrates the common DoE objective functions in relation to the linearized confidence ellipsoid in the case of an unconstrained parameter estimation problem, see Körkel [62].

All the commonly used DoE objective functions are functionals on the covariance matrix \mathcal{C} . As deduced in Section 3.2, this covariance matrix is based on a linearized representation of the parameters and thus a linear approximation itself. Consequently, we do not consider any higher order parameter sensitivities in the DoE problem if we use the given objective functions. In particular, if we have to deal with very highly nonlinear model functions, this may cause some problems which result in an unsatisfactory outcome.

4.3.2 The Q-Criterion

The Q-criterion is a new DoE objective function, which is based on a bound of the quadratically approximated confidence region as it is given in Lemma 3.3.10.

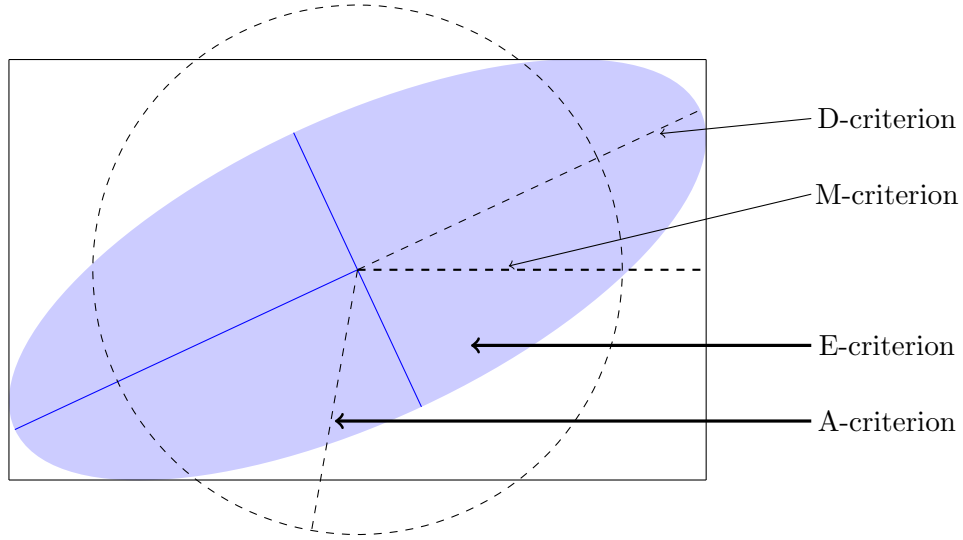


Figure 4.1: Illustration of the commonly used DoE objective functions, Körkel [62].

Definition 4.3.1 Suppose that $\mathcal{C}(\xi)$ is the covariance matrix of the parameters as given in Formula (4.3.1) and let $\xi \in \Xi$ be the design variables according to (4.1.5). Then, the Q -criterion is given by

$$\phi_Q(\xi) := \text{trace}(\mathcal{C}(\xi)) + \left(\tilde{\kappa}(\xi) + \frac{\tilde{\omega}(\xi)}{2} \text{trace}(\mathcal{C}(\xi)) \right) \text{trace}(\mathcal{C}(\xi)), \quad (4.3.2)$$

where

$$\begin{aligned} \tilde{\kappa}(\xi) &= \|\mathcal{C}(\xi)E(\xi)\|, \\ \tilde{\omega}(\xi) &= \left\| J^+(\xi) \frac{\partial J(\xi)}{\partial x} \right\|, \end{aligned}$$

and $\tilde{\kappa}$ depends on

$$E(\xi) = \frac{\partial J_1^T(\xi)}{\partial x} (\mathbb{I} \otimes v(\xi)) + \frac{\partial J_2^T(\xi)}{\partial x} (\mathbb{I} \otimes \lambda(\xi))$$

with

$$v(x) := F_1(\xi) - J_1(\xi)\mathcal{C}(\xi)J_1^T(\xi)F_1(\xi)$$

and

$$\lambda(\xi) := - \begin{pmatrix} 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} J_1^T(\xi)J_1(\xi) & J_2^T(\xi) \\ J_2(\xi) & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T(\xi) & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} F_1(\xi) \\ F_2(\xi) \end{pmatrix}.$$

Thereby, all the functions are assumed to be evaluated in suitable (initial) parameter guesses for p , \tilde{p} .

Some remarks concerning the introduced new objective function are stated below.

Remark 4.3.2

1. Commonly, the value of the Q -criterion depends—especially in the case of nonlinear model functions—on the states y^1, \dots, y^M , the global parameters p and the local parameters \tilde{p} , respectively. For simplicity of notation we refrain from a representation with all function arguments.
2. Especially the choice of $\tilde{\kappa}$ has to be discussed thoroughly, since it depends on the function F_1 and therefore on the measurements. Some options for the choice of $\tilde{\kappa}$ in the context of DoE are given below.

Computation of $\tilde{\kappa}(\xi)$ in the Context of DoE

Subsequently, we discuss several options for the choice of $\tilde{\kappa}(\xi)$ in the context of DoE.

The first option is based on a chance constrained approach and for simplicity of notation we consider an *unconstrained* parameter estimation problem,

$$\min_x \frac{1}{2} \|F_1(x)\|_2^2.$$

As introduced in Theorem 2.6.2, the corresponding κ -estimate is given by

$$\tilde{\kappa} := \rho(B^{-1}(\xi)E(\xi)),$$

where $B(\xi) = J_1^T(\xi)J_1(\xi)$ and $E(\xi) = \sum_{i=1}^{m_1} \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} F_{1i}(\xi)$. Note that in Definition 4.3.1 it is not required that the constant $\tilde{\kappa}(\xi)$ is less than 1. However, in favor of the *Gauss-Newton* convergence properties this should be the case. In other words, we want to ensure that the probability of $\tilde{\kappa}(\xi) \geq 1$ is as small as possible. Hence, we assume that the probability of $\tilde{\kappa}(\xi)$ being greater than or equal to a certain constant c is less than or equal to a probability value α , e.g.

$$\mathbb{P}(\rho(B^{-1}(\xi)E(\xi)) \geq c) \leq \alpha, \tag{4.3.3}$$

where $c < 1$ and $\alpha \ll 1$. Since similar matrices have the same eigenvalues, the spectral

radius in (4.3.3) can be rewritten as

$$\begin{aligned} \rho(B^{-1}(\xi)E(\xi)) &= \rho\left(B^{-\frac{1}{2}}(\xi)\left(B^{-\frac{1}{2}}(\xi)E(\xi)B^{-\frac{1}{2}}(\xi)\right)B^{\frac{1}{2}}(\xi)\right) \\ &= \rho\left(B^{-\frac{1}{2}}(\xi)E(\xi)B^{-\frac{1}{2}}(\xi)\right) \\ &= \rho\left(\sum_{i=1}^{m_1}\left(B^{-\frac{1}{2}}(\xi)\frac{\partial^2 F_{1i}(\xi)}{\partial x^2}B^{-\frac{1}{2}}(\xi)\right)F_{1i}(\xi)\right) \\ &=: \rho\left(\sum_{i=1}^{m_1}A_i(\xi)F_{1i}(\xi)\right), \end{aligned}$$

where we introduced the symmetric and positive-definite matrices

$$A_i(\xi) := B^{-\frac{1}{2}}(\xi)\frac{\partial^2 F_{1i}(\xi)}{\partial x^2}B^{-\frac{1}{2}}(\xi) \in \mathbb{R}^{n_x \times n_x}, \quad (4.3.4)$$

for $i = 1, \dots, m_1$. In the following we often omit the function argument ξ in favor of a more readable notation. The next lemma gives—as described in Oliveira [82]—an estimate of the left hand side of Formula (4.3.3). Here we replace the components F_{1i} by the measurement errors $\varepsilon_i \sim \mathcal{N}(0, \sigma_i^2)$, which correspond to an evaluation of F_{1i} at the true parameter values.

Lemma 4.3.3 *Let us assume that A_1, \dots, A_{m_1} are deterministic, positive definite and symmetric $n_x \times n_x$ matrices and $\{\varepsilon_i\}_{i=1}^{m_1}$ is a standard Gaussian sequence. Then it holds for all $c > 0$ that*

$$\mathbb{P}\left(\rho\left(\sum_{i=1}^{m_1}A_i\varepsilon_i\right) \geq c\right) \leq 2n_x \inf_{s>0} e^{-sc} e^{\frac{s^2\mu^2}{2}} = 2n_x e^{-\frac{c^2}{2\mu^2}},$$

where

$$\mu^2 = \lambda_{\max}\left(\sum_{i=1}^{m_1}A_i^2\right)$$

is the maximum eigenvalue of $\sum_{i=1}^{m_1}A_i^2$.

Proof. The following proof is adapted from Oliveira [82]. As introduced in [82], the usual Bernstein trick implies that for every $c \geq 0$,

$$\mathbb{P}(\|Z_{m_1}\| \geq c) \leq \inf_{s>0} e^{-sc} \mathbb{E}\left(e^{s\|Z_{m_1}\|}\right),$$

where $Z_{m_1} := \sum_{i=1}^{m_1}A_i\varepsilon_i$. Since $\|Z_{m_1}\| = \max\{\lambda_{\max}(Z_{m_1}), \lambda_{\max}(-Z_{m_1})\}$, we obtain the estimate

$$\mathbb{E}\left(e^{s\|Z_{m_1}\|}\right) \leq \mathbb{E}\left(e^{s\lambda_{\max}(Z_{m_1})}\right) + \mathbb{E}\left(e^{s\lambda_{\max}(-Z_{m_1})}\right) = 2\mathbb{E}\left(e^{s\lambda_{\max}(Z_{m_1})}\right).$$

Due to the fact that the trace of a matrix is the sum of all its eigenvalues, it holds that

$$\mathbb{E} \left(e^{s\lambda_{max}(Z_{m_1})} \right) = \mathbb{E} \left(\lambda_{max} \left(e^{sZ_{m_1}} \right) \right) \leq \mathbb{E} \left(\text{trace} \left(e^{sZ_{m_1}} \right) \right)$$

and so far we can conclude for every $c \geq 0$,

$$\mathbb{P} (\|Z_{m_1}\| \geq c) \leq 2 \inf_{s>0} e^{-sc} \mathbb{E} \left(\text{trace} \left(e^{sZ_{m_1}} \right) \right).$$

Considering Lemma 2 in Oliveira [82], it holds that

$$\mathbb{E} \left(\text{trace} \left(e^{sZ_{m_1}} \right) \right) \leq \text{trace} \left(e^{\frac{s^2 \sum_{i=1}^{m_1} A_i^2}{2}} \right), \quad (4.3.5)$$

from which follows for every $c \geq 0$,

$$\begin{aligned} \mathbb{P} (\|Z_{m_1}\| \geq c) &\leq 2 \inf_{s>0} e^{-sc} \mathbb{E} \left(\text{trace} \left(e^{sZ_{m_1}} \right) \right) \\ &\leq 2 \inf_{s>0} e^{-sc} \text{trace} \left(e^{\frac{s^2 \sum_{i=1}^{m_1} A_i^2}{2}} \right) \\ &\leq 2 \inf_{s>0} e^{-sc} n_x \lambda_{max} \left(e^{\frac{s^2 \sum_{i=1}^{m_1} A_i^2}{2}} \right) \\ &\leq 2n_x \inf_{s>0} e^{-sc} e^{\frac{s^2 \mu^2}{2}} \\ &= 2n_x e^{-\frac{c^2}{2\mu^2}}, \end{aligned}$$

where μ^2 is the maximum eigenvalue of $\sum_{i=1}^{m_1} A_i^2$ and $A_i = B^{-\frac{1}{2}} \frac{\partial^2 F_{1i}}{\partial x^2} B^{-\frac{1}{2}}$. ■

Combining this lemma and Formula (4.3.3), we obtain

$$\mathbb{P} \left(\rho \left(B^{-1}(\xi) E(\xi) \right) \geq c \right) \leq 2n_x e^{-\frac{c^2}{2\mu^2}} \stackrel{!}{\leq} \tilde{\alpha}, \quad (4.3.6)$$

and the value of interest is μ^2 , the maximum eigenvalue of a sum of symmetric and positive definite matrices. This leads us to the requirement

$$2n_x e^{-\frac{c^2}{2\mu^2}} \stackrel{!}{\leq} \tilde{\alpha} \iff \mu^2 \stackrel{!}{\leq} \frac{c^2}{2(-\ln(\frac{\tilde{\alpha}}{2n_x}))}. \quad (4.3.7)$$

Because of the \leq -estimates in the proof of Lemma 4.3.3, we cannot expect that inequality (4.3.6) holds for values $c < 1$ and $\alpha \ll 1$, and so it is more like a sufficient condition. For this reason, we do not consider inequality (4.3.7) explicitly but rather the maximum eigenvalue μ^2 . Thus, by minimizing the introduced Q-criterion (4.3.2) during the design of optimum experiment procedure, we minimize μ^2 and consequently $\tilde{\kappa}(\xi)$. Hence, we

transform the computation of $\tilde{\kappa}(\xi)$ to a symmetric eigenvalue problem, which is well investigated. Some efficient algorithms to compute the maximum eigenvalues are e.g. the *Vector-Iteration*, the *Inverse-Iteration*, the *Orthogonal-Iteration*, the *QR-Iteration* or the *Krylov-Methods*, which are e.g. described by Parlett [84] as well as by Saad [95]. We suggest to use an estimate of the maximum eigenvalues using traces of the underlying matrices. The next theorem gives an estimate of the smallest and the largest eigenvalues of a complex matrix with real eigenvalues.

Theorem 4.3.4 *Let B be an $n \times n$ complex matrix with real eigenvalues $\lambda(B)$, and denote*

$$m := \frac{1}{n} \text{trace}(B), \quad s^2 := \frac{1}{n} \text{trace}(B^2) - m^2,$$

then

$$\begin{aligned} m - s(n-1)^{\frac{1}{2}} &\leq \lambda_{\min}(B) \leq m - \frac{s}{(n-1)^{\frac{1}{2}}} \\ m + \frac{s}{(n-1)^{\frac{1}{2}}} &\leq \lambda_{\max}(B) \leq m + s(n-1)^{\frac{1}{2}}. \end{aligned}$$

Proof. The proof of this theorem can be found by Wolkowicz and Styan [111]. ■

Following this theorem, we use the estimate $\tilde{\kappa}(\xi) \approx \mu^2$, where

$$\mu^2 \approx \hat{\kappa} := \frac{1}{n_x} \text{trace}(\mathcal{A}) + \frac{1}{2} \sqrt{\frac{1}{n_x} \text{trace}(\mathcal{A}^2) - \left(\frac{1}{n_x} \text{trace}(\mathcal{A})\right)^2} \frac{n_x}{\sqrt{(n_x - 1)}}, \quad (4.3.8)$$

with $\mathcal{A} := \sum_{i=1}^{m_1} A_i^2$. Here, we use the mean of the lower and the upper bound of the maximum eigenvalue. Note that matrices A_i and therefore \mathcal{A} and $\hat{\kappa}$ are functions on the design variables ξ .

Here, we would like to introduce two more options for the computation of $\tilde{\kappa}(\xi)$. The first option is based on the triangular inequality and on an estimate of F_1 for which we use the $(1 - \alpha)$ -quantile of the χ^2 -distribution. The second approach is based on a generation of synthetic measurement errors. For both approaches we consider an equality constrained parameter estimation problem as

$$\begin{aligned} \min_x \quad & \frac{1}{2} \|F_1(x)\|_2^2 \\ \text{s.t.} \quad & F_2(x) = 0. \end{aligned}$$

Following the results of Section 2.6, a first order estimate of the Lipschitz constant κ is given by

$$\tilde{\kappa}(\xi) := \|\mathcal{C}(\xi)E(\xi)\|, \quad (4.3.9)$$

where $\mathcal{C}(\xi)$ is the linear approximated covariance matrix and

$$E(\xi) := \frac{\partial J_1^T(\xi)}{\partial x} (\mathbb{I} \otimes v(\xi)) + \frac{\partial J_2^T(\xi)}{\partial x} (\mathbb{I} \otimes \lambda(\xi))$$

with

$$\lambda(\xi) := - \begin{pmatrix} 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} J_1^T(\xi) J_1(\xi) & J_2^T(\xi) \\ J_2(\xi) & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T(\xi) & 0 \\ 0 & \mathbb{I} \end{pmatrix} F(\xi)$$

and

$$v(\xi) := F_1(\xi) - J_1(\xi) \mathcal{C}(\xi) J_1^T(\xi) F_1(\xi).$$

For simplicity of notation we neglect the function arguments in the following considerations.

1. $\tilde{\kappa}(\xi)$ -**Estimate with the Triangular Inequality**

If x is a feasible point, function F reduces to $(F_1^T, 0^T)^T$ and we denote $\lambda := A \cdot F_1$, where

$$\begin{aligned} A &:= - \begin{pmatrix} 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T \\ 0 \end{pmatrix} \\ &= -Z J_1^T, \end{aligned}$$

where we assume that the inverse of the KKT-matrix is explicitly given by

$$\begin{pmatrix} C & Z^T \\ Z & T \end{pmatrix} := \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}^{-1}. \quad (4.3.10)$$

Evaluated at the true parameter values \bar{x} , it holds that $F_1 = \Sigma^{-1} \varepsilon$ and therefore we replace F_1 by weighted measurement errors $\Sigma^{-1} \varepsilon$. Assuming $\varepsilon \sim \mathcal{N}(0, \Sigma^2)$ and considering

$$\frac{\partial J^T}{\partial x} = \left(\frac{\partial J_1^T}{\partial x}, \frac{\partial J_2^T}{\partial x} \right),$$

and the triangular inequality, we obtain the following inequality,

$$\begin{aligned} \tilde{\kappa} &= \|\mathcal{C}E\| \\ &= \left\| \mathcal{C} \left(\frac{\partial J_1^T}{\partial x} (\mathbb{I} \otimes v) + \frac{\partial J_2^T}{\partial x} (\mathbb{I} \otimes \lambda) \right) \right\| \\ &= \left\| \mathcal{C} \frac{\partial J^T}{\partial x} \begin{pmatrix} (\mathbb{I} \otimes v) \\ (\mathbb{I} \otimes \lambda) \end{pmatrix} \right\| \\ &\leq \left\| \mathcal{C} \frac{\partial J^T}{\partial x} \begin{pmatrix} (\mathbb{I} \otimes (\mathbb{I} - J_1 \mathcal{C} J_1^T)) \\ (\mathbb{I} \otimes A) \end{pmatrix} \right\| \|\Sigma^{-1} \varepsilon\| \\ &\leq \left\| \mathcal{C} \frac{\partial J^T}{\partial x} \begin{pmatrix} (\mathbb{I} \otimes (\mathbb{I} - J_1 \mathcal{C} J_1^T)) \\ (\mathbb{I} \otimes A) \end{pmatrix} \right\| \gamma_{\bar{m}}(\alpha), \end{aligned} \quad (4.3.11)$$

where $\gamma_{\bar{m}}^2(\alpha)$ is the $(1 - \alpha)$ -quantile of the χ^2 -distribution with $\bar{m} = n_x - m_2$ degrees of freedom. Numerically, matrix A can be computed by using an orthogonal decomposition of the Jacobian $J_2 \in \mathbb{R}^{m_2 \times n_x}$. By considering the regularity condition (CQ), we get

$$J_2 = LQ^T = (L_1 \ 0) \begin{pmatrix} Q_1^T \\ Q_2^T \end{pmatrix} = L_1 Q_1^T,$$

where $L_1 \in \mathbb{R}^{m_2 \times m_2}$ is a regular lower triangular matrix and $Q = (Q_1 \ Q_2) \in \mathbb{R}^{n_x \times n_x}$ is an orthogonal matrix with $Q_1^T \in \mathbb{R}^{m_2 \times n_x}$ satisfying $Q_1^T Q_1 = \mathbb{I} \in \mathbb{R}^{m_2 \times m_2}$. From $\mathbb{I} = ZJ_2^T = ZQ_1 L_1^T$ it follows that $Z = L_1^{-T} Q_1^T$ and hence $A = L_1^{-T} Q_1^T J_1^T$.

2. $\tilde{\kappa}$ -Estimate from Generation of Synthetic Measurement Errors

Another possibility of the computation of $\tilde{\kappa}$ in the context of DoE is based on a generation of synthetic measurement errors. Assuming that all in all we are able to measure at $K \in \mathbb{N}$ points in time, we generate a K -dimensional vector $\tilde{\varepsilon}^S$ with $\tilde{\varepsilon}^S \sim \mathcal{N}(0, \mathbb{I})$ and independent components. In a second step, we determine the variances of the measurement errors ε_i^S in such a way that we consider information about the scale of the corresponding measurement as well as about the assumed size of the measurement errors. If the simplified observation function that describes the measurable system output is given by $h : \mathbb{R} \times \mathbb{R}^{n_x} \rightarrow \mathbb{R}$, where $(t, x) \mapsto h(t, x)$, we set

$$\varepsilon_i^S = \tilde{\varepsilon}_i^S \cdot \sqrt{h(t_i, x_0)} \cdot \sqrt{r}.$$

The vector x_0 is an (initial) guess of the unknown parameters and $r \in (0, 1]$ declares the percentage error rate. Thus, we obtain a random vector ε^S with independent components and

$$\varepsilon_i^S \sim \mathcal{N}(0, h(t_i, x_0) \cdot r), \quad i = 1, \dots, K.$$

If the observation function h is highly nonlinear, the choice of *bad* initial guesses x_0 may cause some problems. In order to robustify the measurement error generation, we suggest to use an adequate average $\hat{h}(t_i, \mathcal{D})$ instead of $h(t_i, x_0)$. Here, the average value is computed in the following way:

Suppose that we have the background information that the unknown parameters are located in a bounded parameter space \mathcal{P} . Let $\mathcal{D} = \{\hat{x}_0, \dots, \hat{x}_D\}$, $D < \infty$, be an appropriate discretization of the parameter space \mathcal{P} . We set

$$\hat{h}(t_i, \mathcal{D}) := \frac{1}{1 + D} \left(\sum_{j=0}^D h(t_i, x_j) \right)$$

and

$$\varepsilon_i^S = \tilde{\varepsilon}_i \cdot \sqrt{\hat{h}(t_i, \mathcal{D})} \cdot \sqrt{r},$$

e.g.

$$\varepsilon_i^S \sim \mathcal{N}\left(0, \hat{h}(t_i, \mathcal{D}) \cdot r\right), \quad i = 1, \dots, K.$$

Considering the number of available measuring times K and the number of discretization points D , the generation of synthetic measurement errors to compute $\tilde{\kappa}$ is much more expensive than with the triangular inequality. However, in practical applications this opportunity seems to be very robust against parameter uncertainties.

After having generated the synthetic measurement errors ε^S , we can replace function F_1 by ε^S , and consequently we are able to compute $\tilde{\kappa}$ according to Formula (4.3.9).

A priori, it is difficult to predict which approximation of $\tilde{\kappa}$ delivers the best result. The first approximation (4.3.8) strongly depends on the quality of the eigenvalue bounds given in Theorem 4.3.4. According to Wolkowicz and Styan [111], the bounds in Theorem 4.3.4 are optimal bounds for eigenvalues in terms of the trace of \mathcal{A} and the trace of \mathcal{A}^2 and they are exact bounds in the case of 2×2 matrices. However, given the second derivatives, the computational effort is low, since we basically compute traces of matrices. Similar statements can be made concerning estimate (4.3.11). Here, in some cases an application of the triangular inequality leads to big losses of accuracy, but still the computational effort remains moderate. The last approach, which is based on the generation of synthetic measurement errors, seems to be the costliest. Next to the computation of the second derivatives, the computational effort mainly depends on the size of \mathcal{D} , the discretized parameter space.

4.4 Solving the DoE problem by Means of Standard Optimization Methods

In this section, we discuss *Sequential Quadratic Programming* (SQP) as a solution method for the introduced DoE problem

$$\begin{aligned} \min_{\substack{\xi \in \Xi \\ y^1, \dots, y^M}} \phi(\xi, y^1, \dots, y^M, p, \tilde{p}) \\ \text{s.t. } m_\psi^k \leq \psi^k(t, y^k, p, \tilde{p}^k, q^k, u^k(t), w^k) \leq M_\psi^k, \quad k = 1, \dots, M, \\ 0 = \chi^k(t, y^k, p, \tilde{p}^k, q^k, u^k(t), w^k), \quad k = 1, \dots, M, \\ w^k \in \{0, 1\}^{K^k}, \quad k = 1, \dots, M. \end{aligned}$$

In order to apply the SQP method, we have to deal with two general difficulties:

Firstly, we have to deal with integer conditions of the sampling variables $w_i^k \in \{0, 1\}$, $i = 1, \dots, K^k, k = 1, \dots, M$, and, secondly, with the solution space of the DoE problem which is infinite due to the control functions and the differential equation systems. In order to overcome these difficulties, we give a brief overview of numerical methods for the treatment of the DoE problem.

Numerical Treatment of the Integer Constraints of the Sampling Variables

The sampling variables w_i are an essential part of the design variables and they are assumed to be 0 or 1. This kind of integer conditions causes difficulties in the application of standard optimization methods, since they work on a continuous parameter space. To counteract this, a common approach is to use adequate relaxations, see e.g. Körkel [62]. Suitable relaxations are e.g.

$$w_i^k \in [0, 1], \quad (4.4.1)$$

or

$$w_i^k \in \mathbb{R}_0^+. \quad (4.4.2)$$

for $i = 1, \dots, K^k$, $k = 1, \dots, M$. An interpretation of these relaxations can be seen in connection with the variances of the measurement errors. Considering the i -th component of the parameter estimation objective function F_1^k , we get

$$\begin{aligned} (F_1^k)_i &= w_i^k \frac{(\eta_i^k - h_i^k(y^k(t_i^k), p, \tilde{p}^k, q^k, u^k(t)))}{\sigma_i^k} \\ &= \frac{(\eta_i^k - h_i^k(y^k(t_i^k), p, \tilde{p}^k, q^k, u^k(t)))}{\frac{\sigma_i^k}{w_i^k}}. \end{aligned}$$

Hence, the distribution of the measurement errors can be written according to $\epsilon_i^k \sim \mathcal{N}(0, (\sigma_i^k)^2/w_i^2)$. Thus, small values of w_i increase the corresponding variance and consequently the inaccuracy of a measurement.

In order to obtain integer solutions, we apply adequate rounding heuristics as given in e.g. Körkel et al. [64]. We apply a simple rounding approach to obtain integer solutions. Depending on the number of allowed measurements, we round up the M_w^k highest values of w_i^k .

The relaxed integer conditions can be added to the inequality constraints (4.1.7)

$$m_\psi^k \leq \psi(t, y^k, p, \tilde{p}^k, q^k, u^k(t), w^k) \leq M_\psi^k, \quad k = 1, \dots, M.$$

Numerical Treatment of the Control Functions

A way of handling the problem of an infinite solution space based on the differential equation system was already discussed in Section 2.2, where we used a *Single Shooting* or a *Multiple Shooting* approach. As result of these methods, we obtain a finite dimensional solution space by introducing discretization variables s . In order to solve the problem of the infinite dimensional space of the control functions $u^k(t)$, we use a direct approach, as suggested by Körkel [62]. Thus, the functions $u^k(t)$ are replaced by approximations $\hat{u}^k(t)$, which have only a finite number of degrees of freedom. This can be done by using a grid, such as

$$t_a^k = t_0^k < t_1^k < \dots < t_{\hat{N}}^k = t_e^k.$$

On this grid, we replace the control functions u^k piecewise by \widehat{u}_i^k , $i = 1, \dots, \widehat{N}$, and denote the parametrization variables by $\widehat{q}^k \in \mathbb{R}^{n_{\widehat{q}}^k}$. Following K orkel [62], potential grid functions are e.g.

- piecewise constant polynomials,

$$\widehat{u}_i^k(t) = \widehat{q}_i^k, \quad t \in [t_{i-1}^k, t_i^k), \quad i = 1, \dots, \widehat{N}, \quad (4.4.3)$$

- piecewise linear polynomials,

$$\widehat{u}_i^k(t) = \widehat{q}_{2i}^k + \widehat{q}_{2i+1}^k \cdot (t - t_{i-1}^k), \quad t \in [t_{i-1}^k, t_i^k), \quad i = 1, \dots, \widehat{N}. \quad (4.4.4)$$

According to (4.1.4) the control functions have to satisfy the constraints

$$m_{u_i}^k \leq u_i^k(t) \leq M_{u_i}^k, \quad i = 1, \dots, n_u^k,$$

and we have to adapt the constraints to the introduced discretizations. If the discretization is performed by using piecewise linear polynomials (4.4.4), the conditions $\widehat{q}_{2i}^k \in [m_{\widehat{q}_{2i}}^k, M_{\widehat{q}_{2i}}^k]$ and $\widehat{q}_{2i}^k + \widehat{q}_{2i+1}^k \cdot (t_i^k - t_{i-1}^k) \in [m_{\widehat{q}_{2i+1}}^k, M_{\widehat{q}_{2i+1}}^k]$ have to be fulfilled.

If the control functions have to be continuous, we need to consider the conditions

$$\lim_{t \rightarrow t_i^k} \widehat{u}_i^k(t) = \widehat{u}_{i+1}^k(t_i), \quad i = 1, \dots, \widehat{N} - 1.$$

Due to the introduced discretizations, this leads to the following conditions of the parametrization variables \widehat{q}_i^k ,

$$\widehat{q}_{2i}^k + \widehat{q}_{2i+1}^k \cdot (t_i^k - t_{i-1}^k) = \widehat{q}_{2i+2}^k.$$

These conditions can also be added to

$$m_{\psi}^k \leq \psi^k(t, y^k, p, \tilde{p}^k, q^k, u^k(t), w^k) \leq M_{\psi}^k,$$

and

$$0 = \chi^k(t, y^k, p, \tilde{p}^k, q^k, u^k(t), w^k),$$

respectively. Here, the variables \widehat{q}_i^k can be seen as a part of the constant controls q .

For the following considerations the design variables are given by $\xi := (q, w, s)$. Here, q consists of the constant controls and the parametrization variables from the discretization of the control functions, w are the relaxed weights from sampling design and s are optimization variables from the *Single Shooting* or the *Multiple Shooting* approach for the discretization of the differential equation systems. Consequently, we get a nonlinear finite dimensional optimization problem with a solution space that is restricted by equality and

inequality conditions. Finally, we can write the resulting optimization problem in the general form as

$$\begin{aligned} \min_{\xi} \quad & \phi(\xi) \\ \text{s.t.} \quad & m_{\psi} \leq \psi(\xi) \leq M_{\psi}, \\ & 0 = \chi(\xi). \end{aligned} \tag{4.4.5}$$

This type of optimization problem can be solved by using standard optimization methods. However, as already mentioned, we suggest to use *Sequential Quadratic Programming*, as discussed in the following subsection.

4.4.1 Sequential Quadratic Programming

Sequential Quadratic Programming (SQP) is one of the most efficient methods for solving nonlinear constrained optimization problems. The SQP method is an iterative scheme, in which a local quadratic approximation is solved in each iteration step. Thereby, the quadratic objective function is determined by the gradient of the objective function and the Hessian of the Lagrange function of the original nonlinear problem (4.4.5). The nonlinear constraints are replaced by linearizations.

In the literature, the SQP method can be found in almost any book about nonlinear optimization. Geiger and Kanzow [51] and Nocedal and Wright [81] offer a great overview of this subject.

In the following, we formulate the SQP method for a nonlinear optimization problem with equality and inequality constraints as given in (4.4.5). Each function is assumed to be at least twice continuously differentiable and the dimensions are given by

$$\phi : \mathbb{R}^{n_{\xi}} \rightarrow \mathbb{R}, \quad \psi : \mathbb{R}^{n_{\xi}} \rightarrow \mathbb{R}^{n_{\psi}}, \quad \chi : \mathbb{R}^{n_{\xi}} \rightarrow \mathbb{R}^{n_{\chi}}.$$

The Lagrange function of problem (4.4.5) is given by

$$L(\xi, \lambda, \mu) = \phi(\xi) - \lambda^T \chi(\xi) - \mu^T \psi(\xi),$$

with the Lagrange multipliers $\lambda \in \mathbb{R}^{n_{\chi}}$ and $\mu \in \mathbb{R}^{2n_{\psi}}$. Thus, the following algorithm describes the SQP method for solving nonlinear constrained optimization problems.

Algorithm 4.4.1 (SQP-Method)

1. Choose an initial guess $(\xi^0, \lambda^0, \mu^0) \in \mathbb{R}^{n_\xi} \times \mathbb{R}^{n_\chi} \times \mathbb{R}^{2n_\psi}$ and set $j = 0$.
2. If $(\xi^j, \lambda^j, \mu^j)$ is a KKT-point of problem (4.4.5): STOP
3. Evaluate the function values

$$\phi^j := \phi(\xi^j), \quad \psi^j := \psi(\xi^j), \quad \chi^j := \chi(\xi^j),$$

determine the gradients

$$\nabla\phi^j := \nabla\phi(\xi^j), \quad \nabla\psi^j := \nabla\psi(\xi^j), \quad \nabla\chi^j := \nabla\chi(\xi^j)$$

and a suitable approximation of the Hessian of the Lagrange function,

$$H^j \approx \nabla_\xi^2 L(\xi^j, \lambda^j, \mu^j).$$

4. Compute a solution $\Delta\xi^j \in \mathbb{R}^{n_\xi}$ of the quadratic problem

$$\begin{aligned} \min_{\Delta\xi} \quad & \frac{1}{2} \Delta\xi^T H^j \Delta\xi + \nabla\phi^{jT} \Delta\xi \\ \text{s.t.} \quad & m_\psi \leq \psi^j + \nabla\psi^{jT} \Delta\xi \leq M_\psi \\ & 0 = \chi^j + \nabla\chi^{jT} \Delta\xi \end{aligned} \tag{4.4.6}$$

and the corresponding Lagrange multipliers $\tilde{\lambda}^j$ and $\tilde{\mu}^j$.

5. Compute a step size $t^j \in (0, 1]$ and iterate according to

$$\begin{aligned} \xi^{j+1} &:= \xi^j + t^j \Delta\xi^j, \\ \lambda^{j+1} &:= \lambda^j + t^j (\tilde{\lambda}^j - \lambda^j), \\ \mu^{j+1} &:= \mu^j + t^j (\tilde{\mu}^j - \mu^j). \end{aligned}$$

Set $j := j + 1$ and Go to step 2.

We proceed with some remarks on the SQP method.

Remark 4.4.2 In order to solve the quadratic problem (4.4.6) with equality and inequality restrictions, we apply an active set method. The active set $I(\Delta\xi^j)$ of a particular point ξ^j is defined by an index set consisting of those components of the inequality constraints where it holds equality in ξ^j , e.g.

$$\begin{aligned} I(\Delta\xi^j) := \{i \in \{1, \dots, n_\psi\} \mid & (\psi^j + \nabla\psi^j \Delta\xi^j)_i - m_{\psi,i} = 0 \\ & \text{or } M_{\psi,i} - (\psi^j + \nabla\psi^j \Delta\xi^j)_i = 0\}. \end{aligned}$$

Due to the fact, that the active set is constant in a neighborhood of the solution, the active-set method aims at identifying $I(\xi^*)$ and therefore ξ^* . If the active set is known, problem (4.4.6) can be reduced to an equality constrained optimization problem, where the inactive inequalities are deleted and the resulting problem can be solved efficiently. For a more thorough description of active-set methods, see e.g. Luenberger [74], Borgwardt [28], and Geiger and Kanzow [51].

Remark 4.4.3 The choice of an adequate step size $t^j \in (0, 1]$ conduces to a globalization of the convergence of the SQP method. If we perform the algorithm without using a suitable step size—meaning $t^j \equiv 1$ —the SQP method is only locally convergent. For the computation of adequate step sizes t^j Line-Search strategies or Trust-Region methods can be used. A thorough treatment of these methods is presented by Nocedal and Wright [81]. The Lagrange multipliers λ^j and μ^j are needed for the computation of the step size t^j . In the case of a full step procedure, the new values λ^{j+1} and μ^{j+1} are independent from the prior values λ^j and μ^j .

Remark 4.4.4 The computation of the exact Hessian $H^j = \nabla_{\xi}^2 L(\xi^j, \lambda^j, \mu^j)$ causes a huge computational effort and it is not necessarily positive definite. Even if the initial guesses and the first iterates are far away from the solution, we cannot expect the positive definiteness of H^j , which leads to problems with the treatment of the quadratic problems. In practice, one often tries to avoid the computation of the exact Hessian and makes use of appropriate approximations and update techniques, where H^{j+1} results from H^j . Powell [91] suggests a rank-2-update technique for the Hessian, where the positive definiteness can be guaranteed. With this update method a new approximation of the Hessian basically consists of the prior approximation and the gradients of the Lagrange function, where the procedure starts with an adequate initial approximation, e.g. the identity matrix or the exact Hessian $H^0 = \nabla_{\xi}^2 L(\xi^0, \lambda^0, \mu^0)$ evaluated at the initial guesses. Nocedal and Wright [81] and Stoer and Bulirsch [103] offer a detailed discussion of update formulas.

Convergence Properties of the SQP Method

While investigating the convergence properties of the SQP method with the exact Hessian, we reveal its correspondence to the Newton method applied to KKT conditions of the nonlinear optimization problem. Consequently, we consider an equality constrained optimization problem

$$\begin{aligned} \min_{\xi} \quad & \phi(\xi) \\ \text{s.t.} \quad & 0 = \widehat{\chi}(\xi), \end{aligned} \tag{4.4.7}$$

which corresponds to (4.4.5) if we are sufficiently close to the solution. The following lemma shows the connection between the SQP method and the Newton method, see Nocedal and Wright [81].

Lemma 4.4.5 *Using the exact Hessian $H^j = \nabla_{\xi}^2 \mathcal{L}(\xi^j, \lambda^j)$, the SQP method is equivalent to Newton's method applied to the Karush-Kuhn-Tucker conditions, if we are close enough to the solution.*

Proof. Let us assume without loss of generality that the initial guesses (ξ^{0T}, λ^{0T}) are close enough to the solution. The Lagrange function of problem (4.4.7) is given by

$$L(\xi, \lambda) = \phi(\xi) - \lambda^T \widehat{\chi}(\xi)$$

and the KKT conditions are

$$\begin{aligned} \nabla \phi(\xi) - \nabla \widehat{\chi}(\xi) \lambda &= 0 \\ \widehat{\chi}(\xi) &= 0. \end{aligned}$$

Using the initial guesses (ξ^{0T}, λ^{0T}) Newton's method iterates according to

$$\begin{pmatrix} \xi^{j+1} \\ \lambda^{j+1} \end{pmatrix} := \begin{pmatrix} \xi^j \\ \lambda^j \end{pmatrix} + \begin{pmatrix} \Delta \xi^j \\ \Delta \lambda^j \end{pmatrix}, \quad j = 0, 1, \dots,$$

where the increment solves the linear system

$$\begin{pmatrix} \nabla_{\xi} L(\xi^j, \lambda^j) \\ \widehat{\chi}(\xi^j) \end{pmatrix} + \begin{pmatrix} \nabla_{\xi}^2 L(\xi^j, \lambda^j) & \nabla \widehat{\chi}(\xi^j) \\ \nabla \widehat{\chi}(\xi^j)^T & 0 \end{pmatrix} \begin{pmatrix} \Delta \xi^j \\ -\Delta \lambda^j \end{pmatrix} = 0.$$

Using the definition of $\nabla_{\xi} L(\xi^j, \lambda^j)$, the first line of the equation can be rearranged to

$$\begin{aligned} \nabla_{\xi} L(\xi^j, \lambda^j) + \nabla_{\xi}^2 L(\xi^j, \lambda^j) \Delta \xi^j - \nabla \widehat{\chi}(\xi^j) \Delta \lambda^j &= 0 \\ \Leftrightarrow \nabla \phi(\xi^j) - \nabla \widehat{\chi}(\xi) \lambda + \nabla_{\xi}^2 L(\xi^j, \lambda^j) \Delta \xi^j - \nabla \widehat{\chi}(\xi^j) \Delta \lambda^j &= 0 \\ \Leftrightarrow \nabla \phi(\xi^j) + \nabla_{\xi}^2 L(\xi^j, \lambda^j) \Delta \xi^j - \nabla \widehat{\chi}(\xi^j) \underbrace{(\lambda + \Delta \lambda^j)}_{=:\bar{\lambda}^j} &= 0. \end{aligned}$$

Therefore, the linear system above is equivalent to

$$\begin{pmatrix} \nabla \phi(\xi^j) \\ \widehat{\chi}(\xi^j) \end{pmatrix} + \begin{pmatrix} \nabla_{\xi}^2 L(\xi^j, \lambda^j) & \nabla \widehat{\chi}(\xi^j) \\ \nabla \widehat{\chi}(\xi^j)^T & 0 \end{pmatrix} \begin{pmatrix} \Delta \xi^j \\ -\bar{\lambda}^j \end{pmatrix} = 0,$$

which corresponds to the KKT-conditions of the quadratic problem

$$\begin{aligned} \min_{\Delta \xi^j} \quad & \frac{1}{2} \Delta \xi^j \nabla_{\xi}^2 L(\xi^j, \lambda^j) \Delta \xi^j + \nabla \phi(\xi^j)^T \Delta \xi^j \\ & 0 = \chi(\xi^j) + \nabla \widehat{\chi}(\xi^j)^T \Delta \xi^j. \end{aligned}$$

Thus, this corresponds to the j -th iteration of the SQP method. ■

Recognizing this lemma, the convergence properties of the SQP method can be adapted from the convergence properties of Newton's method. Hence, the convergence rate of the SQP method is locally quadratic if we use the exact Hessian $H^j = \nabla_{\xi}^2 \mathcal{L}(\xi^j, \lambda^j)$ and the *Local Contraction Theorem* 2.5.1. The convergence rate of the SQP method is still super-linear if an adequate update technique for the computation of the Hessian is used, see Remark 4.4.4. For a thorough treatment of the convergence properties see Powell [90] and Geiger and Kanzow [51].

4.5 DoE Robustification

Considering the common DoE objective functions, we minimize a functional on the covariance matrix with respect to the design variables ξ . In the case of nonlinear model functions, the covariance matrix also depends on the uncertain parameter values which have to be estimated. So far, we were satisfied with the assumption, that the underlying covariance matrix is based on suitable (initial) parameter values, which satisfy the system dynamics and potential constraints. However, the parameter uncertainties can have a significant impact on the DoE problem, and may crucially affect its solution. In order to obtain stable and reliable DoE solutions we robustify the design of optimal experiments procedure by taking the parameter uncertainties into account.

In the following, we consider several approaches of robust design of optimal experiments. The first approach is a sequential approach of parameter estimation and design of optimal experiments and can be found e.g. in Körkel et al. [63] and Bock et al. [22]. The second approach of robustification is a *Worst-Case-Design* and was investigated by Bock et al. [21]. Furthermore, we consider the robustness properties of the introduced Q-criterion, especially with respect to the properties of the *Worst-Case-Design*. Finally we examine a chance constraint approach of design of optimal experiments in combination with the introduced Q-criterion.

4.5.1 A Sequential Approach

The sequential approach of parameter estimation and the design of optimal experiments consists of an alternating determination of (optimal) design variables and an estimation of the unknown parameter values. This strategy allows simultaneously a stepwise improvement of the parameter values and the statistical accuracy of the parameters. In each iteration, we solve a design of experiments problem based on the recent parameter guesses. Afterwards, we estimate the parameters based on the new optimal system settings. The following algorithm can be found in Körkel et al. [63] and was developed for the use of the common design of optimal experiments objective functions as given in Subsection 4.3.1. Actually, the procedure is completely independent from the used objective criterion and the Q-criterion can also be applied.

Algorithm 4.5.1 (Sequential DoE and Parameter Estimation)

-
1. Start with a parameter initial guess x_0 and set $j := 0$;
 2. Identify $N_{ex,j}$ (possibly new) experiments, by solving the DoE-problem (see Section 4.1) based on $x = x_j$. If $j > 0$, use all the information of the prior experiments $N_{ex,0} + \dots + N_{ex,j-1}$;
 3. Get new measurements by performing the experiments $N_{ex,j}$;
 4. Solve a parameter estimation problem by considering all experiments $N_{ex,0} + \dots + N_{ex,j}$ and obtain a new estimate x_j .
 5. Perform a sensitivity analysis to determine the statistical accuracy of the new estimate.
 6. If the statistical accuracy is satisfactory or if the available budget is exhausted:
 Stop the algorithm
 Otherwise:
 Set $j:=j+1$ and go to step 2
-

We proceed with some remarks concerning to Algorithm 4.5.1.

Remark 4.5.2 *In the third step of the algorithm, a DoE for the identification of new experiments $N_{ex,j}$ is performed by considering all prior information $N_{ex,1} + \dots + N_{ex,j-1}$. The determination of the underlying covariance matrix can be done very efficiently by computing only the components of the new experiments. The components of all prior experiments remain unaffected by the new knowledge and can directly be adopted.*

The procedure of the sequential approach for the design of optimal experiments and parameter estimation is illustrated in Figure 4.2.

Remark 4.5.3

1. We are able to consider updated model information in each iteration step of algorithm 4.5.1. This procedure can easily be combined with methods from model discrimination, see e.g. Dienes [40].
2. The convergence properties of the procedure of sequential DoE and parameter estimation of nonlinear models are described by Chaudhuri and Mykland [37].

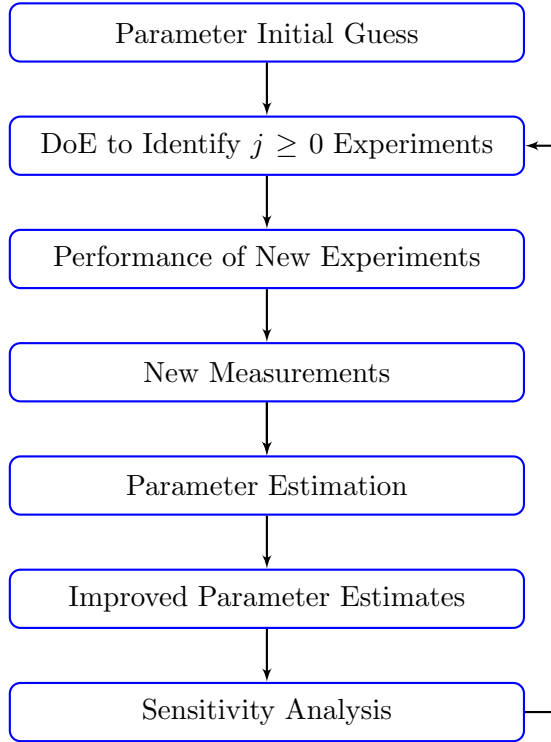


Figure 4.2: Sequential DoE and parameter estimation.

4.5.2 A Worst-Case Formulation

Considering a *Worst-Case* formulation of the DoE problem, we regard the variation of the unknown parameters. This approach is developed for the use of DoE objective functions based on the covariance matrix, as described in Subsection 4.3.1. In the following Subsection 4.5.3, we attend to the connections between the *Worst-Case* approach and the use of the Q-criterion.

For the sake of convenience, we consider an unconstrained DoE problem

$$\min_{\xi \in \Xi} \phi(\mathcal{C}(\xi, x))$$

and deal with the task of an optimal design based on the parameter guess $x = x_0$. The parameters x_0 are subject to uncertainties which we want to take into account during the DoE procedure. We assume that the parameter variation is multivariate normally distributed with a symmetric covariance matrix Σ and the parameters are assumed to lie in the confidence region

$$\mathcal{D} := \{x : (x - x_0)^T \Sigma^{-1} (x - x_0) \leq \gamma_{n_x}^2(\alpha)\}.$$

The value $\gamma_{n_x}^2(\alpha)$ denotes the $(1 - \alpha)$ -quantile of the χ^2 -distribution with n_x degrees of freedom. Abbreviatory, we define a norm $\|\cdot\|_{2,\Sigma^{-1}}$, which is induced by the inner product $\langle y, z \rangle = y^T \Sigma^{-1} z$. Hence, the confidence region may be rewritten as

$$\mathcal{D} := \{x : \|x - x_0\|_{2,\Sigma^{-1}}^2 \leq \gamma_{n_x}^2(\alpha)\}.$$

In order to consider the variation information of the unknown parameters during the DoE procedure, we focus on the parameter values of \mathcal{D} that deliver the worst result. This can mathematically be expressed by the following *Worst-Case-Design*:

$$\min_{\xi \in \Xi} \max_{x \in \mathcal{D}} \phi(C(\xi, x)), \quad (4.5.1)$$

where Ξ represents the underlying design space.

For solving this type of optimization problem, we have to apply methods of semi-infinite programming, the computation of which is very expensive, see e.g. Hettich und Kortanek [54]. Therefore, we consider a simplification of problem (4.5.1) based on a linearization of the objective function with respect to the parameters x , see Körkel [62]. Around a nominal parameter value x_0 , we get up to the first order

$$\min_{\xi \in \Xi} \max_{x \in \mathcal{D}} \phi(C(\xi, x_0)) + \frac{\partial}{\partial x} \phi(C(\xi, x_0))(x - x_0). \quad (4.5.2)$$

The inner max-problem of the linearized version can be easily solved and the following lemma provides its exact solution.

Lemma 4.5.4 *The solution of the inner problem of (4.5.2) is given by*

$$\max_{x \in \mathcal{D}} \phi(C(\xi, x_0)) + \frac{\partial}{\partial x} \phi(C(\xi, x_0))(x - x_0) = \phi(C(\xi, x_0)) + \gamma_{n_x}(\alpha) \left\| \frac{\partial}{\partial x} \phi(C(\xi, x_0)) \right\|_{2,\Sigma}.$$

Proof. Suppose that $\Delta x := x - x_0$ and $a := \frac{\partial}{\partial x} \phi(C(\xi, x_0))^T$. Because of reasons of monotonicity, the problem takes its maximum on the boundary, so we consider

$$\max_{\|\Delta x\|_{2,\Sigma^{-1}}^2 = \gamma_{n_x}^2(\alpha)} a^T \Delta x.$$

The Lagrange function is given by

$$\mathcal{L}(\Delta x, \lambda) := a^T \Delta x - \lambda(\Delta x^T \Sigma^{-1} \Delta x - \gamma_{n_x}^2(\alpha))$$

and the first order necessary optimality conditions are

$$\nabla_{\Delta x} \mathcal{L}(\Delta x, \lambda) = a - 2\lambda \Sigma^{-1} \Delta x = 0 \text{ and } \|\Delta x\|_{2,\Sigma^{-1}}^2 = \gamma_{n_x}^2(\alpha).$$

This yields

$$\Delta x = \frac{1}{2\lambda} \Sigma a$$

for Δx and according to the optimality conditions we get

$$\lambda = \pm \frac{1}{2} \sqrt{\frac{a^T \Sigma a}{\gamma_{n_x}^2(\alpha)}} = \pm \frac{1}{2} \frac{\|a\|_{2,\Sigma}}{\gamma_{n_x}(\alpha)}.$$

The maximum is given in the positive solution

$$\Delta x = \gamma_{n_x}(\alpha) \frac{\Sigma a}{\|a\|_{2,\Sigma}}$$

and the value of the objective function is

$$a^T \Delta x = \gamma_{n_x}(\alpha) \frac{a^T \Sigma a}{\|a\|_{2,\Sigma}} = \gamma_{n_x}(\alpha) \|a\|_{2,\Sigma} = \gamma_{n_x}(\alpha) \|a^T\|_{2,\Sigma}.$$

■

Hence, we get a robust formulation of the design of optimal experiments problem by considering the objective function

$$\min_{\xi \in \Xi} \phi(C(\xi, x_0)) + \gamma_{n_x}(\alpha) \left\| \frac{\partial}{\partial x} \phi(C(\xi, x_0)) \right\|_{2,\Sigma}.$$

The linearization of the objective function requires an adequate adaption of the corresponding constraints. If the DoE constraints are independent from the parameters that are to be estimated, we can adapt the constraint treatments as introduced in Section 4.4 without any changes. Parameter independent constraints are e.g. conditions for the controls or the weights from sampling design.

Let us denote the constraints which depend on the parameters by

$$\psi(\xi, x_0) \leq 0.$$

Due to the *Worst-Case*-idea, the inequality has to be fulfilled for all parameters lying in the region

$$\mathcal{D} := \{x : \|x - x_0\|_{2,\Sigma^{-1}}^2 \leq \gamma_{n_x}^2(\alpha)\}$$

thus, we require

$$\max_{x \in \mathcal{D}} \psi(\xi, x) \leq 0.$$

We linearize the constraints analogously to the considerations of the objective function and we get

$$\max_{x \in \mathcal{D}} \psi(\xi, x_0) + \frac{\partial}{\partial x} \psi(\xi, x_0)(x - x_0) \leq 0.$$

An application of Lemma 4.5.4 yields the explicit representation

$$\max_{x \in \mathcal{D}} \psi(\xi, x_0) + \frac{\partial}{\partial x} \psi(\xi, x_0)(x - x_0) = \psi(\xi, x_0) + \gamma_{n_x}(\alpha) \left\| \frac{\partial}{\partial x} \psi(\xi, x_0) \right\|_{2,\Sigma}.$$

Finally, we get the constraint

$$\psi(\xi, x_0) + \gamma_{n_x}(\alpha) \left\| \frac{\partial}{\partial x} \psi(\xi, x_0) \right\|_{2,\Sigma} \leq 0.$$

4.5.3 Robustness of the Q-Criterion

So far, the discussions of the DoE robustification were based on a linear confidence region. However, it is crucial to see how the robustness reacts in the case of a quadratic approximation. The following considerations show that an A-criterion-based robust design of optimal experiments, as introduced in Subsection 4.5.2, already contains elements of the quadratic approximation or, vice versa, that the Q-criterion covers the *Worst-Case* approach if the A-criterion is used. For simplicity of notation, we only consider an unconstrained parameter estimation problem. Obviously, the results are also valid for the constrained case.

Let us consider the A-criterion as introduced in Subsection 4.3.1. Except for the factor $\frac{1}{n_x}$, it yields $\phi_A(\mathcal{C}(\xi, x)) = \text{trace}(\mathcal{C}(\xi, x))$, with the covariance matrix $\mathcal{C} = J^+ J^{+T} = (J_1^T J_1)^{-1}$. Using the derivative rules of the trace, we get the following equation for $\frac{\partial}{\partial x} \text{trace}(\mathcal{C})$:

$$\begin{aligned} \frac{\partial}{\partial x} \text{trace}(\mathcal{C}) &= \frac{\partial \text{trace}(J^+ J^{+T})}{\partial x} \\ &= \left(\text{trace} \left(\frac{\partial(J^+ J^{+T})}{\partial x_1} \right), \dots, \text{trace} \left(\frac{\partial(J^+ J^{+T})}{\partial x_{n_x}} \right) \right) \\ &= 2 \cdot \left(\text{trace} \left(\frac{\partial J^+}{\partial x_1} J^{+T} \right), \dots, \text{trace} \left(\frac{\partial J^+}{\partial x_{n_x}} J^{+T} \right) \right) \\ &= 2 \cdot \left(\text{trace} \left(-J^+ \frac{\partial J_1}{\partial x_1} J^+ J^{+T} \right), \dots, \text{trace} \left(-J^+ \frac{\partial J_1}{\partial x_{n_x}} J^+ J^{+T} \right) \right) \\ &=: -2 \cdot \text{trace}_{n_x} \left(J^+ \frac{\partial J_1}{\partial x} J^+ J^{+T} \right), \end{aligned}$$

where the derivative of the generalized inverse J^+ is given in Section 6.3. Following Lemma 4.5.4, we can rewrite the inner problem of (4.5.1) according to

$$\begin{aligned} \max_{x \in \mathcal{D}} \phi(\mathcal{C}(\xi, x_0)) + \frac{\partial}{\partial x} \phi(\mathcal{C}(\xi, x_0))(x - x_0) \\ &= \phi(\mathcal{C}(\xi, x_0)) + \gamma_{n_x}(\alpha) \left\| \frac{\partial}{\partial x} \phi(\mathcal{C}(\xi, x_0)) \right\|_{2, \Sigma} \\ &= \text{trace}(\mathcal{C}(\xi, x_0)) + \gamma_{n_x}(\alpha) \left\| \frac{\partial}{\partial x} \text{trace}(\mathcal{C}(\xi, x_0)) \right\|_{2, \Sigma} \\ &= \text{trace}(\mathcal{C}(\xi, x_0)) - 2\gamma_{n_x}(\alpha) \left\| \text{trace}_{n_x} \left(J^+ \frac{\partial J_1}{\partial x} J^+ J^{+T} \right) \right\|_{2, \Sigma}. \end{aligned} \tag{4.5.3}$$

On the other hand, due to the results of Subsection 3.3.3 the set

$$\begin{aligned} \overline{\mathcal{D}}_{quad}(\alpha) &= \left\{ x^* + \Delta x + \frac{1}{2} \overline{\Delta x} \mid \Delta x = -J^+ \eta, \right. \\ &\quad \left. \overline{\Delta x} = -2 \left(dJ^+(\mathbb{I} - J_1 J^+) - \frac{1}{2} J^+ (dJ_1) J^+ \right) \eta, \|\eta\|_2^2 \leq \gamma_{n_x}^2(\alpha) \right\}, \end{aligned}$$

describes a quadratically approximated confidence region.
Let us denote

$$\hat{J} := (dJ^+)(\mathbb{I} - J_1 J^+) - \frac{1}{2} J^+ (dJ_1) J^+$$

and consider the estimation

$$\begin{aligned} \left\| \Delta x + \frac{1}{2} \overline{\Delta x} \right\|_2^2 &= \left\| J^+ \eta + \left((dJ^+)(\mathbb{I} - J_1 J^+) - \frac{1}{2} J^+ (dJ_1) J^+ \right) \eta \right\|_2^2 \\ &\leq \left\| J^+ + \hat{J} \right\|_F^2 \cdot \|\eta\|_2^2 \\ &= \left(\text{trace}(J^+ J^{+T}) + 2 \cdot \text{trace}(\hat{J} J^{+T}) + \text{trace}(\hat{J} \hat{J}^T) \right) \|\eta\|_2^2 \\ &= \left(\text{trace}(\mathcal{C}) - 2 \cdot \text{trace} \left(\frac{1}{2} J^+ (dJ_1) J^+ J^{+T} \right) + \|\hat{J}\|_F^2 \right) \|\eta\|_2^2 \\ &\leq \left(\text{trace}(\mathcal{C}) - 2 \cdot \text{trace}(J^+ (dJ_1) J^+ (J^+)^T) + \|\hat{J}\|_F^2 \right) \gamma_{n_x}^2(\alpha) \\ &=: \left(\text{trace}(\mathcal{C}) - 2 \cdot \text{trace}(J^+ (dJ_1) J^+ (J^+)^T) + c(\xi, x^*, \gamma_{n_x}(\alpha)) \right) \gamma_{n_x}^2(\alpha). \end{aligned} \quad (4.5.4)$$

If we take $\Sigma \approx \mathbb{I}$ and if we neglect the term $c(\xi, x^*, \gamma_{n_x}(\alpha))$ and constant coefficients, Formula (4.5.3) is approximately included in (4.5.4). Consequently, the discussed *Worst-Case* approach already contains components of the quadratic approximation. Vice versa, we perform a robust DoE if we solve the basic DoE problem by using the Q-criterion.

4.5.4 Chance-Constrained Formulation

This section is addressed to the idea to use DoE not only for the identification of those design variables which allow an estimate with an improved statistical accuracy, but also to use DoE to improve the *Gauss-Newton* convergence properties, or to ensure that the *Gauss-Newton* method converges at all.

For reasons of simplification, let us once again consider an unconstrained optimization problem

$$\min_x \frac{1}{2} \|F_1(x)\|_2^2.$$

The Jacobian be given by $J_1(x) = \partial F_1(x) / \partial x$ and the Hessian by $H(x) = B(x) + E(x)$, see also Formula (2.6.3). Matrix $B(x) := J_1^T(x) J_1(x)$ is deterministic and its inverse $B^{-1}(x)$ corresponds to the covariance matrix of the parameters. Matrix $E(x) := \frac{\partial J_1^T(x)}{\partial x} (\mathbb{I}_{n_x} \otimes F_1(x))$ includes the function F_1 and therefore is a random matrix.

As deduced in Section 2.5, the *Gauss-Newton* convergence properties are basically determined by a Lipschitz constant κ , with $\kappa < 1$, and according to Theorem 2.6.2 it holds the equivalence

$$\kappa < 1 \iff \rho(B(x)^{-1} E(x)) < 1.$$

We want to note that the matrices $B(x)$ and $E(x)$ are also depend on the design variables ξ . In order to take the requirement $\rho(B(x)^{-1}E(x)) < 1$ into account in DoE, we consider a chance-constrained optimization problem as

$$\begin{aligned} & \min_{\xi \in \Xi} \phi(\xi) \\ \text{s.t. } & \mathbb{P}(\rho(B(x, \xi)^{-1}E(x, \xi)) \geq c) \leq \alpha, \end{aligned}$$

where c, α are positive constants with $c < 1$ and $\alpha \ll 1$, and ϕ is any DoE objective function of Section 4.3. Obviously, this optimization problem cannot be used for real applications since the random matrix $E(x)$ —more precisely the function $F_1(x)$ —is not evaluable in the context of DoE due to the lack of measurements at this point. Apparently, we can use adequate approximations of $\rho(B(x, \xi)^{-1}E(x, \xi))$, but this increases to problem of finding a suitable constant $c > 0$.

However, if we consider the standard DoE problem (4.4.5), using a common objective function as given in Subsection 4.3.1, the constant κ will be reduced by lowering the *size* of $B(x)^{-1} = \mathcal{C}(x)$, by minimizing a functional on the covariance matrix. Using instead the introduced Q-criterion as an objective function of problem (4.4.5), the constant κ will be reduced by lowering the *size* of an approximation of the whole expression $B(x)^{-1}E(x)$. Thus, a measurement selection based on DoE by using the Q-criterion has very beneficial effects on the *Gauss-Newton* convergence properties. The impressive advantages of the Q-criterion can be seen in the examples given in Chapter 7.

5 Numerical Treatment of Multiple Experiment Parameter Estimation Problems

When considering multiple experiment parameter estimation problems, efficient and numerically stable computation methods are desirable. This is particularly important during the *Gauss-Newton* method where we have to solve a large scale linearized optimization problem in each iteration.

In Section 5.1, we discuss an efficient and numerically stable algorithm for solving the linearized problem in the case of a multiple experiment parameter estimation problem. Moreover, we look at its aspects of parallelization in Subsection 5.1.1. Furthermore, in Section 5.2 a numerical approach to compute a first order approximation of the covariance matrix of multiple experiment parameter estimation problems is developed and we dwell on its parallelization in Subsection 5.2.1. Finally, we conclude this chapter with a section about a parallel approach of computing the trace of the covariance matrix in Section 5.3. Most results of this chapter are also presented in Kostina and Nattermann [67]

5.1 Gauss-Newton Increments for Multiple Experiment Problems

In this section, we establish an explicit representation of the increment of a new *Gauss-Newton* iterate for multiple experiment parameter estimation problems, as developed by Schlöder [96] and Kostina and Nattermann [67]. The representation is basically determined by the use of orthogonal decompositions and it corresponds to the increment in Formula (2.4.6), which one obtains by using the generalized inverse.

Let us once again consider the experiment specific representation of the linearized problem, which we have to solve in each *Gauss-Newton* iteration,

$$\begin{aligned} \min_{\Delta x_1, \dots, \Delta x_M, \Delta p} \frac{1}{2} \sum_{k=1}^M \|F_1^k + A_x^k \Delta x_k + A_p^k \Delta p\|_2^2 \\ \text{s.t. } F_2^k + B_x^k \Delta x_k + B_p^k \Delta p = 0, \text{ for } k = 1, \dots, M. \end{aligned} \quad (5.1.1)$$

For simplicity of notation, we introduced the abbreviated notations

$$\begin{aligned} F_1^k &:= F_1^k(x_k^{(i)}, p^{(i)}) \in \mathbb{R}^{m^k}, & F_2^k &:= F_2^k(x_k^{(i)}, p^{(i)}) \in \mathbb{R}^{m_2^k}, \\ A_x^k &:= \frac{\partial F_1^k}{\partial x_k}(x_k^{(i)}, p^{(i)}) \in \mathbb{R}^{m^k \times n_x^k}, & B_x^k &:= \frac{\partial F_2^k}{\partial x_k}(x_k^{(i)}, p^{(i)}) \in \mathbb{R}^{m_2^k \times n_x^k}, \\ A_p^k &:= \frac{\partial F_1^k}{\partial p}(x_k^{(i)}, p^{(i)}) \in \mathbb{R}^{m^k \times n_p}, & B_p^k &:= \frac{\partial F_2^k}{\partial p}(x_k^{(i)}, p^{(i)}) \in \mathbb{R}^{m_2^k \times n_p}. \end{aligned}$$

Without loss of generality, let

$$M_1 \cup M_2 := \{1, \dots, M\} \quad (5.1.2)$$

be a disjoint decomposition of the experiments, such that for the Jacobian matrices B_x^k it holds that

$$\begin{aligned} m_2^k &\geq n_x^k, \text{ if } k \in M_1, \\ m_2^k &< n_x^k, \text{ if } k \in M_2, \end{aligned}$$

and $M_1 := \{1, \dots, \tilde{m}\}$, $M_2 := \{\tilde{m} + 1, \dots, M\}$, $\tilde{m} \leq M$. In order to compute an explicit representation of the increments, we first compute orthogonal decompositions of B_x^k , depending on the relations of the dimensions. Therefore, we consider the following case differentiation.

1. Decomposition of B_x^k , if $k \in M_1$:

Let

$$B_x^k = Q_k \cdot R_k, \quad (5.1.3)$$

be an orthogonal decomposition, where $Q_k \in \mathbb{R}^{m_2^k \times m_2^k}$ is an orthogonal matrix and

$$R_k = \begin{pmatrix} R_{k1} \\ R_{k2} \end{pmatrix} = \begin{pmatrix} R_{k1} \\ 0 \end{pmatrix} \in \mathbb{R}^{m_2^k \times n_x^k},$$

with a regular upper triangular matrix $R_{k1} \in \mathbb{R}^{n_x^k \times n_x^k}$. If matrix Q_k is partitioned according to $Q_k = (Q_{k1}, Q_{k2})$, where $Q_{k1} \in \mathbb{R}^{m_2^k \times n_x^k}$, it follows for the corresponding linearized constraint in (5.1.1) that

$$\begin{aligned} 0 &= B_x^k \Delta x_k + B_p^k \Delta p + F_2^k \\ &= Q_{k1} \cdot R_{k1} \Delta x_k + B_p^k \Delta p + F_2^k. \end{aligned}$$

Hence, if $k \in M_1$ we get a representation of the experiment specific increments by

$$\Delta x_k = -R_{k1}^{-1} Q_{k1}^T (B_p^k \Delta p + F_2^k). \quad (5.1.4)$$

2. Decomposition of B_x^k if $k \in M_2$:

Let

$$B_x^k = L_k \cdot Q_k^T, \quad (5.1.5)$$

be an orthogonal decomposition, where $Q_k \in \mathbb{R}^{n_x^k \times n_x^k}$ is an orthogonal matrix and $L_k = (L_{k1}, 0) \in \mathbb{R}^{m_2^k \times n_x^k}$ with the regular lower triangular matrix $L_{k1} \in \mathbb{R}^{m_2^k \times m_2^k}$. By using this decomposition and by denoting

$$Q_k^T \Delta x_k =: \Delta y_k =: \begin{pmatrix} \Delta y_{k1} \\ \Delta y_{k2} \end{pmatrix}, \quad (5.1.6)$$

it follows for the corresponding linearized constraint in Formula (5.1.1) that

$$\begin{aligned}
 0 &= B_x^k \Delta x_k + B_p^k \Delta p + F_2^k \\
 &= (L_{k1}, 0) \cdot \begin{pmatrix} \Delta y_{1k} \\ \Delta y_{2k} \end{pmatrix} + B_p^k \Delta p + F_2^k \\
 &= L_{k1} \cdot \Delta y_{k1} + B_p^k \Delta p + F_2^k.
 \end{aligned}$$

Therefore, if $k \in M_2$ we get a vector

$$\Delta y_{k1} = -L_{k1}^{-1}(B_p^k \Delta p + F_2^k). \quad (5.1.7)$$

In order to compute the increments belonging to the global parameters and to the experiment specific parameters if $k \in M_2$, we temporarily split up the objective function regarding the index sets M_1 and M_2 , respectively. Since (5.1.2) is a disjoint decomposition, it holds that the objective function can be partitioned according to

$$\begin{aligned}
 &\sum_{k=1}^M \left\| A_x^k \Delta x_k + A_p^k \Delta p + F_1^k \right\|_2^2 \\
 &= \sum_{k \in M_1} \left\| A_x^k \Delta x_k + A_p^k \Delta p + F_1^k \right\|_2^2 + \sum_{k \in M_2} \left\| A_x^k \Delta x_k + A_p^k \Delta p + F_1^k \right\|_2^2.
 \end{aligned}$$

1. Transformation of the objective function if $k \in M_1$:

By using the orthogonal decompositions of Formula (5.1.3), we get the following relation for the components of the objective functions belonging to the index set M_1 :

$$\begin{aligned}
 &\sum_{k \in M_1} \left\| A_x^k \Delta x_k + A_p^k \Delta p + F_1^k \right\|_2^2 \\
 &= \sum_{k=1}^{\tilde{m}} \left\| -A_x^k R_{k1}^{-1} Q_{k1}^T (B_p^k \Delta p + F_2^k) + A_p^k \Delta p + F_1^k \right\|_2^2 \\
 &= \sum_{k=1}^{\tilde{m}} \left\| (-A_x^k R_{k1}^{-1} Q_{k1}^T B_p^k + A_p^k) \Delta p + (-A_x^k R_{k1}^{-1} Q_{k1}^T F_2^k + F_1^k) \right\|_2^2 \\
 &=: \left\| \Gamma_{p1} \Delta p + (\mathbb{I}, D_1) \begin{pmatrix} F_{11} \\ F_{21} \end{pmatrix} \right\|_2^2,
 \end{aligned}$$

where we introduced the matrix

$$\Gamma_{p1} := \begin{pmatrix} -A_x^1 R_{11}^{-1} Q_{11}^T B_p^1 + A_p^1 \\ \vdots \\ -A_x^{\tilde{m}} R_{\tilde{m}1}^{-1} Q_{\tilde{m}1}^T B_p^{\tilde{m}} + A_p^{\tilde{m}} \end{pmatrix},$$

as well as the block diagonal matrix

$$D_1 := \begin{pmatrix} -A_x^1 R_{11}^{-1} Q_{11}^T & & \\ & \ddots & \\ & & -A_x^{\tilde{m}} R_{\tilde{m}1}^{-1} Q_{\tilde{m}1}^T \end{pmatrix},$$

and the notations

$$F_{11} := \begin{pmatrix} F_1^1 \\ \vdots \\ F_1^{\tilde{m}} \end{pmatrix} \text{ and } F_{21} := \begin{pmatrix} F_2^1 \\ \vdots \\ F_2^{\tilde{m}} \end{pmatrix}.$$

2. Transformation of the objective function if $k \in M_2$:

Due to the orthogonalities of the matrices Q_k of Formula (5.1.5) and the relations (5.1.6), it holds that $\Delta x_k = Q_k \Delta y_k$. Let $Q_k = (Q_{k1}, Q_{k2})$ be a partition, where $Q_{k1} \in \mathbb{R}^{n_x^k \times m_2^k}$ and $Q_{k2} \in \mathbb{R}^{n_x^k \times (n_x^k - m_2^k)}$ and let us consider the components of the objective function belonging to the index set $M_2 = \{\tilde{m} + 1, \dots, M\}$:

$$\begin{aligned} & \sum_{k \in M_2} \|A_x^k \Delta x_k + A_p^k \Delta p + F_1^k\|_2^2 \\ &= \sum_{k=\tilde{m}+1}^M \|A_x^k Q_{k1} \Delta y_{k1} + A_x^k Q_{k2} \Delta y_{k2} + A_p^k \Delta p + F_1^k\|_2^2 \\ &= \sum_{k=\tilde{m}+1}^M \|A_x^k Q_{k1} (-L_{k1}^{-1}) B_p^k \Delta p + A_x^k Q_{k1} (-L_{k1}^{-1}) F_2^k + A_x^k Q_{k2} \Delta y_{k2} + A_p^k \Delta p + F_1^k\|_2^2 \\ &= \sum_{k=\tilde{m}+1}^M \|(A_x^k Q_{k2}) \Delta y_{k2} + (A_x^k Q_{k1} \cdot (-L_{k1}^{-1}) B_p^k + A_p^k) \Delta p + (F_1^k + A_x^k Q_{k1} (-L_{k1}^{-1}) F_2^k)\|_2^2 \\ &= \sum_{k=\tilde{m}+1}^M \|\tilde{A}_x^k \Delta y_{k2} + \tilde{A}_p^k \Delta p + \tilde{F}_1^k\|_2^2, \end{aligned}$$

where we introduced the notations

$$\begin{aligned} \tilde{A}_x^k &:= A_x^k Q_{k2}, \\ \tilde{A}_p^k &:= A_x^k Q_{k1} \cdot (-L_{k1}^{-1}) B_p^k + A_p^k, \\ \tilde{F}_1^k &:= F_1^k + A_x^k Q_{k1} (-L_{k1}^{-1}) F_2^k. \end{aligned} \tag{5.1.8}$$

We consider another orthogonal decomposition of $\tilde{A}_x^k \in \mathbb{R}^{m_k \times (n_x^k - m_2^k)}$. Since it holds that $n_x^k - m_2^k < m_k$ —otherwise we had not enough information to estimate x_k —we consider

$$\tilde{A}_x^k = \tilde{Q}_k \tilde{R}_k, \tag{5.1.9}$$

where $\tilde{Q}_k \in \mathbb{R}^{m_k \times m_k}$ is an orthogonal matrix with $\tilde{Q}_k^T \cdot \tilde{Q}_k = \mathbb{I}$ and

$$\tilde{R}_k = \begin{pmatrix} \tilde{R}_{k1} \\ 0 \end{pmatrix} \in \mathbb{R}^{m_k \times (n_x^k - m_2^k)}.$$

The matrix $\tilde{R}_{k1} \in \mathbb{R}^{(n_x^k - m_2^k) \times (n_x^k - m_2^k)}$ is an upper triangular matrix and let $\tilde{Q}_k = (\tilde{Q}_{k1}, \tilde{Q}_{k2})$ be an appropriate partition of \tilde{Q}_k , with $\tilde{Q}_{k1} \in \mathbb{R}^{m_k \times (n_x^k - m_2^k)}$, $\tilde{Q}_{k2} \in$

$\mathbb{R}^{m_k \times (m_k + m_2^k - n_x^k)}$. Using the new introduced decomposition, it follows for the transformed objective function of the M_2 -components that

$$\begin{aligned}
 & \sum_{k=\tilde{m}+1}^M \left\| \tilde{A}_x^k \Delta y_{k2} + \tilde{A}_p^k \Delta p + \tilde{F}_1^k \right\|_2^2 \\
 &= \sum_{k=\tilde{m}+1}^M \left\| \tilde{Q}_k \tilde{R}_k \Delta y_{k2} + \tilde{A}_p^k \Delta p + \tilde{F}_1^k \right\|_2^2 \\
 &= \sum_{k=\tilde{m}+1}^M \left\| \tilde{R}_k \Delta y_{k2} + \tilde{Q}_k^T \tilde{A}_p^k \Delta p + \tilde{Q}_k^T \tilde{F}_1^k \right\|_2^2 \\
 &= \sum_{k=\tilde{m}+1}^M \left\| \begin{pmatrix} \tilde{R}_{k1} \Delta y_{k2} \\ 0 \end{pmatrix} + \begin{pmatrix} \tilde{Q}_{k1}^T \tilde{A}_p^k \\ \tilde{Q}_{k2}^T \tilde{A}_p^k \end{pmatrix} \Delta p + \begin{pmatrix} \tilde{Q}_{k1}^T \tilde{F}_1^k \\ \tilde{Q}_{k2}^T \tilde{F}_1^k \end{pmatrix} \right\|_2^2 \\
 &= \sum_{k=\tilde{m}+1}^M \left(\left\| \tilde{R}_{k1} \Delta y_{k2} + \tilde{Q}_{k1}^T \tilde{A}_p^k \Delta p + \tilde{Q}_{k1}^T \tilde{F}_1^k \right\|_2^2 + \left\| \tilde{Q}_{k2}^T \tilde{A}_p^k \Delta p + \tilde{Q}_{k2}^T \tilde{F}_1^k \right\|_2^2 \right) \\
 &= \sum_{k=\tilde{m}+1}^M \left\| \tilde{R}_{k1} \Delta y_{k2} + \tilde{Q}_{k1}^T \tilde{A}_p^k \Delta p + \tilde{Q}_{k1}^T \tilde{F}_1^k \right\|_2^2 + \left\| \Gamma_{p2} \Delta p + \tilde{Q}_2^T (\mathbb{I}, D_2) \begin{pmatrix} F_{12} \\ F_{22} \end{pmatrix} \right\|_2^2,
 \end{aligned}$$

where we used Formula (5.1.8) and we introduced the matrices

$$\begin{aligned}
 \Gamma_{p2} &:= \begin{pmatrix} \tilde{Q}_{(\tilde{m}+1)2}^T \tilde{A}_p^{\tilde{m}+1} \\ \vdots \\ \tilde{Q}_{M2}^T \tilde{A}_p^M \end{pmatrix}, \\
 \tilde{Q}_2^T &:= (\tilde{Q}_{(\tilde{m}+1)2}^T, \dots, \tilde{Q}_{M2}^T),
 \end{aligned}$$

as well as the block diagonal matrix

$$D_2 := \begin{pmatrix} -A_x^{(\tilde{m}+1)} Q_{(\tilde{m}+1)1} L_{(\tilde{m}+1)1}^{-1} & & \\ & \ddots & \\ & & -A_x^M Q_{M1} L_{M1}^{-1} \end{pmatrix},$$

and the notations

$$F_{12} := \begin{pmatrix} F_1^{\tilde{m}+1} \\ \vdots \\ F_1^M \end{pmatrix} \text{ and } F_{22} := \begin{pmatrix} F_2^{\tilde{m}+1} \\ \vdots \\ F_2^M \end{pmatrix}.$$

After the separate considerations and transformations of the objective function, we com-

bine the two components and we obtain

$$\begin{aligned}
 & \sum_{k=1}^M \|A_x^k \Delta x_k + A_p^k \Delta p + F_1^k\|_2^2 \\
 &= \left(\sum_{k=\bar{m}+1}^M \left\| \tilde{R}_{k1} \Delta y_{k2} + \tilde{Q}_{k1}^T \tilde{A}_p^k \Delta p + \tilde{Q}_{k1}^T \tilde{F}_1^k \right\|_2^2 \right) \\
 & \quad + \left\| \Gamma_{p2} \Delta p + \tilde{Q}_2^T (\mathbb{I}, D_2) \begin{pmatrix} F_{12} \\ F_{22} \end{pmatrix} \right\|_2^2 + \left\| \Gamma_{p1} \Delta p + (\mathbb{I}, D_1) \begin{pmatrix} F_{11} \\ F_{21} \end{pmatrix} \right\|_2^2 \\
 &= \left(\sum_{k=\bar{m}+1}^M \left\| \tilde{R}_{k1} \Delta y_{k2} + \tilde{Q}_{k1}^T \tilde{A}_p^k \Delta p + \tilde{Q}_{k1}^T \tilde{F}_1^k \right\|_2^2 \right) \\
 & \quad + \left\| \begin{pmatrix} \Gamma_{p1} \\ \Gamma_{p2} \end{pmatrix} \Delta p + \begin{pmatrix} \mathbb{I} & D_1 & 0 & 0 \\ 0 & 0 & \tilde{Q}_2^T & \tilde{Q}_2^T D_2 \end{pmatrix} \begin{pmatrix} F_{11} \\ F_{21} \\ F_{12} \\ F_{22} \end{pmatrix} \right\|_2^2 \\
 &= \left(\sum_{k=\bar{m}+1}^M \left\| \tilde{R}_{k1} \Delta y_{k2} + \tilde{Q}_{k1}^T \tilde{A}_p^k \Delta p + \tilde{Q}_{k1}^T \tilde{F}_1^k \right\|_2^2 \right) + \left\| \Gamma_p \Delta p + \tilde{D} \tilde{F} \right\|_2^2.
 \end{aligned}$$

Here we used the abbreviated notations

$$\Gamma_p := \begin{pmatrix} \Gamma_{p1} \\ \Gamma_{p2} \end{pmatrix}, \tag{5.1.10}$$

$$\tilde{D} := \begin{pmatrix} \mathbb{I} & D_1 & 0 & 0 \\ 0 & 0 & \tilde{Q}_2^T & \tilde{Q}_2^T D_2 \end{pmatrix}, \tag{5.1.11}$$

$$\tilde{F} := \begin{pmatrix} F_{11} \\ F_{21} \\ F_{12} \\ F_{22} \end{pmatrix}. \tag{5.1.12}$$

We chose the increment Δp in such a way that

$$\left\| \Gamma_p \Delta p + \tilde{D} \tilde{F} \right\|_2^2 = 0 \iff \Gamma_p \Delta p + \tilde{D} \tilde{F} = 0.$$

Therefore, we consider an orthogonal decomposition of matrix Γ_p according to

$$\Gamma_p = Q_p R_p \in \mathbb{R}^{(m_1 + \dots + m_M) \times n_p},$$

where $Q_p = (Q_{p1}, Q_{p2}) \in \mathbb{R}^{(m_1 + \dots + m_M) \times (m_1 + \dots + m_M)}$ is an orthogonal matrix with $Q_p^T \cdot Q_p = \mathbb{I}$ and

$$R_p = \begin{pmatrix} R_{p1} \\ 0 \end{pmatrix} \in \mathbb{R}^{(m_1 + \dots + m_M) \times n_p},$$

with a regular upper triangular matrix $R_{p1} \in \mathbb{R}^{n_p \times n_p}$. Using this decomposition it follows that the increment of the global parameters is given by

$$\Delta p = -R_{p1}^{-1} Q_{p1}^T \tilde{D} \tilde{F}. \quad (5.1.13)$$

By means of the representation of Δp and Formula (5.1.8), we are able to formulate optimal values for the components Δy_{k2} by

$$\begin{aligned} \Delta y_{k2} &= -\tilde{R}_{k1}^{-1} \left(\tilde{Q}_{k1}^T \tilde{A}_p^k \Delta p + \tilde{Q}_{k1}^T \tilde{F}_1^k \right) \\ &= -\tilde{R}_{k1}^{-1} \tilde{Q}_{k1}^T \left(-A_x^k Q_{k1} L_{k1}^{-1} B_p^k + A_p^k \right) \Delta p - \tilde{R}_{k1}^{-1} \tilde{Q}_{k1}^T \left(F_1^k - A_x^k Q_{k1} L_{k1}^{-1} F_2^k \right) \\ &= -\tilde{R}_{k1}^{-1} \tilde{Q}_{k1}^T \left(A_p^k \Delta p + F_1^k \right) - \tilde{R}_{k1}^{-1} \tilde{Q}_{k1}^T D_k \left(B_p^k \Delta p + F_2^k \right), \quad k \in M_2, \end{aligned}$$

where $D_k = -A_x^k Q_{k1} L_{k1}^{-1}$. Hence, the experiment specific increments Δx_k for $k \in M_2$ are given according to Formulas (5.1.6) and (5.1.7).

A Generalized Gauss-Newton Method for Multiple Experiment Parameter Estimation Problems

The following algorithm is an efficient and robust formulation of a generalized *Gauss-Newton* method for multiple experiment parameter estimation problems, where the increments are computed by orthogonal decompositions.

Algorithm 2

1. Let $\{1, \dots, M\} = M_1 \cup M_2$ be a disjoint partition of the experiments according to (5.1.2), where $M_1 := \{1, \dots, \tilde{m}\}$ and $M_2 := \{\tilde{m} + 1, \dots, M\}$. Furthermore, set $i := 0$ and start with an initial guess $(x_1^{(0)T}, \dots, x_M^{(0)T}, p^{(0)T})$.

2. For all $k \in \{1, \dots, M\}$ compute

$$\begin{aligned} F_1^k &:= F_1^k \left(x_k^{(i)}, p^{(i)} \right), & F_2^k &:= F_2^k \left(x_k^{(i)}, p^{(i)} \right), \\ A_x^k &:= \frac{\partial F_1^k}{\partial x_k} \left(x_k^{(i)}, p^{(i)} \right), & B_x^k &:= \frac{\partial F_2^k}{\partial x_k} \left(x_k^{(i)}, p^{(i)} \right), \\ A_p^k &:= \frac{\partial F_1^k}{\partial p} \left(x_k^{(i)}, p^{(i)} \right), & B_p^k &:= \frac{\partial F_2^k}{\partial p} \left(x_k^{(i)}, p^{(i)} \right). \end{aligned}$$

3. For $k = 1, \dots, M$

- If $k \in M_1$: compute an orthogonal decomposition

$$B_x^k =: Q_k \cdot R_k = (Q_{k1}, Q_{k2}) \begin{pmatrix} R_{k1} \\ 0 \end{pmatrix}$$

and define

$$\Delta x_k^{(i)} = -R_{k1}^{-1} Q_{k1}^T \left(B_p^k \Delta p^{(i)} + F_2^k \right)$$

- If $k \in M_2$: compute orthogonal decompositions

$$B_x^k =: L_k \cdot Q_k^T = (L_{k1}, L_{k2}) \begin{pmatrix} Q_{k1}^T \\ Q_{k2}^T \end{pmatrix},$$

$$\tilde{A}_x^k = \tilde{Q}_k \tilde{R}_k,$$

where $\tilde{A}_x^k = A_x^k Q_{k2}$ and define

$$\Delta y_{k1}^{(i)} = -L_{k1}^{-1} (B_p^k \Delta p^{(i)} + F_2^k).$$

4. Compute Γ_p , \tilde{D} , and \tilde{F} according to (5.1.10) - (5.1.12) and an orthogonal decomposition

$$\Gamma_p = Q_p R_p = (Q_{p1}, Q_{p2}) \begin{pmatrix} R_{p1} \\ 0 \end{pmatrix}.$$

5. Compute the increment of the global parameters by

$$\Delta p^{(i)} = -R_{p1}^{-1} Q_{p1}^T \tilde{D} \tilde{F}.$$

6. For all $k \in M_2$: compute

$$\Delta y_{k2}^{(i)} = -\tilde{R}_{k1}^{-1} \tilde{Q}_{k1}^T (A_p^k \Delta p + F_1^k) + \tilde{R}_{k1}^{-1} \tilde{Q}_{k1}^T A_x^k Q_{k1} L_{k1}^{-1} (B_p^k \Delta p + F_2^k),$$

and the experiment specific increments by

$$\Delta x_k^{(i)} = Q_k \begin{pmatrix} \Delta y_{k1}^{(i)} \\ \Delta y_{k2}^{(i)} \end{pmatrix}.$$

7. Compute a new iterate according to

$$\begin{pmatrix} x_1^{(i+1)} \\ \vdots \\ x_M^{(i+1)} \\ p^{(i+1)} \end{pmatrix} = \begin{pmatrix} x_1^{(i)} \\ \vdots \\ x_M^{(i)} \\ p^{(i)} \end{pmatrix} + t^{(i)} \begin{pmatrix} \Delta x_1^{(i)} \\ \vdots \\ \Delta x_M^{(i)} \\ \Delta p^{(i)} \end{pmatrix} \quad (5.1.14)$$

with a step size $t^{(i)} \in (0, 1]$.

8. If a suitable termination criterion is fulfilled:

Stop and the solution is

$$x^{*T} := (x_1^{(i+1)T}, \dots, x_M^{(i+1)T}, p^{(i+1)T}).$$

Otherwise

Set $i = i + 1$ and go to step 2.

However, using Algorithm 2, we have to compute $2M - \tilde{m} + 1$ orthogonal decompositions in each *Gauss-Newton* iteration. The decompositions related to the experiment specific components can easily be parallelized, as we will see in the following section. How to compute the needed derivatives is discussed in Chapter 6.

5.1.1 Aspects of Parallelization

This subsection deals with the parallelization of the computation of the *Gauss-Newton* increments for multiple experiment parameter estimation problems, see also Gallitzendörfer [49], and Kostina and Nattermann [67]. In the following considerations, we assume that the number of experiments exceeds the number of available processors. Otherwise the remaining processors could be used for the parallel computation of the Jacobi matrices.

For the parallelization, we use a *Master-Slave* concept, where the master processor (P1) computes all the global components and manages the computation of the independent components on the slave processors (P2), ..., (PN). In a first step, the master processor entrusts a number of experiments to each slave processor. Thus, the slave processor (Pj) receives a number of experiments

$$\text{Ex}_{j_1}, \dots, \text{Ex}_{j_{l_j}}, j=2, \dots, N,$$

where $\sum_{j=2}^N j_{l_j} = M$. The optimal allocation of the experiments to the slave processors is crucial, and such strategies will be discussed at the end of this section. Each slave processor computes the relevant Jacobi matrices evaluated at the current *Gauss-Newton* iterate, as well as the orthogonal decompositions

$$B_x^k = Q_k R_k, \text{ if } k \in M_1,$$

$$B_x^k = L_k Q_k^T \text{ and } \tilde{A}_x^k = \tilde{Q}_k \tilde{R}_k = (\tilde{Q}_{k1}, \tilde{Q}_{k2}) \begin{pmatrix} \tilde{R}_{k1} \\ \tilde{R}_{k2} \end{pmatrix}, \text{ if } k \in M_2,$$

and returns them to the master processor (P1). Furthermore, the matrix products $D_k = -A_x^k R_{k1}^{-1} Q_{k1}^T$, if $k \in M_1$, and $D_k = -A_x^k Q_{k1} L_{k1}^{-1}$, if $k \in M_2$, can also be computed in parallel on the slave processors. In particular, when computing the orthogonal decompositions, the sparse structure of the Jacobians B_x^k resulting from the Multiple Shooting approach, can be exploited. The structure of these Jacobi matrices is given in Chapter 6. The master processor (P1) determines the matrix

$$\Gamma_p = \begin{pmatrix} \Gamma_{p1} \\ \Gamma_{p2} \end{pmatrix},$$

which is defined in (5.1.10), and computes the orthogonal decomposition

$$\Gamma_p = Q_p R_p.$$

Subsequently, the increment of the global parameter values can be computed according to

$$\Delta p = -R_{p1}^{-1} Q_{p1}^T \tilde{D} \tilde{F},$$

see Formula (5.1.13). Finally, the master processor sends Δp to the slave processors, which are now able to compute the local increments according to Formula (5.1.4) if $k \in M_1$ and Formula (5.1.6) $k \in M_2$ in parallel.

In Figure 5.1 the approach of the parallel computation of the *Gauss-Newton* increments of a multiple experiment parameter estimation problem is illustrated.

In order to obtain an optimal speed-up with the parallelization techniques, an optimal partition of the single experiments to the slave processors is crucial. Since the computation rate is determined by the *slowest* slave processor, the partition of the experiments should be arranged in such a way, that each slave processor approximately deals with the same effort. Therefore, it requires a measure, which characterizes the computational effort of each single experiment.

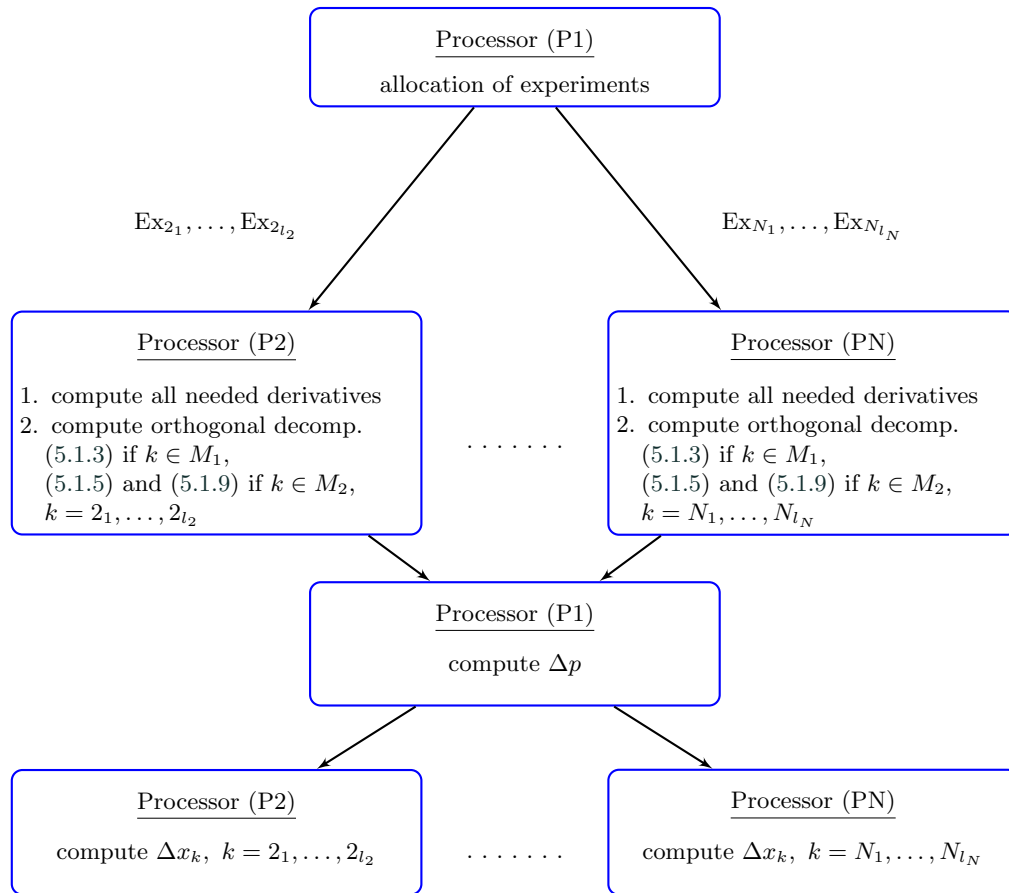


Figure 5.1: Strategy of a parallel increment computation with multiple experiments.

The question of the exact computational effort of an experiment is difficult to address. Nevertheless, by means of some key figures, a statement of the relative computational effort can be figured out and the effort of different experiments can be compared. Therefore, let us assume that e_k denotes the computational effort which has to be raised for

the k -th experiment, $k = 1, \dots, M$. Then e_k is basically proportional to the number of differential equations of the underlying dynamic system, the number of local and global variables, and the number of available measurements

$$e_k \sim \underbrace{(\#\text{differential equations}(\text{Ex}_k))}_{=n_y^k} + \underbrace{(\#\text{variables}(\text{Ex}_k))}_{=(n_x^k+n_p)} + \underbrace{(\#\text{measurements}(\text{Ex}_k))}_{=m^k}$$

$k = 1, \dots, M$. These numbers are easily available and serve for an optimal experiment partition. Furthermore, it is important to consider whether a particular experiment belongs to the index set M_1 or M_2 , which are defined in (5.1.2). If an experiment belongs to M_2 , the computational effort is approximately twice as much as if the experiment belonged to M_1 . This should also be taken into account when determining the computational effort of an experiment.

Using the introduced measure of the computational effort, we can formulate an optimization problem to compute an optimal partition of the experiments, as presented by Galitzendörfer [49]. Therefore, we denote $a := (e_1, \dots, e_M)^T$ and the total effort by e_{eff} . The optimal partition of the experiments to $N - 1$ processors is given by the solution of the mixed-integer optimization problem

$$\begin{aligned} \sum_{i=1}^{N-1} z_i &= \min_{z_1, \dots, z_{N-1}} ! \\ a^T v^i - \frac{e_{eff}}{N-1} + z_i &\geq 0, \quad i = 1, \dots, N-1, \\ -a^T v^i - \frac{e_{eff}}{N-1} + z_i &\geq 0, \quad i = 1, \dots, N-1, \\ \text{with } v^i &= (v_1^i, \dots, v_M^i)^T, \\ \sum_{i=1}^{N-1} v_j^i &= 1, \quad j = 1, \dots, M, \\ z_i \in \mathbb{R}, v_j^i &\in \{0, 1\}. \end{aligned}$$

This type of optimization problem can be solved by using e.g. *Cutting-Plane* methods. For example, Gallitzendörfer [49] and Nemhauser and Wolsey [80] offer an overview of the subject.

5.2 The Numerical Computation of the Covariance Matrix with Multiple Experiments

In this subsection, we compute an explicit representation of the covariance matrix of multiple experiment parameter estimation problems. Following Subsection 5.1, the experiment specific *Gauss-Newton* increments Δx_k and the *Gauss-Newton* increment of the global parameters Δp can be computed by using appropriate orthogonal decompositions

of the Jacobians, according to

$$\begin{aligned}\Delta p &= -R_{p1}^{-1}Q_{p1}^T\tilde{D}\tilde{F} \\ \Delta x_k &= -R_{k1}^{-1}Q_{k1}^T\left(B_p^k\Delta p + F_2^k\right), \text{ if } k \in M_1, \\ \Delta x_k &= Q_k\begin{pmatrix} 0 & -L_{k1}^{-1} \\ -\tilde{R}_{k1}^{-1}\tilde{Q}_{k1}^T & -\tilde{R}_{k1}^{-1}\tilde{Q}_{k1}^TD_k \end{pmatrix}\left(\begin{pmatrix} F_1^k \\ F_2^k \end{pmatrix} + \begin{pmatrix} A_p^k \\ B_p^k \end{pmatrix}\Delta p\right), \text{ if } k \in M_2,\end{aligned}$$

where we use the disjoint decomposition $\{1, \dots, M\} = M_1 \cup M_2$ according to (5.1.2). In the following, we compute the expected value and the covariance matrix of $(\Delta x^T, \Delta p^T)^T$ at the solution point of the generalized *Gauss-Newton* method. As before, we assume that the randomness in the parameter estimation is only determined by the independent and normally distributed measurement errors, $\varepsilon_j^k \sim \mathcal{N}(0, (\sigma_j^k)^2)$, $j = 1, \dots, m^k$, for $k = 1, \dots, M$. Furthermore, we want to note that the measurements—and therefore the random parts—only occur in the experiment specific objective functions F_1^k , and not in any Jacobi matrix.

In the following, all the functions are assumed to be evaluated at the solution point of the generalized *Gauss-Newton* method, such that the equality constraints $F_2^k = 0$ are fulfilled, for all experiments $k = 1, \dots, M$. Consequently, the expected value of the increment of the global parameter vector is given by

$$\begin{aligned}\mathbb{E}(\Delta p) &= \mathbb{E}\left(-R_{p1}^{-1}Q_{p1}^T\tilde{D}\tilde{F}\right) \\ &= -R_{p1}^{-1}Q_{p1}^T\begin{pmatrix} \mathbb{I} & D_1 & 0 & 0 \\ 0 & 0 & \tilde{Q}_2^T & \tilde{Q}_2^TD_2 \end{pmatrix}\begin{pmatrix} \mathbb{E}(F_{11}) \\ 0 \\ \mathbb{E}(F_{12}) \\ 0 \end{pmatrix} = 0.\end{aligned}$$

Hence, for the expected values of the experiment specific components Δx_k belonging to the index set M_1 , we get

$$\begin{aligned}\mathbb{E}(\Delta x_k) &= \mathbb{E}\left(-R_{k1}^{-1}Q_{k1}^T(B_p^k\Delta p + F_2^k)\right) \\ &= -R_{k1}^{-1}Q_{k1}^T\left(B_p^k \cdot \mathbb{E}(\Delta p) + 0\right) = 0.\end{aligned}$$

Finally, if $k \in M_2$, the expected values of the increments belonging to the local components are also given by

$$\begin{aligned}\mathbb{E}(\Delta x_k) &= \mathbb{E}\left(Q_k\begin{pmatrix} 0 & -L_{k1}^{-1} \\ -\tilde{R}_{k1}^{-1}\tilde{Q}_{k1}^T & -\tilde{R}_{k1}^{-1}\tilde{Q}_{k1}^TD_k \end{pmatrix}\left(\begin{pmatrix} F_1^k \\ F_2^k \end{pmatrix} + \begin{pmatrix} A_p^k \\ B_p^k \end{pmatrix}\Delta p\right)\right) \\ &= Q_k\begin{pmatrix} 0 & -L_{k1}^{-1} \\ -\tilde{R}_{k1}^{-1}\tilde{Q}_{k1}^T & -\tilde{R}_{k1}^{-1}\tilde{Q}_{k1}^TD_k \end{pmatrix}\left(\begin{pmatrix} \mathbb{E}(F_1^k) \\ 0 \end{pmatrix} + \begin{pmatrix} A_p^k \\ B_p^k \end{pmatrix}\mathbb{E}(\Delta p)\right) \\ &= 0.\end{aligned}$$

Thus, it holds that the expected values of all the increments are zero

$$\mathbb{E}\begin{pmatrix} \Delta x \\ \Delta p \end{pmatrix} = 0,$$

and therefore the covariance matrix is per definition given by

$$\begin{aligned}
 \mathcal{C} &= \mathbb{E} \left(\left[\begin{pmatrix} \Delta x \\ \Delta p \end{pmatrix} - \mathbb{E} \begin{pmatrix} \Delta x \\ \Delta p \end{pmatrix} \right] \left[\begin{pmatrix} \Delta x \\ \Delta p \end{pmatrix} - \mathbb{E} \begin{pmatrix} \Delta x \\ \Delta p \end{pmatrix} \right]^T \right) \\
 &= \mathbb{E} \left(\begin{pmatrix} \Delta x \\ \Delta p \end{pmatrix} (\Delta x^T, \Delta p^T) \right) \\
 &= \begin{pmatrix} \mathbb{E}(\Delta x_1 \Delta x_1^T) & \cdots & \mathbb{E}(\Delta x_1 \Delta x_M^T) & \mathbb{E}(\Delta x_1 \Delta p^T) \\ \vdots & \ddots & \vdots & \vdots \\ \mathbb{E}(\Delta x_M \Delta x_1^T) & \cdots & \mathbb{E}(\Delta x_M \Delta x_M^T) & \mathbb{E}(\Delta x_M \Delta p^T) \\ \mathbb{E}(\Delta p \Delta x_1^T) & \cdots & \mathbb{E}(\Delta p \Delta x_M^T) & \mathbb{E}(\Delta p \Delta p^T) \end{pmatrix} \\
 &=: \begin{pmatrix} Cov_{11} & \cdots & Cov_{1M} & Cov_{1p} \\ \vdots & \ddots & \vdots & \vdots \\ Cov_{M1} & \cdots & Cov_{MM} & Cov_{Mp} \\ Cov_{p1} & \cdots & Cov_{pM} & Cov_{pp} \end{pmatrix}. \tag{5.2.1}
 \end{aligned}$$

Hence, to compute the covariance matrix, we need the expected values $\mathbb{E}(\Delta p \Delta p^T)$, $\mathbb{E}(\Delta p \Delta x_i^T)$, $\mathbb{E}(\Delta x_i \Delta x_j^T)$, and $\mathbb{E}(\Delta x_i \Delta x_j^T)$, $i, j \in \{1, \dots, M\}$, $i \neq j$. Under consideration of the notations of Subsection 5.1, we now compute the single expected values one by one:

Computation of the expected value $\mathbb{E}(\Delta p \Delta p^T)$:

It holds that

$$\begin{aligned}
 \mathbb{E}(\Delta p \Delta p^T) &= R_{p1}^{-1} Q_{p1}^T \tilde{D} \cdot \mathbb{E}(\tilde{F} \tilde{F}^T) \cdot \tilde{D}^T Q_{p1} R_{p1}^{-T} \\
 &= R_{p1}^{-1} Q_{p1}^T \tilde{D} \begin{pmatrix} \mathbb{I} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \mathbb{I} & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tilde{D}^T Q_{p1} R_{p1}^{-T} \\
 &= R_{p1}^{-1} Q_{p1}^T \begin{pmatrix} \mathbb{I} & 0 \\ 0 & \tilde{Q}_2^T \tilde{Q}_2 \end{pmatrix} Q_{p1} R_{p1}^{-T} = R_{p1}^{-1} R_{p1}^{-T},
 \end{aligned}$$

where we use the orthogonalities $\tilde{Q}_2^T \tilde{Q}_2 = \mathbb{I}$ and $Q_{p1}^T Q_{p1} = \mathbb{I}$, as well as

$$\mathbb{E}(\tilde{F} \tilde{F}^T) = \begin{pmatrix} \mathbb{E}(F_{11} F_{11}^T) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \mathbb{E}(F_{21} F_{21}^T) & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} = \begin{pmatrix} \mathbb{I} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \mathbb{I} & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Computation of the expected values $\mathbb{E}(\Delta x_i \Delta x_i^T)$, $i \in \{1, \dots, M\}$:

- Let $i \in M_1$. Then it holds that

$$\begin{aligned}
 \mathbb{E}(\Delta x_i \Delta x_i^T) &= \mathbb{E} \left(R_{i1}^{-1} Q_{i1}^T (B_p^i \Delta p + F_2^i) (R_{i1}^{-1} Q_{i1}^T (B_p^i \Delta p + F_2^i))^T \right) \\
 &= R_{i1}^{-1} Q_{i1}^T \cdot B_p^i \mathbb{E}(\Delta p \Delta p^T) B_p^{iT} \cdot Q_{i1} R_{i1}^{-T} \\
 &= R_{i1}^{-1} Q_{i1}^T B_p^i R_{p1}^{-1} R_{p1}^{-T} B_p^{iT} Q_{i1} R_{i1}^{-T}.
 \end{aligned}$$

- Let $i \in M_2$. If we introduce the notation

$$K_i := Q_i \begin{pmatrix} 0 & -L_{i1}^{-1} \\ -\tilde{R}_{i1}^{-1} \tilde{Q}_{i1}^T & -\tilde{R}_{i1}^{-1} \tilde{Q}_{i1}^T D_i \end{pmatrix},$$

we obtain

$$\begin{aligned} \mathbb{E}(\Delta x_i \Delta x_i^T) &= \mathbb{E} \left(K_i \left(\begin{pmatrix} F_1^i \\ F_2^i \end{pmatrix} + \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} \Delta p \right) \left(K_i \left(\begin{pmatrix} F_1^i \\ F_2^i \end{pmatrix} + \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} \Delta p \right) \right)^T \right) \\ &= K_i \left(\mathbb{E} \begin{pmatrix} F_1^i F_1^{iT} & 0 \\ 0 & 0 \end{pmatrix} + \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} \cdot \mathbb{E}(\Delta p \Delta p^T) \cdot \begin{pmatrix} A_p^{iT} & B_p^{iT} \end{pmatrix} \right) K_i^T \\ &= K_i \left(\begin{pmatrix} \mathbb{I}_i & 0 \\ 0 & 0 \end{pmatrix} + \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} R_{p1}^{-1} R_{p1}^{-T} \begin{pmatrix} A_p^{iT} & B_p^{iT} \end{pmatrix} \right) K_i^T \\ &= Q_i \begin{pmatrix} 0 & 0 \\ 0 & \tilde{R}_{i1}^{-1} \tilde{R}_{i1}^{-T} \end{pmatrix} Q_i^T + K_i \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} R_{p1}^{-1} R_{p1}^{-T} \begin{pmatrix} A_p^{iT} & B_p^{iT} \end{pmatrix} K_i^T. \end{aligned}$$

Here we used the properties $\tilde{Q}_{i1}^T \tilde{Q}_{i1} = \mathbb{I}$ and $\tilde{Q}_{i2}^T \tilde{Q}_{i1} = 0$, as well as

$$\begin{aligned} K_i \cdot \mathbb{E} \left(\begin{pmatrix} F_1^i \\ F_2^i \end{pmatrix} \Delta p^T \right) &= K_i \cdot \mathbb{E} \left(\begin{pmatrix} F_1^i \\ F_2^i \end{pmatrix} \tilde{F}^T \tilde{D}^T Q_{p1} (-R_{p1}^{-T}) \right) \\ &= K_i \begin{pmatrix} 0 & 0 & \mathbb{E}(F_1^i F_{12}^T) \tilde{Q}_2 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} Q_{p1} (-R_{p1}^{-T}) \\ &= Q_i \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & -\tilde{R}_{i1}^{-1} \tilde{Q}_{i1}^T \mathbb{E}(F_1^i F_{12}^T) \tilde{Q}_2 & 0 \end{pmatrix} Q_{p1} (-R_{p1}^{-T}) = 0, \end{aligned}$$

because of

$$\begin{aligned} \tilde{Q}_{i1}^T \mathbb{E}(F_1^i F_{12}^T) \tilde{Q}_2 &= \begin{pmatrix} 0 & \dots & 0 & \tilde{Q}_{i1}^T & 0 & \dots & 0 \end{pmatrix} \tilde{Q}_2 \\ &= \tilde{Q}_{i1}^T \tilde{Q}_{i2} = 0. \end{aligned}$$

Analogously it follows $\mathbb{E}(\Delta p (F_1^{iT}, F_2^{iT})) K_i^T = 0$.

Computation of the expected values $\mathbb{E}(\Delta x_i \Delta x_j^T)$, $i, j \in \{1, \dots, M\}, j \neq i$:

- If $i, j \in M_1$, it holds that

$$\begin{aligned} \mathbb{E}(\Delta x_i \Delta x_j^T) &= \mathbb{E} \left(R_{i1}^{-1} Q_{i1}^T (B_p^i \Delta p + F_2^i) (\Delta p^T B_p^{jT} + F_2^{jT}) Q_{j1} R_{j1}^{-T} \right) \\ &= R_{i1}^{-1} Q_{i1}^T B_p^i \cdot \mathbb{E}(\Delta p \Delta p^T) \cdot B_p^{jT} Q_{j1} R_{j1}^{-T} \\ &= R_{i1}^{-1} Q_{i1}^T B_p^i R_{p1}^{-1} R_{p1}^{-T} B_p^{jT} Q_{j1} R_{j1}^{-T}. \end{aligned}$$

- If $i \in M_1$ and $j \in M_2$, it holds that

$$\begin{aligned} \mathbb{E}(\Delta x_i \Delta x_j^T) &= \mathbb{E} \left(R_{i1}^{-1} Q_{i1}^T (B_p^i \Delta p + F_2^i) (\Delta p^T (A_p^{jT}, B_p^{jT}) + (F_1^{jT}, F_2^{jT})) K_j^T \right) \\ &= R_{i1}^{-1} Q_{i1}^T \mathbb{E} \left((B_p^i \Delta p \Delta p^T (A_p^{jT}, B_p^{jT})) + B_p^i \Delta p (F_1^{jT}, F_2^{jT}) \right) K_j^T \\ &= R_{i1}^{-1} Q_{i1}^T B_p^i R_{p1}^{-1} R_{p1}^{-T} (A_p^{jT}, B_p^{jT}) K_j^T, \end{aligned}$$

where we used that $\mathbb{E}(\Delta p(F_1^{jT}, F_2^{jT})K_j^T) = 0$.

- if $i, j \in M_2$, it holds that

$$\begin{aligned}\mathbb{E}(\Delta x_i \Delta x_j^T) &= \mathbb{E}\left(K_i \left(\begin{pmatrix} F_1^i \\ F_2^i \end{pmatrix} + \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} \Delta p \right) \left(\begin{pmatrix} F_1^i \\ F_2^i \end{pmatrix} + \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} \Delta p \right)^T K_i^T\right) \\ &= K_i \left(\mathbb{E} \begin{pmatrix} F_1^i F_1^{iT} & 0 \\ 0 & 0 \end{pmatrix} + \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} \mathbb{E}(\Delta p \Delta p^T) \begin{pmatrix} A_p^{iT} & B_p^{iT} \end{pmatrix} \right) K_i^T \\ &= K_i \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} R_{p1}^{-1} R_{p1}^{-T} \begin{pmatrix} A_p^{iT} & B_p^{iT} \end{pmatrix} K_i^T.\end{aligned}$$

Computation of the expected values $\mathbb{E}(\Delta x_i \Delta p^T)$, $i \in \{1, \dots, M\}$:

- If $i \in M_1$, it holds that

$$\begin{aligned}\mathbb{E}(\Delta x_i \Delta p^T) &= \mathbb{E}(R_{i1}^{-1} Q_{i1}^T (B_p^i \Delta p + F_2^i) \Delta p^T) \\ &= R_{i1}^{-1} Q_{i1}^T B_p^i \cdot \mathbb{E}(\Delta p \Delta p^T) \\ &= R_{i1}^{-1} Q_{i1}^T B_p^i R_{p1}^{-1} R_{p1}^{-T}.\end{aligned}$$

- If $i \in M_2$, it holds hat

$$\begin{aligned}\mathbb{E}(\Delta x_i \Delta p^T) &= \mathbb{E}\left(K_i \left(\begin{pmatrix} F_1^i \\ F_2^i \end{pmatrix} + \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} \Delta p \right) \Delta p^T\right) \\ &= K_i \mathbb{E}\left(\begin{pmatrix} F_1^i \\ F_2^i \end{pmatrix} \Delta p^T \right) + K_i \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} \mathbb{E}(\Delta p \Delta p^T) \\ &= K_i \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} R_{p1}^{-1} R_{p1}^{-T},\end{aligned}$$

where we used that $K_i \mathbb{E}\left(\begin{pmatrix} F_1^i \\ F_2^i \end{pmatrix} \Delta p^T \right) = 0$.

All in all, the components of the covariance matrix of parameter estimation problems with a multiple experiment structure are given by

$$Cov_{pp} = R_{p1}^{-1} R_{p1}^{-T}, \quad (5.2.2)$$

$$Cov_{pi}^T = Cov_{ip} = \begin{cases} R_{i1}^{-1} Q_{i1}^T B_p^i R_{p1}^{-1} R_{p1}^{-T}, & i \in M_1, \\ K_i \begin{pmatrix} A_p^i \\ B_p^i \end{pmatrix} R_{p1}^{-1} R_{p1}^{-T}, & i \in M_2, \end{cases} \quad (5.2.3)$$

$$Cov_{ii} = \begin{cases} Cov_{ip}(R_{p1}^T R_{p1}) Cov_{pi}, & i \in M_1, \\ Q_i \begin{pmatrix} 0 & 0 \\ 0 & \tilde{R}_{i1}^{-1} \tilde{R}_{i1}^{-T} \end{pmatrix} Q_i^T + Cov_{ip}(R_{p1}^T R_{p1}) Cov_{pi}, & i \in M_2, \end{cases} \quad (5.2.4)$$

and

$$Cov_{ij} = \begin{cases} Cov_{ip}(R_{p1}^T R_{p1})Cov_{pj}, & i, j \in M_1, i \neq j, \\ Cov_{ip}(R_{p1}^T R_{p1})Cov_{pj}, & i, j \in M_2, i \neq j, \\ Cov_{ip}(R_{p1}^T R_{p1})Cov_{pj}, & i \in M_1, j \in M_2. \end{cases} \quad (5.2.5)$$

5.2.1 Aspects of Parallelization

The parallelization procedure of the computation of the components of the covariance matrix can be performed quite similarly to the parallel computation of the *Gauss-Newton* increments as discussed in Subsection 5.1.1. As already seen in the previous section, we need the block entries Cov_{pp} , Cov_{pi} , Cov_{ip} , Cov_{ii} and Cov_{ij} , $i, j = 1, \dots, M$, $i \neq j$, for a full description of the covariance matrix, where the main computational effort is basically determined by the computation of the components Cov_{ij} , $i \neq j$. When considering Formulas (5.2.2) to (5.2.5) we recognize a hierarchical structure of the entries of the covariance matrix according to

$$Cov_{pp} \rightarrow \begin{matrix} cov_{p1} \\ \vdots \\ cov_{pM} \end{matrix} \rightarrow \begin{matrix} COV_{11} \\ \vdots \\ COV_{MM} \end{matrix} \rightarrow cov_{ij}, \quad i, j = 1, \dots, M, \quad i \neq j,$$

which we need to take into account. Note that the required matrices and decompositions already exist from the computation of the increments and their parallel computation, respectively. For the parallel computation of the covariance matrix we use the *Master-Slave* concept, where we denote the master processor by (P1) and the slave processors by (P2), ..., (PN). In a first step, the master processor computes the matrix product $Cov_{pp} = R_{p1}^{-1} R_{p1}^{-T}$ and allocates each slave processor a number of experiments. Hence, the slave processor (Pj) receives the experiments

$$\text{Exp}_{j_1}, \dots, \text{Exp}_{j_{l_j}}, \quad j = 2, \dots, N,$$

and computes the components

$$Cov_{pi}^T = Cov_{ip} = \begin{cases} \underbrace{R_{i1}^{-1} Q_{i1}^T B_p^i}_{=: \tilde{C}_{i1}} Cov_{pp} & , \text{ if } i \in M_1 \\ Q_i \underbrace{\begin{pmatrix} 0 & -L_{i1}^{-1} \\ -\tilde{R}_{i1}^{-1} \tilde{Q}_{i1}^T & -\tilde{R}_{i1}^{-1} \tilde{Q}_{i1}^T D_i \end{pmatrix} \begin{pmatrix} A_{ip} \\ B_{ip} \end{pmatrix}}_{=: \tilde{C}_{i2}} Cov_{pp} & , \text{ if } i \in M_2, \end{cases}$$

for $i = j_1, \dots, j_{l_j}$. Subsequently, the components

$$Cov_{ii} = \begin{cases} \tilde{C}_{i1} Cov_{pp} \tilde{C}_{i1}^T & , \text{ if } i \in M_1, \\ Q_i \begin{pmatrix} 0 & 0 \\ 0 & \tilde{R}_{i1}^{-1} \tilde{R}_{i1}^{-T} \end{pmatrix} Q_i^T + \tilde{C}_{ip} Cov_{pp} \tilde{C}_{ip}^T & , \text{ if } i \in M_2, \end{cases}$$

can also be computed in parallel. A sketch of the parallelization procedure is given in Figure 5.2. By then—and after the computation of Cov_{pp} by the master processor—the parallelization can be performed intuitively.

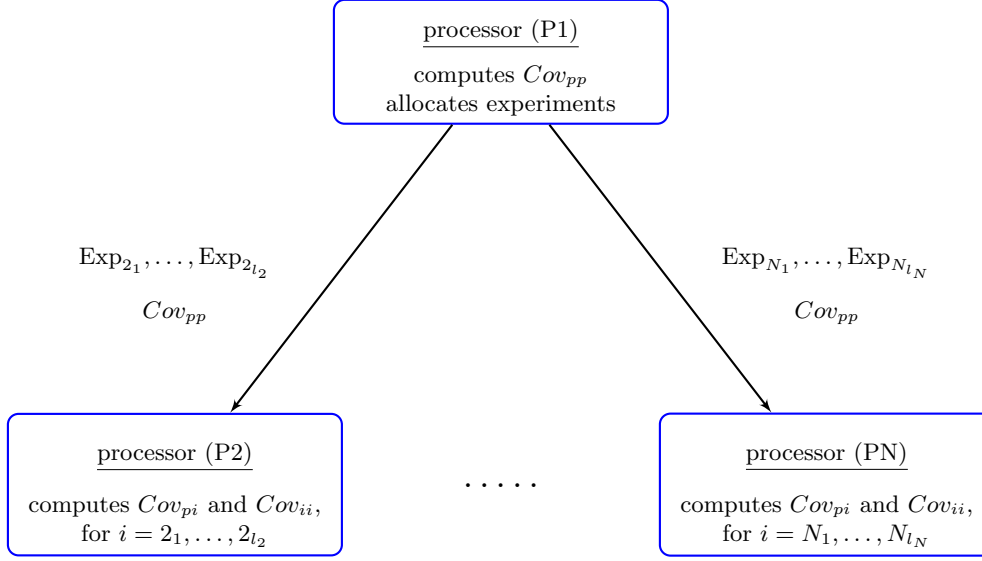


Figure 5.2: Procedure of parallel computing of the covariance matrix.

In order to compute the components

$$Cov_{ij} = Cov_{ip}(R_{p1}^T R_{p1})Cov_{pj} = \tilde{C}_{is}Cov_{pp}\tilde{C}_{js}^T,$$

for $i, j = 1, \dots, M$, with $i \neq j$, and $s = 1, 2$, an exchange of the parallel computed matrices \tilde{C}_{is} is needed. To realize this adequately, the slave processor (Pj) commits the matrices \tilde{C}_{is} , $i = j_1, \dots, j_{l_j}$, to the slave processor (Pj+1), for $j = 2, \dots, N - 1$, and processor (P2) receives the matrices $\tilde{C}_{N_1s}, \dots, \tilde{C}_{N_{l_N}s}$ in a first step. At this point processor (Pj) is able to compute the components Cov_{lk} , $l = (j - 1)_1, \dots, (j - 1)_{l_{(j-1)}}$, $k = j_1, \dots, j_{l_j}$, for $j = 3, \dots, N$ and processor (P2) computes Cov_{lk} , $l = 2_1, \dots, 2_{l_1}$, for $k = N_1, \dots, N_{l_N}$. In the following steps, the matrices can be committed to the processor after the next, and so on. Because of the symmetry of the matrices Cov_{ij} , this procedure stops after $\lceil \frac{N-1}{2} \rceil$ steps.

In order to obtain an optimal speed-up by using parallelization techniques, an optimal partition of the single experiments to the slave processors is crucial. How to realize an optimal partition is discussed in Subsection 5.1.1.

5.3 The Numerical and Parallel Computation of $\text{trace}(C)$

When using an A-criterion- or a Q-criterion-based DoE approach for the determination of optimal system settings for the parameter estimation procedure, the trace of the co-

variance matrix is required. In this section, we introduce a parallel computation of

$$\phi_A(\mathcal{C}) = \frac{1}{n_x} \text{trace}(\mathcal{C}),$$

in case of a multiple experiment parameter estimation problem, see also Kostina and Nattermann [67]. To this end, we consider the covariance matrix

$$\mathcal{C} = \begin{pmatrix} \mathbb{E}(\Delta x_1 \Delta x_1^T) & \cdots & \mathbb{E}(\Delta x_1 \Delta x_M^T) & \mathbb{E}(\Delta x_1 \Delta p^T) \\ \vdots & \ddots & \vdots & \vdots \\ \mathbb{E}(\Delta x_M \Delta x_1^T) & \cdots & \mathbb{E}(\Delta x_M \Delta x_M^T) & \mathbb{E}(\Delta x_M \Delta p^T) \\ \mathbb{E}(\Delta p \Delta x_1^T) & \cdots & \mathbb{E}(\Delta p \Delta x_M^T) & \mathbb{E}(\Delta p \Delta p^T) \end{pmatrix}$$

as introduced in Subsection 5.2. Considering the disjoint decomposition $\{1, \dots, M\} = M_1 \cup M_2$ according to (5.1.2), it holds that

$$\begin{aligned} \text{trace}(\mathcal{C}) &= \text{trace}(\mathbb{E}(\Delta p \Delta p^T)) + \sum_{i=1}^M \text{trace}(\mathbb{E}(\Delta x_i \Delta x_i^T)) \\ &= \text{trace}(\mathbb{E}(\Delta p \Delta p^T)) + \sum_{i \in M_1} \text{trace}(\mathbb{E}(\Delta x_i \Delta x_i^T)) + \sum_{i \in M_2} \text{trace}(\mathbb{E}(\Delta x_i \Delta x_i^T)). \end{aligned}$$

Recognizing the results of Subsection 5.2, it follows immediately from the linearity of the trace and the relation

$$\text{trace}(A^T A) = \|A\|_F^2$$

for any matrix $A \in \mathbb{R}^{m \times n}$, that

$$\begin{aligned} \text{trace}(\mathbb{E}(\Delta p \Delta p^T)) &= \text{trace}(R_{p1}^{-1} R_{p1}^{-T}) = \|R_{p1}^{-1}\|_F^2, \\ \text{trace}(\mathbb{E}(\Delta x_i \Delta x_i^T)) &= \|R_{i1}^{-1} Q_{i1}^T B_p^i R_{p1}^{-1}\|_F^2, \quad i \in M_1, \\ \text{trace}(\mathbb{E}(\Delta x_i \Delta x_i^T)) &= \|\tilde{R}_{i1}^{-1}\|_F^2 + \|L_{i1}^{-1} B_p^i R_{p1}^{-1}\|_F^2 + \|\tilde{R}_{i1}^{-1} \tilde{Q}_{i1}^T \tilde{A}_p^i R_{p1}^{-1}\|_F^2, \quad i \in M_2, \end{aligned}$$

where $\tilde{A}_p^i = D_i B_p^i + A_p^i = A_x^i Q_{i1} (-L_{i1}^{-1}) B_p^i + A_p^i$. Hence, all in all we get the following representation

$$\begin{aligned} \text{trace}(\mathcal{C}) &= \|R_{p1}^{-1}\|_F^2 + \sum_{i \in M_1} \|R_{i1}^{-1} Q_{i1}^T B_p^i R_{p1}^{-1}\|_F^2 \\ &\quad + \sum_{i \in M_2} \left(\|L_{i1}^{-1} B_p^i R_{p1}^{-1}\|_F^2 + \|\tilde{R}_{i1}^{-1} \tilde{Q}_{i1}^T \tilde{A}_p^i R_{p1}^{-1}\|_F^2 + \|\tilde{R}_{i1}^{-1}\|_F^2 \right). \end{aligned} \tag{5.3.1}$$

The parallel computation of the trace of the covariance matrix proceeds in a similar way to the parallel computation of the single components of the covariance matrix as given in Subsection 5.1. Nevertheless, if we only need the trace of the covariance matrix, the

costly computation of the components $\mathbb{E}(\Delta x_i \Delta x_j)$, $i \neq j$, can be saved. If we assume that all needed matrices are available from the parallel computation of the increments of a new *Gauss-Newton* iterate, we basically need to compute norms of matrices. After an appropriate partitioning of the single experiments to the slave processors, the norm $\left\| R_{p1}^{-1} \right\|_F^2$ can be determined by the master processor. The slave processor (Pj), for $j = 2, \dots, N$, computes the following norms

$$\|L_{i1}^{-1} B_p^i R_{p1}^{-1}\|_F^2, \|\tilde{R}_{i1}^{-1} \tilde{Q}_{i1}^T \tilde{A}_p^i R_{p1}^{-1}\|_F^2, \|\tilde{R}_{i1}^{-1}\|_F^2, \|R_{i1}^{-1} Q_{i1}^T B_p^i R_{p1}^{-1}\|_F^2$$

for $i = j_1, \dots, j_{l_j}$. After having received all the single norm components, the master processor computes the sum (5.3.1). Hence, the computation speed essentially depends on the partitioning of the experiments to the slave-processors. Suitable approaches to an optimal partitioning of the experiments are given in Subsection 5.1.1.

6 Derivatives

In this thesis, almost every considered problem and solution method is based on derivatives. In order to solve the parameter estimation problem as introduced in Chapter 2, we need the first derivative of the underlying model functions. The quadratically approximated confidence region from Chapter 3, as well as the Q-criterion as introduced in Chapter 4 are based on the first and second order derivatives. In addition to that, we need derivatives with respect to the design variables to solve the DoE problem by means of the SQP method. In this chapter we consider all these relevant derivatives and dwell on methods of their numerical computation.

In the first Section 6.1, we consider the first and the second order derivatives of the model functions from the parameter estimation problem with respect to the parameters. The derivative of the newly introduced Q-criterion for the design of optimal experiments is discussed in Section 6.2. There, we also consider the derivative of the covariance matrix and we dwell on aspects of a parallel computation of its derivative. The derivative of generalized inverses is treated in Section 6.3. There, we deal with both cases, the unconstrained case, where J^+ is a Moore-Penrose pseudo-inverse, and the constrained case, where J^+ is not a Moore-Penrose pseudo-inverse. Numerical methods for the computation of derivatives are given in Section 6.4.

6.1 Derivatives of the Parameter Estimation Problem

In order to investigate the derivatives of the parameter estimation problem, we consider the finite dimensional multiple experiment parameter estimation problem

$$\begin{aligned} \min_{x_1, \dots, x_M, p} \frac{1}{2} \sum_{k=1}^M \left\| F_1^k(x_k, p) \right\|_2^2 \\ \text{s.t. } F_2^k(x_k, p) = 0, \quad k = 1, \dots, M, \end{aligned} \quad (6.1.1)$$

as introduced in Subsection 2.3.1. Thereby, the functions $F_1^k : \mathbb{R}^{n_x^k} \times \mathbb{R}^{n_p} \rightarrow \mathbb{R}^{m^k}$ and $F_2^k : \mathbb{R}^{n_x^k} \times \mathbb{R}^{n_p} \rightarrow \mathbb{R}^{m_2^k}$ are assumed to be at least twice continuously differentiable, and they are explicitly given by

$$F_1^k(x_k, p) := \Sigma_k^{-1} \begin{pmatrix} \eta_1^k - h_1^k(y^k(t_1^k; s^k), p, \tilde{p}^k) \\ \vdots \\ \eta_{m^k}^k - h_{m^k}^k(y^k(t_{m^k}^k; s^k), p, \tilde{p}^k) \end{pmatrix}$$

and

$$F_2^k(x_k, p) := \begin{pmatrix} r^k(s^k, p, \tilde{p}^k) \\ b_0^k(s_0^k, s_1^k, p, \tilde{p}^k) \\ \vdots \\ b_{l_k-1}^k(s_{l_k-1}^k, s_{l_k}^k, p, \tilde{p}^k) \end{pmatrix},$$

for all experiments $k = 1, \dots, M$. Note that at this point we only consider the case where the differential systems have been discretized by the *Multiple Shooting* approach, see Section 2.2. The vector $p \in \mathbb{R}^{n_p}$ includes the global unknown parameter values and the experiment specific optimization variables are given by $x_k^T = (s^{kT}, \tilde{p}^{kT}) \in \mathbb{R}^{n_x^k}$, where x_k consists of the optimization variables s^k of the *Multiple Shooting* approach and the unknown experiment specific model coefficients \tilde{p}^k .

In the following two subsections, we discuss the structures of the first and the second order derivatives of the model functions F_1^k, F_2^k with respect to the global and the local parameters.

6.1.1 The Structure of the Jacobi Matrices

When solving problem (6.1.1) by means of a generalized *Gauss-Newton* method, we have to solve a linearized problem,

$$\begin{aligned} \min_{\Delta x_1, \dots, \Delta x_M, \Delta p} \sum_{k=1}^M \left\| F_1^k(x_k, p) + A_x^k \Delta x_k + A_p^k \Delta p \right\|_2^2 \\ \text{s.t. } F_2^k(x_k, p) + B_x^k \Delta x_k + B_p^k \Delta p = 0, \quad k = 1, \dots, M, \end{aligned} \quad (6.1.2)$$

at each iteration. By analogy with Section 5.1, we introduce the following abbreviated notations,

$$\begin{aligned} A_x^k &:= \frac{\partial F_1^k(x_k, p)}{\partial x_k} \in \mathbb{R}^{m^k \times n_x^k}, & B_x^k &:= \frac{\partial F_2^k(x_k, p)}{\partial x_k} \in \mathbb{R}^{m_2^k \times n_x^k}, \\ A_p^k &:= \frac{\partial F_1^k(x_k, p)}{\partial p} \in \mathbb{R}^{m^k \times n_p}, & B_p^k &:= \frac{\partial F_2^k(x_k, p)}{\partial p} \in \mathbb{R}^{m_2^k \times n_p}, \end{aligned}$$

for the first derivatives. Considering representation (2.4.1) of the parameter estimation problem, it holds that the Jacobians are composed of

$$J_1^k(x_k, p) := \left(A_x^k, A_p^k \right) = \frac{\partial F_1^k(x_k, p)}{\partial (x_k, p)} \quad (6.1.3)$$

and

$$J_2^k(x_k, p) := \left(B_x^k, B_p^k \right) = \frac{\partial F_2^k(x_k, p)}{\partial (x_k, p)}. \quad (6.1.4)$$

In the following, we consider the Jacobi matrices more precisely.

- **Computation of the Jacobians A_x^k**

The Jacobians of the experiment specific objective functions with respect to the local optimization variables are given by

$$\begin{aligned} A_x^k &= \left(\frac{\partial F_1^k(x_k, p)}{\partial s_0^k}, \dots, \frac{\partial F_1^k(x_k, p)}{\partial s_{l_k}^k}, \frac{\partial F_1^k(x_k, p)}{\partial \tilde{p}^k} \right) \\ &=: \left(D_{1,0}^k, \dots, D_{1,l_k}^k, D_{1,\tilde{p}}^k \right), \end{aligned}$$

where we introduced the derivative matrices $D_{1,\tilde{p}}^k := \frac{\partial F_1^k(x_k, p)}{\partial \tilde{p}^k} \in \mathbb{R}^{m^k \times n_{\tilde{p}}^k}$ and $D_{1,j}^k = \frac{\partial F_1^k(x_k, p)}{\partial s_j^k} \in \mathbb{R}^{m^k \times n_y^k}$, for $j = 0, \dots, l_k$. More precisely, it holds that the derivatives with respect to the discretization variables s_j^k are

$$D_{1,j}^k = -\Sigma_k^{-1} \begin{pmatrix} \frac{\partial h_1^k(y^k(t_1^k; s^k), p, \tilde{p}^k)}{\partial y^k} \frac{\partial y^k(t_1^k; s^k, p, \tilde{p}^k)}{\partial s_j^k} \\ \vdots \\ \frac{\partial h_{m^k}^k(y^k(t_{m^k}^k; s^k), p, \tilde{p}^k)}{\partial y^k} \frac{\partial y^k(t_{m^k}^k; s^k, p, \tilde{p}^k)}{\partial s_j^k} \end{pmatrix} =: -\Sigma_k^{-1} \begin{pmatrix} \frac{\partial h^k}{\partial y^k} \frac{\partial y^k}{\partial s_j^k} \end{pmatrix} \quad (6.1.5)$$

and the derivatives with respect to the local parameters are

$$\begin{aligned} D_{1,\tilde{p}}^k &= -\Sigma_k^{-1} \begin{pmatrix} \frac{\partial h_1^k(y^k(t_1^k; s^k), p, \tilde{p}^k)}{\partial \tilde{p}^k} + \frac{\partial h_1^k(y^k(t_1^k; s^k), p, \tilde{p}^k)}{\partial y^k} \frac{\partial y^k(t_1^k; s^k, p, \tilde{p}^k)}{\partial \tilde{p}^k} \\ \vdots \\ \frac{\partial h_{m^k}^k(y^k(t_{m^k}^k; s^k), p, \tilde{p}^k)}{\partial \tilde{p}^k} + \frac{\partial h_{m^k}^k(y^k(t_{m^k}^k; s^k), p, \tilde{p}^k)}{\partial y^k} \frac{\partial y^k(t_{m^k}^k; s^k, p, \tilde{p}^k)}{\partial \tilde{p}^k} \end{pmatrix} \\ &=: -\Sigma_k^{-1} \left(\frac{\partial h^k}{\partial \tilde{p}^k} + \frac{\partial h^k}{\partial y^k} \frac{\partial y^k}{\partial \tilde{p}^k} \right). \end{aligned} \quad (6.1.6)$$

- **Computation of the Jacobians A_p^k**

The Jacobians of the experiment specific objective functions with respect to the global optimization variables are given by

$$\begin{aligned} A_p^k &= -\Sigma_k^{-1} \begin{pmatrix} \frac{\partial h_1^k(y^k(t_1^k; s^k), p, \tilde{p})}{\partial p} + \frac{\partial h_1^k(y^k(t_1^k; s^k), p, \tilde{p}^k)}{\partial y^k} \frac{\partial y^k(t_1^k; s^k, p, \tilde{p}^k)}{\partial p} \\ \vdots \\ \frac{\partial h_{m^k}^k(y^k(t_{m^k}^k; s^k), p, \tilde{p}^k)}{\partial p} + \frac{\partial h_{m^k}^k(y^k(t_{m^k}^k; s^k), p, \tilde{p}^k)}{\partial y^k} \frac{\partial y^k(t_{m^k}^k; s^k, p, \tilde{p}^k)}{\partial p} \end{pmatrix} \\ &=: -\Sigma_k^{-1} \left(\frac{\partial h^k}{\partial p} + \frac{\partial h^k}{\partial y^k} \frac{\partial y^k}{\partial p} \right) \\ &=: D_{1,p}^k \in \mathbb{R}^{m^k \times n_p}. \end{aligned} \quad (6.1.7)$$

• **Computation of the Jacobians B_x^k**

The Jacobians of the experiment specific constraint functions with respect to the local optimization variables are given by

$$\begin{aligned}
 B_x^k &= \left(\frac{\partial F_2^k(x_k, p)}{\partial s_0^k}, \dots, \frac{\partial F_2^k(x_k, p)}{\partial s_{l_k}^k}, \frac{\partial F_2^k(x_k, p)}{\partial \tilde{p}^k} \right) \\
 &= \begin{pmatrix} \frac{\partial r^k(s^k, p, \tilde{p}^k)}{\partial s_0^k} & \cdots & \frac{\partial r^k(s^k, p, \tilde{p}^k)}{\partial s_{l_k}^k} & \frac{r^k(s^k, p, \tilde{p}^k)}{\partial \tilde{p}^k} \\ \frac{b_0^k(s_0^k, s_1^k, p, \tilde{p}^k)}{\partial s_0^k} & \cdots & \frac{b_0^k(s_0^k, s_1^k, p, \tilde{p}^k)}{\partial s_{l_k}^k} & \frac{b_0^k(s_0^k, s_1^k, p, \tilde{p}^k)}{\partial \tilde{p}^k} \\ \vdots & & \vdots & \vdots \\ \frac{b_{l_k-1}^k(s_{l_k-1}^k, s_{l_k}^k, p, \tilde{p}^k)}{\partial s_0^k} & \cdots & \frac{b_{l_k-1}^k(s_{l_k-1}^k, s_{l_k}^k, p, \tilde{p}^k)}{\partial s_{l_k}^k} & \frac{b_{l_k-1}^k(s_{l_k-1}^k, s_{l_k}^k, p, \tilde{p}^k)}{\partial \tilde{p}^k} \end{pmatrix} \\
 &=: \begin{pmatrix} D_{2,0}^k & \cdots & \cdots & D_{2,l_k}^k & D_{2,\tilde{p}^k}^k \\ G_0^k & -\mathbb{I} & & & G_{0,\tilde{p}^k}^k \\ & \ddots & \ddots & & \vdots \\ & & G_{l_k-1}^k & -\mathbb{I} & G_{l_k-1,\tilde{p}^k}^k \end{pmatrix},
 \end{aligned}$$

where we introduced the following notations for the derivatives of the restriction functions r^k with respect to s_j^k and \tilde{p}^k ,

$$D_{2,j}^k := \frac{\partial r^k(s^k, p, \tilde{p}^k)}{\partial y^k} \frac{\partial y^k}{\partial s_j^k} \in \mathbb{R}^{m_{2r} \times n_y^k}, \quad j = 0, \dots, l_k, \quad (6.1.8)$$

and

$$D_{2,\tilde{p}^k}^k := \frac{\partial r^k(s^k, p, \tilde{p}^k)}{\partial \tilde{p}^k} + \frac{\partial r^k(s^k, p, \tilde{p}^k)}{\partial y^k} \frac{\partial y^k}{\partial \tilde{p}^k} \in \mathbb{R}^{m_{2r} \times n_{\tilde{p}^k}^k}. \quad (6.1.9)$$

The derivatives of the *Multiple Shooting* continuity conditions with respect to the local parameters are

$$G_j^k := \frac{\partial b_j^k(s_j^k, s_{j+1}^k, p, \tilde{p}^k)}{\partial s_j^k} = \frac{\partial y^k(\tau_{j+1}; s_j^k, p, \tilde{p}^k)}{\partial s_j^k} \in \mathbb{R}^{n_y^k \times n_y^k} \quad (6.1.10)$$

and

$$G_{j,\tilde{p}^k}^k := \frac{\partial b_j^k(s_j^k, s_{j+1}^k, p, \tilde{p}^k)}{\partial \tilde{p}^k} = \frac{\partial y^k(\tau_{j+1}; s_j^k, p, \tilde{p}^k)}{\partial \tilde{p}^k} \in \mathbb{R}^{n_y^k \times n_{\tilde{p}^k}^k}, \quad (6.1.11)$$

for $j = 0, \dots, l_k - 1$.

The sparse structure of matrices B_x^k results from the matching conditions of the *Multiple Shooting* approach. This allows very efficient implementations, in particular if $M = 1$, as given in Bock [19], Schlöder [96], Stoer and Bulirsch [103], or Ascher et al. [3]. Approaches of a parallel computation of the independent components are given in Gallitzendörfer [49].

- **Computation of the Jacobians B_p^k**

The Jacobians of the experiment specific constraint functions with respect to the global optimization variables are given by

$$B_p^k = \frac{\partial F_2^k(x_k, p)}{\partial p} =: \begin{pmatrix} D_{2,p}^k \\ G_{0,p}^k \\ \vdots \\ G_{l_k-1,p}^k \end{pmatrix},$$

where we introduced the derivative matrices

$$D_{2,p}^k := \frac{\partial r^k(s^k, p, \tilde{p}^k)}{\partial p} + \frac{\partial r^k(s^k, p, \tilde{p}^k)}{\partial y^k} \frac{\partial y^k}{\partial p} \in \mathbb{R}^{m_{2r}^k \times n_p} \quad (6.1.12)$$

and

$$G_{j,p}^k := \frac{\partial b_j^k(s_j^k, s_{j+1}^k, p, \tilde{p}^k)}{\partial p} = \frac{\partial y^k(\tau_{j+1}; s_j^k, \tilde{p}^k, p)}{\partial p} \in \mathbb{R}^{n_y^k \times n_p}, \quad (6.1.13)$$

for all $j = 0, \dots, l_k - 1$.

6.1.2 The Structure of the Second Derivatives

In order to compute the quadratically approximated confidence region and especially for the robust formulation of the design of optimal experiment problem with the Q-criterion, we need the second derivatives of the model functions with respect to the optimization variables of the parameter estimation. The following components are needed for the entire representation of the second derivative,

$$\begin{aligned} A_{xx}^k &:= \frac{\partial A_x^k}{\partial x_k} = \frac{\partial^2 F_1^k(x_k, p)}{\partial x_k^2} \in \mathbb{R}^{m_1^k \times (n_x^k)^2}, & B_{xx}^k &:= \frac{\partial B_x^k}{\partial x_k} = \frac{\partial^2 F_2^k(x_k, p)}{\partial x_k^2} \in \mathbb{R}^{m_2^k \times (n_x^k)^2}, \\ A_{xp}^k &:= \frac{\partial A_p^k}{\partial x_k} = \frac{\partial^2 F_1^k(x_k, p)}{\partial x_k \partial p} \in \mathbb{R}^{m_1^k \times (n_x^k \cdot n_p)}, & B_{xp}^k &:= \frac{\partial B_p^k}{\partial x_k} = \frac{\partial^2 F_2^k(x_k, p)}{\partial x_k \partial p} \in \mathbb{R}^{m_2^k \times (n_x^k \cdot n_p)}, \\ A_{px}^k &:= \frac{\partial A_x^k}{\partial p} = \frac{\partial^2 F_1^k(x_k, p)}{\partial p \partial x_k} \in \mathbb{R}^{m_1^k \times (n_p \cdot n_x)}, & B_{px}^k &:= \frac{\partial B_x^k}{\partial p} = \frac{\partial^2 F_2^k(x_k, p)}{\partial p \partial x_k} \in \mathbb{R}^{m_2^k \times (n_p \cdot n_x)}, \\ A_{pp}^k &:= \frac{\partial A_p^k}{\partial p} = \frac{\partial^2 F_1^k(x_k, p)}{\partial p^2} \in \mathbb{R}^{m_1^k \times n_p^2}, & B_{pp}^k &:= \frac{\partial B_p^k}{\partial p} = \frac{\partial^2 F_2^k(x_k, p)}{\partial p^2} \in \mathbb{R}^{m_2^k \times n_p^2}. \end{aligned}$$

In the following the single derivative matrices are given in detail. Thus, for simplicity of notation we omit the function arguments.

- **Computation of the Second Derivative A_{xx}^k**

It holds that the second derivative of the experiment specific objective functions F_1^k with respect to the experiment specific variables is given by

$$A_{xx}^k = \left(\frac{\partial A_x^k}{\partial s_0^k}, \dots, \frac{\partial A_x^k}{\partial s_{l_k}^k}, \frac{\partial A_x^k}{\partial \tilde{p}^k} \right),$$

where $k = 1, \dots, M$. The derivatives with respect to the optimization variables from the *Multiple Shooting* are composed by

$$\frac{\partial A_x^k}{\partial s_j^k} = \left(\frac{\partial D_{1,0}^k}{\partial s_j^k}, \dots, \frac{\partial D_{1,l_k}^k}{\partial s_j^k}, \frac{\partial D_{1,\tilde{p}}^k}{\partial s_j^k} \right) =: (D_{1,0,j}^k, \dots, D_{1,l_k,j}^k, D_{1,\tilde{p},j}^k)$$

and the derivatives with respect the the local parameters can be described by

$$\frac{\partial A_x^k}{\partial \tilde{p}^k} = \left(\frac{\partial D_{1,0}^k}{\partial \tilde{p}^k}, \dots, \frac{\partial D_{1,l_k}^k}{\partial \tilde{p}^k}, \frac{\partial D_{1,\tilde{p}}^k}{\partial \tilde{p}^k} \right) =: (D_{1,0,\tilde{p}}^k, \dots, D_{1,l_k,\tilde{p}}^k, D_{1,\tilde{p},\tilde{p}}^k).$$

If we take notations (6.1.5) and (6.1.6) into account, each single derivative matrix is explicitly given by

$$D_{1,i,j}^k := -\Sigma_k^{-1} \left(\left(\frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial s_j^k} \right) \frac{\partial y^k}{\partial s_i^k} + \frac{\partial h^k}{\partial y^k} \frac{\partial^2 y^k}{\partial s_i^k \partial s_j^k} \right),$$

$$D_{1,\tilde{p},j}^k := -\Sigma_k^{-1} \left(\frac{\partial^2 h^k}{\partial \tilde{p}^k \partial y^k} \frac{\partial y^k}{\partial s_j^k} + \left(\frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial s_j^k} \right) \frac{\partial y^k}{\partial \tilde{p}^k} + \frac{\partial h^k}{\partial y^k} \frac{\partial y^k}{\partial \tilde{p}^k \partial s_j^k} \right),$$

$$D_{1,i,\tilde{p}}^k := -\Sigma_k^{-1} \left(\left(\frac{\partial^2 h^k}{\partial y^k \partial \tilde{p}^k} + \frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial \tilde{p}^k} \right) \frac{\partial y^k}{\partial s_i^k} + \frac{\partial h^k}{\partial y^k} \frac{\partial^2 y^k}{\partial s_i^k \partial \tilde{p}^k} \right),$$

$$D_{1,\tilde{p},\tilde{p}}^k := -\Sigma_k^{-1} \left(\frac{\partial^2 h^k}{\partial (\tilde{p}^k)^2} + \frac{\partial^2 h^k}{\partial \tilde{p}^k \partial y^k} \frac{\partial y^k}{\partial \tilde{p}^k} + \left(\frac{\partial^2 h^k}{\partial y^k \partial \tilde{p}^k} + \frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial \tilde{p}^k} \right) \frac{\partial y^k}{\partial \tilde{p}^k} + \frac{\partial h^k}{\partial y^k} \frac{\partial^2 y^k}{\partial (\tilde{p}^k)^2} \right),$$

where $i, j = 0, \dots, l_k$.

- **Computation of the Second Derivative A_{xp}^k**

The second derivatives of the experiment specific objective functions F_1^k with respect to the local and the global variables are given by

$$A_{xp}^k = \frac{\partial A_x^k}{\partial p} = \left(\frac{\partial D_{1,0}^k}{\partial p}, \dots, \frac{\partial D_{1,l_k}^k}{\partial p}, \frac{\partial D_{1,\tilde{p}}^k}{\partial p} \right) =: (D_{1,0,p}^k, \dots, D_{1,l_k,p}^k, D_{1,\tilde{p},p}^k),$$

for all experimental settings $k = 1, \dots, M$. Considering notations (6.1.5) and (6.1.6) it holds for $0 = 1, \dots, l_k$ that

$$D_{1,j,p}^k := -\Sigma_k^{-1} \left(\left(\frac{\partial^2 h^k}{\partial y^k \partial p} + \frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial p} \right) \frac{\partial y^k}{\partial s_j^k} + \frac{\partial h^k}{\partial y^k} \frac{\partial^2 y^k}{\partial s_j^k \partial p} \right)$$

and

$$D_{1,\tilde{p},p}^k := -\Sigma_k^{-1} \left(\frac{\partial^2 h^k}{\partial \tilde{p}^k \partial p} + \frac{\partial^2 h^k}{\partial \tilde{p}^k \partial y^k} \frac{\partial y^k}{\partial p} + \left(\frac{\partial^2 h^k}{\partial y^k \partial p} + \frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial p} \right) \frac{\partial y^k}{\partial \tilde{p}^k} + \frac{\partial h^k}{\partial y^k} \frac{\partial^2 y^k}{\partial \tilde{p}^k \partial p} \right).$$

- **Computation of the Second Derivative A_{px}^k**

The second derivatives of the experiment specific objective functions F_1^k with respect to the global and the local optimization variables coincide with the second derivatives A_{xp}^k except of the order of the elements. In particular, we obtain for $k = 1, \dots, M$ that

$$A_{px}^k = \frac{\partial A_p}{\partial x_k} = \left(\frac{\partial D_{1,p}^k}{\partial s_0^k}, \dots, \frac{\partial D_{1,p}^k}{\partial s_{l_k}^k}, \frac{\partial D_{1,p}^k}{\partial \tilde{p}^k} \right) =: \left(D_{1,p,0}^k, \dots, D_{1,p,l_k}^k, D_{1,p,\tilde{p}}^k \right).$$

If we take notation (6.1.7) into account, it holds for $0 = 1, \dots, l_k$ that

$$D_{1,p,j}^k := -\Sigma_k^{-1} \left(\frac{\partial^2 h^k}{\partial p \partial y^k} \frac{\partial y^k}{\partial s_j^k} + \left(\frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial s_j^k} \right) \frac{\partial y^k}{\partial p} + \frac{\partial h^k}{\partial y^k} \frac{\partial^2 y^k}{\partial p \partial s_j^k} \right)$$

and

$$D_{1,p,\tilde{p}}^k := -\Sigma_k^{-1} \left(\frac{\partial^2 h^k}{\partial p \partial \tilde{p}^k} + \frac{\partial^2 h^k}{\partial p \partial y^k} \frac{\partial y^k}{\partial \tilde{p}^k} + \left(\frac{\partial^2 h^k}{\partial y^k \partial \tilde{p}^k} + \frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial \tilde{p}^k} \right) \frac{\partial y^k}{\partial p} + \frac{\partial h^k}{\partial y^k} \frac{\partial^2 y^k}{\partial p \partial \tilde{p}^k} \right).$$

- **Computation of the Second Derivative A_{pp}^k**

It holds that the second derivatives of the experiment specific objective functions F_1^k with respect to the global optimization parameters are given by

$$\begin{aligned} A_{pp}^k &= \frac{\partial D_{1,p}^k}{\partial p} \\ &= -\Sigma_k^{-1} \left(\frac{\partial^2 h^k}{\partial p^2} + \frac{\partial^2 h^k}{\partial y^k \partial p} \frac{\partial y^k}{\partial p} + \left(\frac{\partial^2 h^k}{\partial p \partial y^k} + \frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial p} \right) \frac{\partial y^k}{\partial p} + \frac{\partial h^k}{\partial y^k} \frac{\partial^2 y^k}{\partial p^2} \right) \\ &=: D_{1,p,p}^k, \end{aligned}$$

for $k = 1, \dots, M$, where we used the notation from (6.1.7).

• **Computation of the Second Derivative B_{xx}^k**

For all $k = 1, \dots, M$, the derivatives of the experiment specific constraint functions with respect to the local optimization variables are given by

$$B_{xx}^k = \left(\frac{\partial B_x^k}{\partial s_0^k}, \dots, \frac{\partial B_x^k}{\partial s_{l_k}^k}, \frac{\partial B_x^k}{\partial \tilde{p}^k} \right),$$

where the single derivative matrices are

$$\begin{aligned} \frac{\partial B_x^k}{\partial s_j^k} &= \frac{\partial}{\partial s_j^k} \begin{pmatrix} D_{2,0}^k & \cdots & \cdots & D_{2,l_k}^k & D_{2,\tilde{p}^k}^k \\ G_0^k & -\mathbb{I} & & & G_{0,\tilde{p}^k}^k \\ & \ddots & \ddots & & \vdots \\ & & G_{l_k-1}^k & -\mathbb{I} & G_{l_k-1,\tilde{p}^k}^k \end{pmatrix} \\ &=: \begin{pmatrix} D_{2,0,j}^k & \cdots & \cdots & D_{2,l_k,j}^k & D_{2,\tilde{p}^k,j}^k \\ G_{0,j}^k & & & & G_{0,\tilde{p}^k,j}^k \\ & \ddots & & & \vdots \\ & & G_{l_k-1,j}^k & 0 & G_{l_k-1,\tilde{p}^k,j}^k \end{pmatrix} \end{aligned}$$

for $j = 0, \dots, l_k$, and

$$\begin{aligned} \frac{\partial B_x^k}{\partial \tilde{p}^k} &= \frac{\partial}{\partial \tilde{p}^k} \begin{pmatrix} D_{2,0}^k & \cdots & \cdots & D_{2,l_k}^k & D_{2,\tilde{p}^k}^k \\ G_0^k & -\mathbb{I} & & & G_{0,\tilde{p}^k}^k \\ & \ddots & \ddots & & \vdots \\ & & G_{l_k-1}^k & -\mathbb{I} & G_{l_k-1,\tilde{p}^k}^k \end{pmatrix} \\ &=: \begin{pmatrix} D_{2,0,\tilde{p}^k}^k & \cdots & \cdots & D_{2,l_k,\tilde{p}^k}^k & D_{2,\tilde{p}^k,\tilde{p}^k}^k \\ G_{0,\tilde{p}^k}^k & & & & G_{0,\tilde{p}^k,\tilde{p}^k}^k \\ & \ddots & & & \vdots \\ & & G_{l_k-1,\tilde{p}^k}^k & 0 & G_{l_k-1,\tilde{p}^k,\tilde{p}^k}^k \end{pmatrix}. \end{aligned}$$

If we take the notations from (6.1.8) - (6.1.11) into account we get for $j = 0, \dots, l_k$

$$D_{2,i,j}^k := \frac{\partial^2 r^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial s_i^k} + \left(\frac{\partial r^k}{\partial y^k} \frac{\partial^2 y^k}{\partial s_i^k} \right) \frac{\partial^2 y^k}{\partial s_j^k}, \quad i = 0, \dots, l_k,$$

$$D_{2,\tilde{p}^k,j}^k := \frac{\partial^2 r^k}{\partial \tilde{p}^k \partial y^k} \frac{\partial y^k}{\partial s_j^k} + \left(\frac{\partial^2 r^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial s_j^k} \right) \frac{\partial y^k}{\partial \tilde{p}^k} + \frac{\partial r^k}{\partial y^k} \frac{\partial^2 y^k}{\partial \tilde{p}^k \partial s_j^k},$$

$$\begin{aligned}
 G_{i,j}^k &:= \begin{cases} \frac{\partial^2 y^k(\tau_{i+1}; s_i^k, \tilde{p}^k, p)}{\partial (s_i^k)^2}, & \text{if } i = j, \\ 0, & \text{if } i \neq j \end{cases}, \quad 0 = 1, \dots, l_k, \\
 G_{i,\tilde{p}^k,j}^k &:= \begin{cases} \frac{\partial^2 y^k(\tau_{i+1}; s_i^k, \tilde{p}^k, p)}{\partial s_i^k \partial \tilde{p}^k}, & \text{if } i = j, \\ 0, & \text{if } i \neq j \end{cases}, \quad 0 = 1, \dots, l_k, \\
 D_{2,i,\tilde{p}^k}^k &:= \left(\frac{\partial^2 r^k}{\partial y^k \partial \tilde{p}^k} + \frac{\partial^2 r^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial \tilde{p}^k} \right) \frac{\partial y^k}{\partial s_i^k} + \frac{\partial r^k}{\partial y^k} \frac{\partial^2 y^k}{\partial s_i^k \partial \tilde{p}^k}, \\
 D_{2,\tilde{p}^k,\tilde{p}^k}^k &:= \frac{\partial^2 r^k}{\partial (\tilde{p}^k)^2} + \frac{\partial^2 r^k}{\partial y^k \partial \tilde{p}^k} \frac{\partial y^k}{\partial \tilde{p}^k} + \left(\frac{\partial^2 r^k}{\partial \tilde{p}^k \partial y^k} + \frac{\partial^2 r^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial \tilde{p}^k} \right) \frac{\partial y^k}{\partial \tilde{p}^k} + \frac{\partial r^k}{\partial y^k} \frac{\partial^2 y^k}{\partial (\tilde{p}^k)^2}, \\
 G_{i,\tilde{p}}^k &:= \frac{\partial^2 y^k(\tau_{i+1}; s_i^k, \tilde{p}^k, p)}{\partial s_i^k \partial \tilde{p}^k}, \quad i = 0, \dots, l_k - 1, \\
 G_{i,\tilde{p}^k,\tilde{p}^k}^k &:= \frac{\partial^2 y^k(\tau_{i+1}; s_i^k, \tilde{p}^k, p)}{\partial (\tilde{p}^k)^2}, \quad i = 0, \dots, l_k.
 \end{aligned}$$

- **Computation of the Second Derivative B_{xp}^k**

For all experimental setups $k = 1, \dots, M$, the derivatives of the experiment specific constraint functions with respect to the local and the global optimization variables are given by

$$\begin{aligned}
 B_{xp}^k &= \frac{\partial}{\partial p} \begin{pmatrix} D_{2,0}^k & \cdots & \cdots & D_{2,l_k}^k & D_{2,\tilde{p}^k}^k \\ G_0^k & -\mathbb{I} & & & G_{0,\tilde{p}^k}^k \\ & \ddots & \ddots & & \vdots \\ & & G_{l_k-1}^k & -\mathbb{I} & G_{l_k-1,\tilde{p}^k}^k \end{pmatrix} \\
 &=: \begin{pmatrix} D_{2,0,p}^k & \cdots & \cdots & D_{2,l_k,p}^k & D_{2,\tilde{p}^k,p}^k \\ G_{0,p}^k & & & & G_{0,\tilde{p}^k,p}^k \\ & \ddots & & & \vdots \\ & & G_{l_k-1,p}^k & 0 & G_{l_k-1,\tilde{p}^k,p}^k \end{pmatrix},
 \end{aligned}$$

where we introduced the following derivative matrices,

$$D_{2,i,p}^k := \left(\frac{\partial^2 r^k}{\partial y^k \partial p} + \frac{\partial^2 r^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial p} \right) \frac{\partial y^k}{\partial s_i^k} + \frac{\partial r^k}{\partial y^k} \frac{\partial^2 y^k}{\partial s_i^k \partial p}, \quad 0 = 1, \dots, l_k,$$

$$D_{2,\tilde{p}^k,p}^k := \frac{\partial^2 r^k}{\partial \tilde{p}^k \partial p} + \frac{\partial^2 r^k}{\partial \tilde{p}^k \partial y^k} \frac{\partial y^k}{\partial p} + \left(\frac{\partial^2 r^k}{\partial y^k \partial p} + \frac{\partial^2 r^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial p} \right) \frac{\partial y^k}{\partial \tilde{p}^k} + \frac{\partial r^k}{\partial y^k} \frac{\partial^2 y^k}{\partial \tilde{p}^k \partial p},$$

$$G_{i,p}^k := \frac{\partial^2 y^k(\tau_{i+1}; s_i^k, \tilde{p}^k, p)}{\partial s_i^k \partial p}, \quad i = 0, \dots, l_k - 1,$$

$$G_{i,\tilde{p}^k,p}^k := \frac{\partial^2 y^k(\tau_{i+1}; s_i^k, \tilde{p}^k, p)}{\partial p \partial \tilde{p}^k}, \quad i = 0, \dots, l_k,$$

considering (6.1.8) - (6.1.11).

• **Computation of the Second Derivative B_{px}^k**

The derivatives of the experiment specific constraint functions with respect to the global and the local optimization variables coincide with the second derivatives B_{xp}^k except of the order of the elements. In particular, it holds for all $k = 1, \dots, M$ that

$$\begin{aligned} B_{px}^k &= \frac{\partial B_p^k}{\partial x_k} = \left(\frac{\partial B_p^k}{\partial s_0^k}, \dots, \frac{\partial B_p^k}{\partial s_{l_k}^k}, \frac{\partial B_p^k}{\partial \tilde{p}^k} \right) \\ &=: \begin{pmatrix} D_{2,p,0}^k & \dots & \dots & D_{2,p,l_k}^k & D_{2,p,\tilde{p}}^k \\ G_{0,p,0}^k & & & & G_{0,p,\tilde{p}}^k \\ & \ddots & & & \vdots \\ & & G_{l_k-1,p,l_k-1}^k & 0 & G_{l_k-1,p,\tilde{p}}^k \end{pmatrix} \end{aligned}$$

and by using (6.1.12) and (6.1.13) we get the derivative matrices

$$D_{2,p,i} := \frac{\partial^2 r^k}{\partial p \partial y^k} \frac{\partial y^k}{\partial s_i} + \left(\frac{\partial^2 r^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial s_i} \right) \frac{\partial y^k}{\partial p} + \frac{\partial r^k}{\partial y^k} \frac{\partial^2 y^k}{\partial p \partial s_i} \quad i = 0, \dots, l_k,$$

$$D_{2,p,\tilde{p}}^k := \frac{\partial^2 r^k}{\partial p \partial \tilde{p}^k} + \frac{\partial^2 r^k}{\partial p \partial y^k} \frac{\partial y^k}{\partial \tilde{p}^k} + \left(\frac{\partial^2 r^k}{\partial y^k \partial \tilde{p}^k} + \frac{\partial^2 r^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial \tilde{p}^k} \right) \frac{\partial y^k}{\partial p} + \frac{\partial r^k}{\partial y^k} \frac{\partial^2 y^k}{\partial p \partial \tilde{p}^k},$$

$$G_{i,p,i}^k := \frac{\partial y^k(\tau_{i+1}; s_i^k, \tilde{p}^k, p)}{\partial p \partial s_i^k}, \quad i = 0, \dots, l_k - 1,$$

$$G_{i,p,\tilde{p}}^k := \frac{\partial y^k(\tau_{i+1}; s_i^k, \tilde{p}^k, p)}{\partial p \partial \tilde{p}^k}, \quad i = 0, \dots, l_k - 1.$$

• **Computation of the Second Derivative** B_{pp}^k

For all experiments $k = 1, \dots, M$, it holds that the derivatives of the experiment specific constraint functions with respect to the global optimization variables are given by

$$B_{pp}^k = \frac{\partial}{\partial p} \begin{pmatrix} D_{2,p}^k \\ G_{0,p}^k \\ \vdots \\ G_{l_k-1,p}^k \end{pmatrix} =: \begin{pmatrix} D_{2,p,p}^k \\ G_{0,p,p}^k \\ \vdots \\ G_{l_k-1,p,p}^k \end{pmatrix},$$

and according to (6.1.12) and (6.1.13) we obtain

$$D_{2,p,p}^k := \frac{\partial^2 r^k}{\partial p^2} + \frac{\partial^2 r^k}{\partial p \partial y^k} \frac{\partial y^k}{\partial p} + \left(\frac{\partial^2 r^k}{\partial y^k \partial p} + \frac{\partial^2 r^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial p} \right) \frac{\partial y^k}{\partial p} + \frac{\partial r^k}{\partial y^k} \frac{\partial^2 y^k}{\partial p^2}$$

and

$$G_{i,p,p}^k := \frac{\partial^2 y^k(\tau_{i+1}; s_i^k, \tilde{p}^k, p)}{\partial p^2}, \quad i = 0, \dots, l_k - 1.$$

6.2 Derivatives in the Design of Optimal Experiments

In Chapter 4, we introduced the design of optimal experiment problems, which can be written in the general form of an equality and inequality constrained optimization problem as

$$\begin{aligned} \min_{\xi} \quad & \phi(\xi) \\ \text{s.t.} \quad & m_\psi \leq \psi(\xi) \leq M_\psi, \\ & 0 = \chi(\xi). \end{aligned}$$

In order to use derivative based methods for solving the DoE problem, we need the derivative of the objective function ϕ with respect to the design variables ξ . The common objective functions—as introduced in Subsection 4.3.1—are functions of the covariance matrix. The covariance matrix can be seen as a function of the Jacobians J_1 and J_2 , whereas the Jacobians are functions of the design variables. Therefore, an application of the chain rule gives us the following derivative of the common objective functions,

$$\frac{d\phi}{d\xi} = \frac{\partial \phi}{\partial \mathcal{C}} \frac{\partial \mathcal{C}}{\partial J} \frac{\partial J}{\partial \xi}. \quad (6.2.1)$$

The derivatives of the common objective functions are extensively discussed in literature. For a thorough treatment of the derivatives of the A-, D-, and E-criterion, see e.g. Körkel [62], Magnus and Neudecker [75], and Pazman [85]. The derivative of the M-criterion can be found in Lohmann [73].

In the following subsection, we will focus on the derivative of the newly introduced Q-criterion. In favor of a more readable notation, we often use the notation $\partial_\xi := \frac{\partial}{\partial \xi}$.

6.2.1 Derivative of the Q-criterion

Following Subsection 4.3.2, the Q-criterion is defined by

$$\phi_Q(\xi) := \text{trace}(\mathcal{C}(\xi)) + \left(\tilde{\kappa}(\xi) + \frac{\tilde{\omega}(\xi)}{2} \text{trace}(\mathcal{C}(\xi)) \right) \text{trace}(\mathcal{C}(\xi)).$$

If we denote $\phi_A(\xi) := \text{trace}(\mathcal{C}(\xi))$, the derivative of the Q-criterion with respect to the design variables is given by

$$\begin{aligned} \partial_\xi \phi_Q(\xi) &= \partial_\xi \phi_A(\xi) + \left(\tilde{\kappa}(\xi) + \frac{\tilde{\omega}(\xi)}{2} \phi_A(\xi) \right) \partial_\xi \phi_A(\xi) \\ &\quad + \left(\partial_\xi \tilde{\kappa}(\xi) + \frac{1}{2} (\partial_\xi \tilde{\omega}(\xi) \phi_A(\xi) + \tilde{\omega}(\xi) \partial_\xi \phi_A(\xi)) \right) \phi_A(\xi). \end{aligned}$$

Hence, we need the derivative of the trace of the covariance matrix with respect to ξ , as well as the derivatives of $\tilde{\kappa}(\xi)$ and $\tilde{\omega}(\xi)$ with respect to ξ . Since it holds that the derivative of the trace of a matrix is the trace of the derivative of the matrix, i.e.

$$\partial_\xi \phi_A(\xi) := \partial_\xi \text{trace}(\mathcal{C}(\xi)) = \text{trace}(\partial_\xi \mathcal{C}(\xi)),$$

the computation of $\partial_\xi \phi_A$ is basically reduced to the computation of the derivative of the covariance matrix. How to compute the derivative of the covariance matrix is thoroughly discussed in Subsection 6.2.2.

The Derivative of $\tilde{\omega}(\xi)$

In order to compute the derivative of $\tilde{\omega}(\xi)$ with respect to the design variables, we use the estimate of Section 2.5, namely $\tilde{\omega}(\xi) = c_1(\xi) \cdot c_2(\xi)$, with $c_1(\xi) := \|J^+(\xi)\|_F$ and $c_2(\xi) := \|dJ(\xi)\|_F$. Here, J^+ is the generalized inverse according to (2.4.7) and $dJ = \partial J / \partial x$ denotes the second derivative of the model functions of the parameter estimation problem with respect to x . Thus, considering the product rule we obtain the following derivative

$$\partial_\xi \tilde{\omega}(\xi) = (\partial_\xi c_1(\xi)) \cdot c_2(\xi) + c_1(\xi) \cdot (\partial_\xi c_2(\xi)).$$

Since it holds that the Frobenius norm can be represented by $\|A\|_F = \text{trace}(A^T A)^{\frac{1}{2}}$, the derivatives of $c_1(\xi)$ and $c_2(\xi)$ are explicitly given by

$$\begin{aligned} \partial_\xi c_1(\xi) &= \partial_\xi \|J^+(\xi)\|_F \\ &= \partial_\xi \text{trace}(J^+(\xi) J^{+T}(\xi))^{\frac{1}{2}} \\ &= \frac{1}{2} \text{trace}(\partial_\xi (J^+(\xi) J^{+T}(\xi))) \text{trace}(J^+(\xi) J^{+T}(\xi))^{-\frac{1}{2}} \\ &= \text{trace}(J^+(\xi) (\partial_\xi J^{+T}(\xi))) \text{trace}(J^+(\xi) J^{+T}(\xi))^{-\frac{1}{2}} \end{aligned}$$

and

$$\begin{aligned}
 \partial_\xi c_2(\xi) &= \partial_\xi \|dJ(\xi)\|_F \\
 &= \partial_\xi \text{trace} (dJ(\xi)dJ^T(\xi))^{\frac{1}{2}} \\
 &= \frac{1}{2} \text{trace} (\partial_\xi (dJ(\xi)dJ^T(\xi))) \text{trace} (dJ(\xi)dJ^T(\xi))^{-\frac{1}{2}} \\
 &= \text{trace} (dJ(\xi)(\partial_\xi dJ^T(\xi))) \text{trace} (dJ(\xi)dJ^T(\xi))^{-\frac{1}{2}},
 \end{aligned}$$

where we used the linearity of the trace as well as the property $\text{trace}(DH) = \text{trace}(HD)$.

The Derivative of $\tilde{\kappa}(\xi)$

For simplicity of notation, we consider an unconstrained parameter estimation problem for the computation of the derivative of $\tilde{\kappa}(\xi)$, or more specifically of an adequate approximation. Using (4.3.8), we get an approximation of $\tilde{\kappa}(\xi)$ by

$$\mu^2(\xi) \approx \hat{\kappa}(\xi) = \frac{1}{n_x} \text{trace}(\mathcal{A}(\xi)) + \frac{1}{2} \sqrt{\frac{1}{n_x} \text{trace}(\mathcal{A}^2(\xi)) - \left(\frac{1}{n_x} \text{trace}(\mathcal{A}(\xi))\right)^2} \frac{n_x}{(n_x - 1)^{\frac{1}{2}}},$$

with $\mathcal{A}(\xi) = \sum_{i=1}^{m_1} A_i^2(\xi) = \sum_{i=1}^{m_1} \left(B^{-\frac{1}{2}}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} B^{-\frac{1}{2}}(\xi) \right)^2$.

If we denote

$$s(\xi) := \sqrt{\frac{1}{n_x} \text{trace}(\mathcal{A}^2(\xi)) - \left(\frac{1}{n_x} \text{trace}(\mathcal{A}(\xi))\right)^2},$$

the derivative of $\hat{\kappa}(\xi)$ is given by

$$\partial_\xi \hat{\kappa}(\xi) = \frac{1}{n_x} \partial_\xi \text{trace}(\mathcal{A}(\xi)) + \frac{1}{4s(\xi)} \left(\partial_\xi \text{trace}(\mathcal{A}^2(\xi)) - \frac{1}{n_x} \partial_\xi \text{trace}(\mathcal{A}(\xi))^2 \right) \frac{1}{(n_x - 1)^{\frac{1}{2}}}.$$

So we basically need the derivatives of the traces. Corresponding to the notations of Subsection 4.3.2, we obtain

$$\begin{aligned}
 \partial_\xi \text{trace}(\mathcal{A}(\xi)) &= \partial_\xi \text{trace} \left(\sum_{i=1}^{m_1} \left(B^{-\frac{1}{2}}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} B^{-\frac{1}{2}}(\xi) \right)^2 \right) \\
 &= \partial_\xi \text{trace} \left(\sum_{i=1}^{m_1} B^{-\frac{1}{2}}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} B^{-1}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} B^{-\frac{1}{2}}(\xi) \right) \\
 &= \partial_\xi \text{trace} \left(\sum_{i=1}^{m_1} B^{-1}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} B^{-1}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} \right) \\
 &= \partial_\xi \text{trace} \left(\sum_{i=1}^{m_1} \left(B^{-1}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} \right)^2 \right),
 \end{aligned}$$

where we apply the fact that similar matrices have the same trace. Additionally, due to the linearity of the trace and because of $\text{trace}(DH) = \text{trace}(HD)$ it holds that

$$\begin{aligned} \partial_\xi \text{trace} \left(\sum_{i=1}^{m_1} \left(B^{-1}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} \right)^2 \right) &= \sum_{i=1}^{m_1} \text{trace} \left(\partial_\xi \left(B^{-1}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} \right)^2 \right) \\ &= 2 \sum_{i=1}^{m_1} \text{trace} \left(\left(B^{-1}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} \right) \partial_\xi \left(B^{-1}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} \right) \right), \end{aligned}$$

with

$$\partial_\xi \left(B^{-1}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} \right) = B^{-1}(\xi) \left(\partial_\xi \frac{\partial^2 F_{1i}(\xi)}{\partial x^2} \right) - B^{-1}(\xi) (\partial_\xi B(\xi)) B^{-1}(\xi) \frac{\partial^2 F_{1i}(\xi)}{\partial x^2}.$$

Recognizing the derivative $\partial_\xi \text{trace}(\mathcal{A}(\xi))$, the derivative $\partial_\xi (\text{trace}(\mathcal{A}(\xi)))^2$ can be written as

$$\partial_\xi (\text{trace}(\mathcal{A}(\xi)))^2 = 2 \cdot \text{trace}(\mathcal{A}(\xi)) (\partial_\xi \text{trace} \mathcal{A}(\xi)).$$

Finally, we have to compute the derivative $\partial_\xi \text{trace}(\mathcal{A}^2)$. Considering that the trace is invariant under a similarity transformation, it holds that

$$\begin{aligned} \text{trace}(\mathcal{A}^2) &= \text{trace} \left[\sum_{j=1}^{m_1} \left(B^{-\frac{1}{2}} \frac{\partial^2 F_{1j}}{\partial x^2} B^{-\frac{1}{2}} \right)^2 \sum_{i=1}^{m_1} \left(B^{-\frac{1}{2}} \frac{\partial^2 F_{1i}}{\partial x^2} B^{-\frac{1}{2}} \right)^2 \right] \\ &= \text{trace} \left[\left(\sum_{j=1}^{m_1} B^{-1} \frac{\partial^2 F_{1j}}{\partial x^2} B^{-1} \frac{\partial^2 F_{1j}}{\partial x^2} \right) \left(\sum_{i=1}^{m_1} B^{-1} \frac{\partial^2 F_{1i}}{\partial x^2} B^{-1} \frac{\partial^2 F_{1i}}{\partial x^2} \right) \right] \\ &=: \text{trace} \left[\left(\sum_{j=1}^{m_1} \tilde{B}_j^2 \right) \left(\sum_{i=1}^{m_1} \tilde{B}_i^2 \right) \right], \end{aligned}$$

where we omit the argument ξ , and denote $\tilde{B}_i := B^{-1} \frac{\partial^2 F_{1i}}{\partial x^2}$.

As a result, we get

$$\begin{aligned} \partial_\xi \text{trace}(\mathcal{A}^2(\xi)) &= 2 \cdot \text{trace} \left[\left(\sum_{j=1}^{m_1} \tilde{B}_j^2 \right) \left(\sum_{i=1}^{m_1} \partial_\xi \tilde{B}_i^2 \right) \right] \\ &= 2 \cdot \text{trace} \left[\left(\sum_{j=1}^{m_1} \tilde{B}_j^2 \right) \left(\sum_{i=1}^{m_1} (\partial_\xi \tilde{B}_i)(\tilde{B}_i) + (\tilde{B}_i)(\partial_\xi \tilde{B}_i) \right) \right] \end{aligned}$$

and

$$\partial_\xi \tilde{B}_i = -B^{-1} (\partial_\xi B) B^{-1} \frac{\partial^2 F_{1i}}{\partial x^2} + B^{-1} \frac{\partial^3 F_{1i}}{\partial \xi \partial x^2}.$$

Overall, we basically need the derivatives $\partial_\xi \frac{\partial F_{1i}(\xi)}{\partial x^2}$ and $\partial_\xi B(\xi) = (\partial_\xi J_1^T(\xi)) J_1(\xi) + J_1^T(\xi) (\partial_\xi J_1(\xi))$ for the computation of $\partial_\xi \hat{\kappa}(\xi)$. The derivative of the Jacobian with respect

to the design variables is presented Subsection 6.2.3. We omit the computation of $\frac{\partial^3 F_{1i}}{\partial \xi \partial x^2}$ in this thesis and refer to Walter [109] for a general treatment of higher order derivatives in the context of the design of optimal experiments.

Remark 6.2.1 *According to (4.3.4), the single matrices A_i are independent from each other and therefore their computation can be parallelized in a natural way by using a Master-Slave concept.*

6.2.2 Derivative of the Covariance Matrix

In this subsection, we determine the derivative of the linear approximated covariance matrix with respect to the design variables ξ . For simplicity of notation, we denote

$$\mathcal{J}^{-1}(\xi) := \begin{pmatrix} C(\xi) & Z^T(\xi) \\ Z(\xi) & T(\xi) \end{pmatrix} := \begin{pmatrix} J_1^T(\xi)J_1(\xi) & J_2^T(\xi) \\ J_2(\xi) & 0 \end{pmatrix}^{-1}.$$

Thus, we obtain

$$\begin{aligned} C(\xi) &= J^+(\xi) \begin{pmatrix} \mathbb{I} & 0 \\ 0 & 0 \end{pmatrix} (J^+(\xi))^T \\ &= (\mathbb{I} \ 0) \mathcal{J}^{-1}(\xi) \begin{pmatrix} J_1^T(\xi)J_1(\xi) & 0 \\ 0 & 0 \end{pmatrix} \mathcal{J}^{-1}(\xi) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \\ &= C(\xi) J_1^T(\xi) J_1(\xi) C(\xi) \\ &= (\mathbb{I} \ 0) \mathcal{J}^{-1}(\xi) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix}, \end{aligned} \tag{6.2.2}$$

where we used $C(\xi) J_1^T(\xi) J_1(\xi) C(\xi) = C(\xi)$. This follows easily from $\mathcal{J}(\xi) \mathcal{J}^{-1}(\xi) = \mathbb{I}$. Accordingly, we get the following equation for the derivative of the covariance matrix

$$\begin{aligned} \frac{\partial C(\xi)}{\partial \xi} &= \frac{\partial}{\partial \xi} \left((\mathbb{I} \ 0) \mathcal{J}^{-1}(\xi) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \right) \\ &= - (\mathbb{I} \ 0) \mathcal{J}^{-1}(\xi) \left(\frac{\partial \mathcal{J}(\xi)}{\partial \xi} \right) \mathcal{J}^{-1}(\xi) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \\ &= - (C(\xi) \ Z^T(\xi)) \begin{pmatrix} \frac{\partial}{\partial \xi} (J_1^T(\xi) J_1(\xi)) & \frac{\partial}{\partial \xi} J_2^T(\xi) \\ \frac{\partial}{\partial \xi} J_2(\xi) & 0 \end{pmatrix} \begin{pmatrix} C(\xi) \\ Z(\xi) \end{pmatrix}. \end{aligned}$$

Hence, for the computation of the derivative of the covariance matrix, we basically have to compute the derivatives of the Jacobians J_1, J_2 with respect to ξ as well as the matrices $C(\xi)$ and $Z(\xi)$. Before discussing the derivatives of J_1 and J_2 in the following subsection, we dwell on the computation of $C(\xi)$ and $Z(\xi)$. Regarding Formula (6.2.2), $C(\xi)$ corresponds to the covariance matrix. Its (parallel) computation is discussed in Subsection

3.2. In the following, we consider a numerical approach for the computation of $Z(\xi)$ in the case of a multiple experiment parameter estimation problem, where

$$J_1^T J_1 = \begin{pmatrix} (A_x^1)^T A_x^1 & & & & (A_x^1)^T A_p^1 \\ & (A_x^2)^T A_x^2 & & & (A_x^2)^T A_p^2 \\ & & \ddots & & \vdots \\ & & & (A_x^M)^T A_x^M & (A_x^M)^T A_p^M \\ (A_p^1)^T A_x^1 & (A_p^2)^T A_x^2 & \dots & (A_p^M)^T A_x^M & \sum_{k=1}^M (A_p^k)^T A_p^k \end{pmatrix}$$

and

$$J_2 = \begin{pmatrix} B_x^1 & & & B_p^1 \\ & B_x^2 & & B_p^2 \\ & & \ddots & \vdots \\ & & & B_x^M & B_p^M \end{pmatrix}.$$

We consider the identity

$$\begin{pmatrix} J_1^T(\xi) J_1(\xi) & J_2^T(\xi) \\ J_2(\xi) & 0 \end{pmatrix} \begin{pmatrix} C(\xi) & Z^T(\xi) \\ Z(\xi) & T(\xi) \end{pmatrix} = \begin{pmatrix} \mathbb{I} & 0 \\ 0 & \mathbb{I} \end{pmatrix}$$

$$\implies J_1^T(\xi) J_1(\xi) C(\xi) + J_2^T(\xi) Z(\xi) = \mathbb{I}, \quad (6.2.3)$$

and we denote

$$Z = \begin{pmatrix} Z_{11} & Z_{12} & \dots & Z_{1M} & Z_{1p} \\ Z_{21} & Z_{22} & \dots & Z_{2M} & Z_{2p} \\ \vdots & \vdots & & \vdots & \vdots \\ Z_{M1} & Z_{M2} & \dots & Z_{MM} & Z_{Mp} \end{pmatrix},$$

where $Z_{ij} \in \mathbb{R}^{m_2^i \times n_x^j}$, $Z_{ip} \in \mathbb{R}^{m_2^i \times n_p}$, $i, j = 1, \dots, M$. Using representation (5.2.1) of the covariance matrix, we get the following relation for the i -th block-row of (6.2.3)

$$(A_x^i)^T A_x^i Cov_i + (A_x^i)^T A_p^i Cov_p + (B_x^i)^T (Z_{i1} \dots Z_{iM}, Z_{ip}) = \tilde{\mathbb{I}}_i, \quad (6.2.4)$$

for $i = 1, \dots, M$. Here, we introduced the matrix $\tilde{\mathbb{I}}_i = (0 \dots \mathbb{I} \dots 0)$. By Cov_i and Cov_p we denote the i -th and the last block-row of the covariance matrix, respectively. In order to solve equation (6.2.4) for the components $Z_{i1}, \dots, Z_{iM}, Z_{ip}$, we follow the same procedure as introduced in Section 5.1 and consider the disjoint decomposition of the experiments $M = M_1 \cup M_2$. A case analysis of the index sets M_1 and M_2 delivers the following results.

- If i belongs to the index set M_1 :

Using the orthogonal decomposition $B_x^i = Q_i R_i = (Q_{i1}, Q_{i2}) \begin{pmatrix} R_{i1} \\ 0 \end{pmatrix}$ from (5.1.3), equation (6.2.4) can be rewritten according to

$$\begin{aligned} & (A_x^i)^T (A_x^i Cov_i + A_p^i Cov_p) + R_{i1}^T Q_{i1}^T (Z_{i1} \dots Z_{iM}, Z_{ip}) = \tilde{\mathbb{I}}_i \\ \iff & R_{i1}^{-T} (A_x^i)^T (A_x^i Cov_i + A_p^i Cov_p) + Q_{i1}^T (Z_{i1} \dots Z_{iM}, Z_{ip}) = R_{i1}^{-T} \tilde{\mathbb{I}}_i \\ \iff & Q_{i1} R_{i1}^{-T} \left(\tilde{\mathbb{I}}_i - (A_x^i)^T (A_x^i Cov_i + A_p^i Cov_p) \right) = (Z_{i1} \dots Z_{iM}, Z_{ip}). \end{aligned}$$

Hence, if i belongs to the index set M_1 , it holds that

$$\begin{aligned} Z_{ii} &= Q_{i1} R_{i1}^{-T} - Q_{i1} R_{i1}^{-T} (A_x^i)^T (A_x^i Cov_{ii} + A_p^i Cov_{pi}), \\ Z_{ij} &= -Q_{i1} R_{i1}^{-T} (A_x^i)^T (A_x^i Cov_{ij} + A_p^i Cov_{pj}), \end{aligned}$$

for $j = 1, \dots, M$ and $i \neq j$.

- If i belongs to the index set M_2 :

Here, we use the orthogonal decomposition $B_x^i = L_i Q_i^T = (L_{1i}, 0) \begin{pmatrix} Q_{1i}^T \\ Q_{2i}^T \end{pmatrix}$ as given in (5.1.5). So equation (6.2.4) can be rewritten as follows,

$$\begin{aligned} & (A_x^i)^T (A_x^i Cov_i + A_p^i Cov_p) + Q_{1i} L_{1i}^T (Z_{i1} \dots Z_{iM}, Z_{ip}) = \tilde{\mathbb{I}}_i \\ \iff & Q_{1i}^T (A_x^i)^T (A_x^i Cov_i + A_p^i Cov_p) + L_{1i}^T (Z_{i1} \dots Z_{iM}, Z_{ip}) = Q_{1i}^T \tilde{\mathbb{I}}_i \\ \iff & L_{1i}^{-T} Q_{1i}^T \left(\tilde{\mathbb{I}}_i - (A_x^i)^T (A_x^i Cov_i + A_p^i Cov_p) \right) = (Z_{i1} \dots Z_{iM}, Z_{ip}). \end{aligned}$$

Consequently, if i belongs to the index set M_2 , we get

$$\begin{aligned} Z_{ii} &= L_{1i}^{-T} Q_{1i}^T - L_{1i}^{-T} Q_{1i}^T (A_x^i)^T (A_x^i Cov_{ii} + A_p^i Cov_{pi}), \\ Z_{ij} &= -L_{1i}^{-T} Q_{1i}^T (A_x^i)^T (A_x^i Cov_{ij} + A_p^i Cov_{pj}), \end{aligned}$$

for $j = 1, \dots, M$ and $i \neq j$.

If the covariance matrix is available, the computation of the matrix Z can be parallelized in a natural way. Each processor (P_j) receives a number of lines j_1, \dots, j_{r_j} of the matrix Z , which can be computed as given above.

6.2.3 Derivative of the Jacobians with Respect to the Design Variables

In this subsection, we compute the derivatives of the Jacobians $J_1(x)$ and $J_2(x)$, with respect to the design variables q , w , and s . In the context of DoE, the objective function of the parameter estimation problem is given by

$$F_1(x) = \sqrt{W} \begin{pmatrix} F_1^1(x_1, p) \\ \vdots \\ F_1^M(x_M, p) \end{pmatrix},$$

see (4.2.1), where the diagonal matrix $W = \text{diag}(w)$ contains the sampling variables. Considering (6.1.3) and (6.1.4), the derivatives of the model functions are

$$J_1(x) := \sqrt{W} \begin{pmatrix} J_1^1(x_1, p) \\ \vdots \\ J_1^M(x_M, p) \end{pmatrix} = \sqrt{W} \begin{pmatrix} (A_x^1, A_p^1) \\ \vdots \\ (A_x^M, A_p^M) \end{pmatrix}$$

and

$$J_2(x) := \begin{pmatrix} J_2^1(x_1, p) \\ \vdots \\ J_2^M(x_M, p) \end{pmatrix} = \begin{pmatrix} (B_x^1, B_p^1) \\ \vdots \\ (B_x^M, B_p^M) \end{pmatrix},$$

respectively. In the following, we compute the derivatives of J_1 and J_2 with respect to the design variables one by one. However, in favor of a clearer notation, we neglect the function arguments.

- **The Derivative with Respect to the Control Variables q**

Considering the experiments separately, it holds for the Jacobian of the objective function with respect to the controls that

$$\frac{\partial J_1^k}{\partial q^k} = \sqrt{W_k} \begin{pmatrix} \frac{\partial A_x^k}{\partial q^k} & \frac{\partial A_p^k}{\partial q^k} \end{pmatrix}.$$

If we take (6.1.5) and (6.1.6) into account, we get for the first expression that

$$\frac{\partial A_x^k}{\partial q^k} = \sqrt{W_k} \frac{\partial}{\partial q^k} \left(D_{1,0}^k, \dots, D_{1,l_k}^k, D_{1,\tilde{p}}^k \right),$$

where

$$\begin{aligned} \frac{\partial D_{1,\tilde{p}}^k}{\partial q^k} &= -\sqrt{W_k} \Sigma_k^{-1} \left(\frac{\partial^2 h^k}{\partial q^k \partial \tilde{p}^k} + \frac{\partial^2 h^k}{\partial y^k \partial \tilde{p}^k} \frac{\partial y^k}{\partial q^k} \right. \\ &\quad \left. + \left(\frac{\partial^2 h^k}{\partial q^k \partial y^k} + \frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial q^k} \right) \frac{\partial y^k}{\partial \tilde{p}^k} + \frac{\partial h^k}{\partial y^k} \frac{\partial^2 y^k}{\partial q^k \partial \tilde{p}^k} \right) \end{aligned}$$

and

$$\frac{\partial D_{1,j}^k}{\partial q^k} = -\sqrt{W_k} \Sigma_k^{-1} \left(\left(\frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial q^k} \right) \frac{\partial y^k}{\partial s_j^k} + \frac{\partial^2 h^k}{\partial q^k \partial y^k} \frac{\partial y^k}{\partial s_j^k} + \frac{\partial h^k}{\partial y^k} \frac{\partial^2 y^k}{\partial q^k \partial s_j^k} \right),$$

for $j = 0, \dots, l_k$. Using (6.1.7) for the second expression, it follows

$$\begin{aligned} \frac{\partial A_p^k}{\partial q^k} &= -\sqrt{W_k} \Sigma_k^{-1} \left(\frac{\partial^2 h^k}{\partial q^k \partial p} + \frac{\partial^2 h^k}{\partial y^k \partial p} \frac{\partial y^k}{\partial q^k} \right. \\ &\quad \left. + \left(\frac{\partial^2 h^k}{\partial q^k \partial y^k} + \frac{\partial^2 h^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial q^k} \right) \frac{\partial y^k}{\partial p} + \frac{\partial h^k}{\partial y^k} \frac{\partial^2 y^k}{\partial q^k \partial p} \right). \end{aligned}$$

For the derivative of the Jacobian of the restriction function with respect to the controls, it holds for each experiment that

$$\frac{\partial J_2^k}{\partial q^k} = \left(\frac{\partial B_x^k}{\partial q^k}, \frac{\partial B_p^k}{\partial q^k} \right). \quad (6.2.5)$$

Hereby, the first expression is determined by

$$\frac{\partial B_x^k}{\partial q^k} = \frac{\partial}{\partial q^k} \begin{pmatrix} D_{2,0}^k & \cdots & \cdots & D_{2,l_k}^k & D_{2,\tilde{p}}^k \\ G_0^k & -\mathbb{I} & & & G_{0,\tilde{p}}^k \\ & \ddots & \ddots & & \vdots \\ & & G_{l_k-1}^k & -\mathbb{I} & G_{l_k-1,\tilde{p}}^k \end{pmatrix},$$

where

$$\frac{\partial D_{2,i}}{\partial q^k} := \frac{\partial^2 r^k}{\partial q^k \partial y^k} \frac{\partial y^k}{\partial s_i^k} + \left(\frac{\partial^2 r^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial q^k} \right) \frac{\partial y^k}{\partial s_i^k} + \frac{\partial r^k}{\partial y^k} \frac{\partial y^k}{\partial q^k \partial s_i^k} \quad i = 0, \dots, l_k,$$

$$\frac{\partial D_{2,\tilde{p}}^k}{\partial q^k} := \frac{\partial^2 r^k}{\partial q^k \partial \tilde{p}^k} + \frac{\partial^2 r^k}{\partial y^k \partial \tilde{p}^k} \frac{\partial y^k}{\partial q^k} + \left(\frac{\partial^2 r^k}{\partial q^k \partial y^k} + \frac{\partial^2 r^k}{\partial (y^k)^2} \frac{\partial y^k}{\partial q^k} \right) \frac{\partial y^k}{\partial \tilde{p}^k} + \frac{\partial r^k}{\partial y^k} \frac{\partial^2 y^k}{\partial q^k \partial \tilde{p}^k},$$

$$\frac{\partial G_i^k}{\partial q^k} := \frac{\partial y(\tau_{i+1}; s_i^k, \tilde{p}^k, p)}{\partial q^k \partial s_i^k}, \quad i = 0, \dots, l_k - 1,$$

$$\frac{\partial G_{i,\tilde{p}}^k}{\partial q^k} := \frac{\partial y(\tau_{i+1}; s_i^k, \tilde{p}^k, p)}{\partial q^k \partial \tilde{p}^k}, \quad i = 0, \dots, l_k - 1.$$

For the second expression of (6.2.5), we obtain

$$\frac{\partial B_p^k}{\partial q^k} = \frac{\partial}{\partial q^k} \begin{pmatrix} D_{2,p}^k \\ G_{0,p}^k \\ \cdots \\ G_{l_k-1,p}^k \end{pmatrix},$$

where

$$\frac{\partial D_{2,p}^k}{\partial q^k} = \frac{\partial^2 r}{\partial q^k \partial p} + \frac{\partial^2 r}{\partial y^k \partial p} \frac{\partial y^k}{\partial q^k} + \left(\frac{\partial^2 r}{\partial q^k \partial y^k} + \frac{\partial^2 r}{\partial (y^k)^2} \frac{\partial y^k}{\partial q^k} \right) \frac{\partial y^k}{\partial p} + \frac{\partial r}{\partial y^k} \frac{\partial^2 y^k}{\partial q^k \partial p}$$

and

$$\frac{\partial G_{j,p}^k}{\partial q^k} = \frac{\partial^2 y^k}{\partial q^k \partial p}, \quad i = 0, \dots, l_k - 1.$$

• **The Derivative with Respect to the Discretization Variables s**

For each single experiment we get for the Jacobian of the objective function with respect to the discretization variables the following relation

$$\frac{\partial J_1^k}{\partial s^k} = \sqrt{W_k} \begin{pmatrix} \frac{\partial A_x^k}{\partial s^k} & \frac{\partial A_p^k}{\partial s^k} \end{pmatrix}.$$

These derivatives are part of the second derivatives A_{xx}^k and A_{px}^k as given in Subsection 6.1.2 and they can be adapted for the derivatives in the context of DoE.

The derivative of the Jacobians of the restriction functions with respect to s is given by

$$\frac{\partial J_2^k}{\partial s^k} = \begin{pmatrix} \frac{\partial B_x^k}{\partial s^k} & \frac{\partial B_p^k}{\partial s^k} \end{pmatrix}.$$

The needed derivatives are parts of B_{xx}^k and B_{px}^k , respectively, and they can also be adapted from Subsection 6.1.2.

• **The Derivative with Respect to the Sampling Variables w**

The Jacobians J_2^k are independent of the sampling variables, and therefore we get $\partial J_2^k / \partial w = 0$ for all $k = 1, \dots, M$. The derivatives of J_1^k with respect to the design sampling variables are given by

$$\begin{aligned} \frac{\partial \sqrt{W_k} J_1^k}{\partial w} &= \frac{\partial}{\partial w} \begin{pmatrix} \sqrt{w_1^k} & & 0 \\ & \ddots & \\ 0 & & \sqrt{w_{K^k}^k} \end{pmatrix} J_1^k \\ &= \frac{1}{2} \begin{pmatrix} \frac{1}{\sqrt{w_1^k}} & & 0 \\ & \ddots & \\ 0 & & \frac{1}{\sqrt{w_{K^k}^k}} \end{pmatrix} J_1^k, \end{aligned}$$

where we get singularities if for a particular index $i = 1, \dots, K^k$ it holds that $w_i^k = 0$. Considering the covariance matrix, the matrices $\sqrt{W_k} J_1^k$ only occur in the product $J_1^{kT} \sqrt{W_k} \sqrt{W_k} J_1^k = J_1^{kT} W_k J_1^k$. This results in

$$\frac{\partial J_1^{kT} W_k J_1^k}{\partial w} = J_1^{kT} J_1^k,$$

and the problem of the existence of singularities is avoided.

6.3 Derivatives of the Generalized Inverses

For the definition of the quadratically approximated confidence region and for several estimates, we use the derivative of the generalized inverse J^+ . The representation and properties of this derivative are discussed in this section. In the first part, we consider the derivative of a Moore-Penrose pseudo-inverse, which covers the situation of an unconstrained parameter estimation problem. Thus, in the second part, we look at the derivative of J^+ in the case of a constrained parameter estimation problem.

6.3.1 Derivative of a Moore-Penrose Pseudo-Inverse

Based on Magnus and Neudecker [75], we consider the derivative of a Moore-Penrose pseudo-inverse A^+ , which is uniquely defined by the four axioms given in Subsection 2.4. The first lemma delivers equivalent conditions to the k -times differentiability of the pseudo-inverse.

Lemma 6.3.1 *Suppose that $x_0 \in S \subset \mathbb{R}^{n \times q}$, where S is an open subset and let $A : S \rightarrow \mathbb{R}^{m \times p}$ be a matrix function. We assume that A is k -times (continuously) differentiable ($k \geq 1$) in a neighborhood $U(x_0) \subset S$ of x_0 . Then it holds that the following conditions are equivalent*

- i. $\text{rank}(A(x))$ is constant on $U(x_0)$.
- ii. A^+ is continuously on $U(x_0)$.
- iii. A^+ is k -times (continuously) differentiable on $U(x_0)$.

Proof. This proof is explored thoroughly in Magnus and Neudecker [75].

■

Therefore, Lemma 6.3.1 reveals the conditions of the existence of the derivative of the Moore-Penrose pseudo-inverse. In order to get an explicit representation of the derivative of A^+ the following lemma is useful.

Lemma 6.3.2 *Let $S \subset \mathbb{R}^{n \times q}$ be an open subset and $A : S \rightarrow \mathbb{R}^{m \times p}$ a k -times (continuously) differentiable matrix function ($k \geq 1$). If $\text{rank}(A(x))$ is constant on S , then $A^+A : S \rightarrow \mathbb{R}^{p \times p}$ and $AA^+ : S \rightarrow \mathbb{R}^{m \times m}$ are k -times (continuously) differentiable on S , and it holds that*

$$dA^+A = A^+(dA)(\mathbb{I} - A^+A) + (A^+(dA)(\mathbb{I} - A^+A))^T \quad (6.3.1)$$

and

$$dAA^+ = (\mathbb{I} - AA^+)(dA)A^+ + ((\mathbb{I} - AA^+)(dA)A^+)^T. \quad (6.3.2)$$

Proof. The proof of this lemma can be found in Magnus and Neudecker [75].

■

Considering this lemma, we can formulate an explicit representation of the derivative of a Moore-Penrose pseudo-inverse.

Theorem 6.3.3 *Let $S \subset \mathbb{R}^{n \times q}$ be an open subset and $A : S \rightarrow \mathbb{R}^{m \times p}$ a k -times (continuously) differentiable matrix function ($k \geq 1$). If $\text{rank}(A(x))$ is constant on S , then it holds that $A^+ : S \rightarrow \mathbb{R}^{p \times m}$ is k -times (continuously) differentiable on S , and dA^+ is given by*

$$dA^+ = -A^+(dA)A^+ + A^+(A^+)^T(dA^T)(\mathbb{I} - AA^+) + (\mathbb{I} - A^+A)(dA^T)(A^+)^T A^+. \quad (6.3.3)$$

Proof. The proof is based on Lemma 6.3.2.

It holds that

$$dA^+ = d(A^+AA^+) = (dA^+A)A^+ + A^+A(dA^+) \quad (6.3.4)$$

and

$$dAA^+ = (dA)A^+ + A(dA^+). \quad (6.3.5)$$

From (6.3.4) and (6.3.5) we obtain

$$dA^+ = (dA^+A)A^+ + A^+(dAA^+) - A^+(dA)A^+. \quad (6.3.6)$$

Replacing the corresponding terms by (6.3.1) and (6.3.2), it follows

$$\begin{aligned} dA^+ &= (A^+(dA)(\mathbb{I} - A^+A) + (A^+(dA)(\mathbb{I} - A^+A))^T)A^+ \\ &\quad + A^+((\mathbb{I} - AA^+)(dA)A^+ + ((\mathbb{I} - AA^+)(dA)A^+)^T) - A^+(dA)A^+ \\ &= (A^+(dA)(\mathbb{I} - A^+A))^T A^+ + A^+((\mathbb{I} - AA^+)(dA)A^+)^T - A^+(dA)A^+ \\ &= -A^+(dA)A^+ + A^+(A^+)^T(dA^T)(\mathbb{I} - AA^+) + (\mathbb{I} - A^+A)(dA^T)(A^+)^T A^+. \end{aligned}$$

■

In the case of an unconstrained parameter estimation problem, the generalized inverse for the computation of a new *Gauss-Newton* iterate is given by $J^+ = (J^T J)^{-1} J^T$, and it holds that $J^+ J = \mathbb{I}$. If we take $J^+ J = \mathbb{I}$ into account, Formula (6.3.3) can be simplified as given in the following remark.

Remark 6.3.4 *If in addition to the requirements of Theorem 6.3.3 it holds that $A^+ A = \mathbb{I}$, then (6.3.3) simplifies to*

$$dA^+ = A^+(A^+)^T(dA^T)(\mathbb{I} - AA^+) - A^+(dA)A^+. \quad (6.3.7)$$

6.3.2 Derivative of the Generalized Inverse J^+

In the case of a constrained parameter estimation problem, matrix J^+ with

$$J^+(x) = (\mathbb{I} \quad 0) \begin{pmatrix} J_1^T(x) J_1(x) & J_2^T(x) \\ J_2(x) & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T(x) & 0 \\ 0 & \mathbb{I} \end{pmatrix},$$

is not a Moore-Penrose pseudo-inverse since the axiom $(JJ^+)^T = JJ^+$ is not necessarily fulfilled. Consequently, this requires a specific consideration of the derivative of J^+ . For the constrained case the following theorem holds.

Theorem 6.3.5 *Let $x \in U$, where $U \subset \mathbb{R}^{n_x}$ is an open subset. Furthermore, we assume that $J^T = (J_1^T, J_2^T) \in \mathbb{R}^{n_x \times (m_1+m_2)}$ is k -times (continuously) differentiable for all $x \in U$ ($k \geq 1$), and the regularity assumptions (CQ) and (PD) are fulfilled. If $\text{rank}(J)$ is constant on U , then it holds that J^+ is (continuously) differentiable on U and*

$$dJ^+ = \mathcal{C}(dJ^T) \left(\begin{pmatrix} \mathbb{I} & 0 \\ 0 & 0 \end{pmatrix} - \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \right) - J^+(dJ)J^+,$$

where \mathcal{C} denotes the covariance matrix and

$$\mathcal{J} := \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}.$$

Proof. It holds that

$$\begin{aligned} dJ^+ &= (\mathbb{I} \ 0) d \left(\mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \right) \\ &= (\mathbb{I} \ 0) \left(\mathcal{J}^{-1} \begin{pmatrix} dJ_1^T & 0 \\ 0 & 0 \end{pmatrix} - \mathcal{J}^{-1}(d\mathcal{J})\mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \right). \end{aligned} \quad (6.3.8)$$

We consider

$$\begin{aligned} (\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} dJ_1^T & 0 \\ 0 & 0 \end{pmatrix} &= (\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} (dJ_1^T \ 0) \begin{pmatrix} \mathbb{I} & 0 \\ 0 & 0 \end{pmatrix} \\ &= \mathcal{C}(dJ^T) \begin{pmatrix} \mathbb{I} & 0 \\ 0 & 0 \end{pmatrix} \end{aligned} \quad (6.3.9)$$

and an appropriate partition of

$$\begin{aligned} d\mathcal{J} &= \begin{pmatrix} (dJ_1^T)J_1 + J_1^T(dJ_1) & dJ_2^T \\ dJ_2 & 0 \end{pmatrix} \\ &= \begin{pmatrix} (dJ_1^T)J_1 & dJ_2^T \\ 0 & 0 \end{pmatrix} + \begin{pmatrix} J_1^T(dJ_1) & 0 \\ dJ_2 & 0 \end{pmatrix}. \end{aligned}$$

a) Considering the first summand, the corresponding expression of (6.3.8) can be rewritten to

$$\begin{aligned} & - (\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} (dJ_1^T)J_1 & dJ_2^T \\ 0 & 0 \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \\ &= - (\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} ((dJ_1^T)J_1 \ dJ_2^T) \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \\ &= -\mathcal{C}(dJ^T) \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix}. \end{aligned}$$

b) For the second summand, the corresponding expression of (6.3.8) results in

$$\begin{aligned}
 & - (\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} J_1^T(dJ_1) & 0 \\ dJ_2 & 0 \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \\
 & = - (\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} dJ_1 \\ dJ_2 \end{pmatrix} (\mathbb{I} \ 0) \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \\
 & = - J^+(dJ)J^+.
 \end{aligned}$$

Combining (6.3.9) with items a) and b), we obtain the complete derivative

$$dJ^+ = \mathcal{C}(dJ^T) \left(\begin{pmatrix} \mathbb{I} & 0 \\ 0 & 0 \end{pmatrix} - \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \right) - J^+(dJ)J^+.$$

■

Remark 6.3.6 For the definition of the quadratically approximated confidence regions, it is unnecessary to have the complete derivative of J^+ . Here, it is sufficient to have the derivative of J^+ multiplied by a vector $\begin{pmatrix} \frac{1}{\sigma}\epsilon \\ 0 \end{pmatrix}$, i.e.

$$d \left(J^+ \begin{pmatrix} \frac{1}{\sigma}\epsilon \\ 0 \end{pmatrix} \right).$$

Considering this and due to the fact that

$$\begin{aligned}
 \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & \mathbb{I} \end{pmatrix} \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} & = \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} J_1^T \\ 0 \end{pmatrix} \\
 & = \begin{pmatrix} J_1 & 0 \\ 0 & \mathbb{I} \end{pmatrix} \mathcal{J}^{-1} \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} (J_1^T \ J_2^T) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \\
 & = (J^+)^T J^T \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} \\
 & = (JJ^+)^T \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix},
 \end{aligned}$$

it holds that

$$dJ^+ \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix} = (\mathcal{C}(dJ^T) (\mathbb{I} - (JJ^+)^T) - J^+(dJ)J^+) \begin{pmatrix} \mathbb{I} \\ 0 \end{pmatrix}. \quad (6.3.10)$$

Therefore, we get a similar representation to the one given in Remark 6.3.4, when dealing with a Moore-Penrose pseudo-inverse.

6.4 Computation of Derivatives

For the computation of the first and the second order derivatives, we use concepts of automatic differentiation as well as internal numerical differentiation as described in the following Subsections 6.4.1 and 6.4.3, respectively. The third derivatives are obtained by an application of finite differences as discussed in Subsection 6.4.2.

6.4.1 Automatic Differentiation

The idea of automatic differentiation is based on the fact that any function is composed by a sequence of elementary functions—including exponential, logarithmic and trigonometric functions—which are combined by elementary arithmetic operations, e.g. addition and multiplication. Considering this, the derivative of a function f can be computed by successively applying the chain rule to each combination of elementary operations and functions belonging to f . Accordingly, given smooth functions $w : \mathbb{R}^m \rightarrow \mathbb{R}$ and $v : \mathbb{R}^n \rightarrow \mathbb{R}^m$, and $f(x) = w(v(x))$ the derivative of the composition with respect to $x \in \mathbb{R}^n$, is given by

$$\frac{\partial f}{\partial x}(x) = \sum_{i=1}^m \frac{\partial w}{\partial v_i} \frac{\partial v_i}{\partial x}.$$

The derivatives computed by automatic differentiation are exact up to machine precision. Even higher order derivatives can be computed without loss of accuracy. For a thorough treatment to automatic differentiation see e.g. Rall [93] and Griewank [53].

6.4.2 Finite Differences

Let us attend to the task of the numerical computation of the derivative of a nonlinear and smooth function $f : D \subseteq \mathbb{R}^{n_x} \rightarrow \mathbb{R}$. A possibility to approximate the partial derivative with respect to the component x_i is given by

$$\frac{\partial f}{\partial x_i}(x) \approx \frac{f(x + he_i) - f(x)}{h},$$

where h is a small positive scalar and e_i denotes the i -th unit vector. This approximation is called the *forward difference* or the *one-sided difference*. The computational effort of this approach is comparatively low. For a computation of the entire derivative of f , $n + 1$ function evaluations at the points x and $x + he_i$ are required for $i = 1, \dots, n_x$. However, an optimal choice of the constant h and an estimate of the resulting approximation error is to be clarified. Following Nocedal and Wright [81], an optimal choice of the scalar h is $h = \sqrt{\epsilon}$, where ϵ is of the size of the machine-precision. If we denote the approximation error by δ_h , i.e.

$$\frac{\partial f}{\partial x_i}(x) = \frac{f(x + he_i) - f(x)}{h} + \delta_h,$$

it holds the bound $|\delta_h| \leq \sqrt{\epsilon}$. A more accurate, but also more expensive approach is given by the *central differences*

$$\frac{\partial f}{\partial x_i}(x) \approx \frac{f(x + he_i) - f(x - he_i)}{2h}.$$

For an entire representation of the derivative $2n + 1$ function evaluations are required. This is twice as much as it is the case if *forward differences* are used. As presented by

Nocedal and Wright [81], an optimal value of h is given by $h = \epsilon^{1/3}$ in the case of the *central differences* and the approximation error is reduced to $|\delta_h| \leq \epsilon^{2/3}$.

A thorough treatment of the numerical computation of derivatives by means of finite differences can be found in e.g. Jordán [57] and Nocedal and Wright [81].

6.4.3 Internal Numerical Differentiation

Considering the introduced derivatives from Sections 6.1 and 6.2, we have to provide the derivatives of the states y^k with respect to the parameters p , \tilde{p}^k , the controls q^k and the corresponding initial values s^k , for each experimental layout $k = 1, \dots, M$. In order to investigate these derivatives, we exemplarily consider an ordinary differential equation

$$\dot{y} = f(t, y(t), v), \quad (6.4.1)$$

depending on the time $t \in [t_a, t_e] \subset \mathbb{R}$, the states $y(t) \in \mathbb{R}^{n_y}$, and the constants $v \in \mathbb{R}^{n_v}$, representing the global and local parameters and the control variables, respectively. Furthermore, the initial value condition $y(t_a) = y_a$ has to be fulfilled. The solution of (6.4.1) with respect to a particular triple (t_a, y_a, v) can be written by the integral formula

$$y(t) = y_a + \int_{t_a}^t f(\tau, y(\tau), v) d\tau, \quad (6.4.2)$$

and we denote it by $y(t; t_a, y_a, v) := y(t)$. In the following, we consider the variational ordinary differential equations in order to compute the first and the second order derivatives of $y(t; t_a, y_a, v)$ with respect to y_a and v , respectively.

First Order Derivatives of the States

If we denote $G_{y_a}(t; t_a, y_a, v) := \partial y(t; t_a, y_a, v) / \partial y_a \in \mathbb{R}^{n_y \times n_y}$, a differentiation of (6.4.2) with respect to the initial value y_a yields

$$\begin{aligned} G_{y_a}(t; t_a, y_a, v) &= \frac{\partial}{\partial y_a} \left(y_a + \int_{t_a}^t f(\tau, y(\tau), v) d\tau \right) \\ &= \mathbb{I} + \int_{t_a}^t \frac{\partial f(\tau, y(\tau), v)}{\partial y} G_{y_a}(t; t_a, y_a, v) d\tau. \end{aligned} \quad (6.4.3)$$

A backward application of (6.4.2) yields that $G_{y_a}(t; t_a, y_a, v)$ can be obtained by solving the linear ordinary differential equation system

$$\frac{\partial G_{y_a}(t; t_a, y_a, v)}{\partial t} = \frac{\partial f(t, y(t), v)}{\partial y} G_{y_a}(t; t_a, y_a, v) \quad (6.4.4)$$

with the initial value condition $G_{y_a}(t_a; t_a, y_a, v) = \mathbb{I}$.

Suppose that the derivative of the states with respect to the constants v is given by $G_v(t; t_a, y_a, v) := \partial y(t; t_a, y_a, v) / \partial v \in \mathbb{R}^{n_y \times n_v}$. Then it holds that

$$\begin{aligned} G_v(t; t_a, y_a, v) &= \frac{\partial}{\partial v} \left(y_a + \int_{t_0}^t f(\tau, y(\tau), v) d\tau \right) \\ &= \int_{t_0}^t \left(\frac{\partial f(\tau, y(\tau), v)}{\partial v} + \frac{\partial f(\tau, y(\tau), v)}{\partial y} G_v(\tau; t_a, y_a, v) \right) d\tau. \end{aligned} \quad (6.4.5)$$

Here, a backward application of the integral formula yields that $G_v(t; t_a, y_a, v)$ is the solution of the linear ordinary differential equation system

$$\frac{\partial G_v(t; t_a, y_a, v)}{\partial t} = \frac{\partial f(t, y(t), v)}{\partial v} + \frac{\partial f(t, y(t), v)}{\partial y} G_v(t; t_a, y_a, v) \quad (6.4.6)$$

and the initial value condition is $G_v(t_a; t_a, y_a, v) = 0$.

Second Order Derivatives of the States

If we denote the second derivative of the states with respect to the initial values by $G_{y_a, y_a}(t; t_a, y_a, v) := \partial^2 y(t; t_a, y_a, v) / \partial y_a^2 \in \mathbb{R}^{n_y \times n_y^2}$, we obtain

$$\begin{aligned} G_{y_a, y_a}(t; t_a, y_a, v) &= \frac{\partial}{\partial y_a} \left(\mathbb{I} + \int_{t_0}^t \frac{\partial f(\tau, y(\tau), v)}{\partial y} G_{y_a}(t; t_a, y_a, v) d\tau \right) \\ &= \int_{t_0}^t \left(\left(\frac{\partial^2 f}{\partial y^2} G_{y_a} \right) G_{y_a} + \frac{\partial f}{\partial y} G_{y_a, y_a} \right) d\tau, \end{aligned}$$

by differentiating (6.4.3). For having a more readable notation, we omitted the function arguments in the second line. Thus, a backward application of the integral formula delivers that $G_{y_a, y_a}(t; t_a, y_a, v)$ is the solution of

$$\frac{\partial G_{y_a, y_a}}{\partial t} = \left(\frac{\partial^2 f}{\partial y^2} G_{y_a} \right) G_{y_a} + \frac{\partial f}{\partial y} G_{y_a, y_a},$$

where we have to consider the initial value condition $G_{y_a, y_a}(t_a; t_a, y_a, v) = 0$.

By a differentiating (6.4.5) with respect to the constants v , we obtain the second derivative of the states with respect to v by

$$\begin{aligned} G_{v, v}(t; t_a, y_a, v) &= \frac{\partial}{\partial v} \left(\int_{t_0}^t \left(\frac{\partial f(\tau, y(\tau), v)}{\partial v} + \frac{\partial f(\tau, y(\tau), v)}{\partial y} G_v(\tau; t_a, y_a, v) \right) d\tau \right) \\ &= \int_{t_0}^t \left(\frac{\partial^2 f}{\partial v^2} + \frac{\partial^2 f}{\partial v \partial y} G_v + \left(\frac{\partial^2 f}{\partial y \partial v} + \frac{\partial^2 f}{\partial y^2} G_v \right) G_v + \frac{\partial f}{\partial y} G_{v, v} \right) d\tau, \end{aligned}$$

where $G_{v, v}(t; t_a, y_a, v) := \partial^2 y(t; t_a, y_a, v) / \partial v^2 \in \mathbb{R}^{n_y \times n_v^2}$. Again, for simplicity of notation we omitted the function arguments in the second line. Considering the integral formula, $G_{v, v}(t; t_a, y_a, v)$ is the solution of the linear ordinary differential equation system

$$\frac{\partial G_{v, v}}{\partial t} = \frac{\partial^2 f}{\partial v^2} + \frac{\partial^2 f}{\partial v \partial y} G_v + \left(\frac{\partial^2 f}{\partial y \partial v} + \frac{\partial^2 f}{\partial y^2} G_v \right) G_v + \frac{\partial f}{\partial y} G_{v, v},$$

where the initial value condition is given by $G_{v,v}(t_a; t_a, y_a, v) = 0$.

The same procedure yields that the mixed second derivatives are given by

$$G_{v,y_a}(t; t_a, y_a, v) = \int_{t_0}^t \left(\left(\frac{\partial^2 f}{\partial v \partial y} + \frac{\partial^2 f}{\partial y^2} G_v \right) G_{y_a} + \frac{\partial f}{\partial y} G_{v,y_a} \right) d\tau$$

and

$$G_{y_a,v}(t; t_a, y_a, v) = \int_{t_0}^t \left(\frac{\partial^2 f}{\partial y \partial v} G_{y_a} + \left(\frac{\partial^2 f}{\partial y^2} G_{y_a} \right) G_v + \frac{\partial f}{\partial y} G_{y_a,v} \right) d\tau,$$

where we denote

$$G_{v,y_a}(t; t_a, y_a, v) := \frac{\partial^2 y(t; t_a, y_a, v)}{\partial v \partial y_a} \in \mathbb{R}^{n_y \times n_v n_y}$$

and

$$G_{y_a,v}(t; t_a, y_a, v) := \frac{\partial^2 y(t; t_a, y_a, v)}{\partial y_a \partial v} \in \mathbb{R}^{n_y \times n_y n_v}.$$

Hence, according to Formula (6.4.2), the second derivatives are the solutions of the linear ordinary differential equation systems

$$\frac{\partial G_{v,y_a}}{\partial t} = \left(\frac{\partial^2 f}{\partial v \partial y} + \frac{\partial^2 f}{\partial y^2} G_v \right) G_{y_a} + \frac{\partial f}{\partial y} G_{v,y_a}$$

and

$$\frac{\partial G_{y_a,v}}{\partial t} = \frac{\partial^2 f}{\partial y \partial v} G_{y_a} + \left(\frac{\partial^2 f}{\partial y^2} G_{y_a} \right) G_v + \frac{\partial f}{\partial y} G_{y_a,v},$$

respectively. Here, both initial value conditions are given by $G_{v,y_a}(t_a; t_a, y_a, v) = 0$ and $G_{y_a,v}(t_a; t_a, y_a, v) = 0$, respectively.

All the derivatives of the states can be computed by solving a linear ordinary differential equation system. During the parameter estimation and the design of optimal experiments procedure, this can be done efficiently by solving all the differential equations simultaneously. Thus, the used integrator needs to be called only once for a computation of the states and their derivatives evaluated at the needed time points.

7 Numerical Examples

In this chapter, we deal with numerical examples to investigate the benefit and basic properties of the newly introduced Q-criterion for the design of optimal experiments. Thereby, the considerations are based on the following strategy:

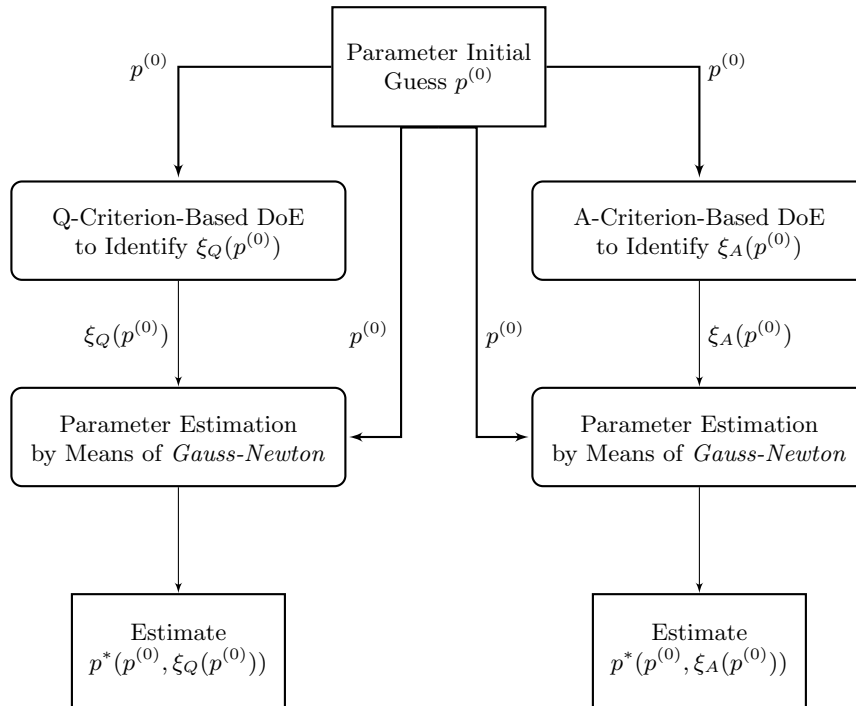


Figure 7.1: Strategy for investigating the properties of the Q-criterion.

Given a particular initial guess $p^{(0)}$ of the parameter values, we solve a Q-criterion-based and an A-criterion-based DoE problem. Thus, we obtain two different system settings $\xi_Q(p^{(0)})$ and $\xi_A(p^{(0)})$ for the parameter estimation problem. Subsequently, we solve the parameter estimation problems for both system settings and therefore we get solutions $p^*(p^{(0)}, \xi_Q(p^{(0)}))$ and $p^*(p^{(0)}, \xi_A(p^{(0)}))$, respectively. Thereby, we are interested in investigating the following issues.

- Whether there are general differences between the statistical accuracy of the estimates $p^*(p^{(0)}, \xi_Q(p^{(0)}))$ and $p^*(p^{(0)}, \xi_A(p^{(0)}))$.

- How robust the estimates $p^*(p^{(0)}, \xi_Q(p^{(0)}))$ and $p^*(p^{(0)}, \xi_A(p^{(0)}))$ are against variations in the parameter initial values $p^{(0)}$.
- How the convergence properties of the *Gauss-Newton* method are depending on $\xi_Q(p^{(0)})$ and $\xi_A(p^{(0)})$, respectively.

This procedure is also illustrated in Figure 7.1.

7.1 A Nonlinear Example

As a first example, we consider the nonlinear function

$$h(t, p) = \frac{p_1 (e^{-tp_2} - e^{-tp_1})}{p_1 - p_2}, \quad (7.1.1)$$

as it can be found by Gallant [48]. Suppose that the true parameters are given by $\bar{p} := (p_1, p_2)^T = (1.4, 4)^T$, and that all in all we are able to measure at the time points $t_i = i \cdot 0.1$, where $i = 0, \dots, 50$. The measurements are assumed to be affected by independent and normally distributed errors of the order of 10% of the size of the measurements.

In the following considerations, we want to deal with the task of estimating the two unknown parameters by means of four (suitable) measurements, identified by DoE. Especially, we want to investigate how the estimate depends on uncertain initial values $p^{(0)}$, when using the A-criterion or the Q-criterion for the DoE-based measurement selection. The design variables are given by the sampling variables $\xi = w \in \{0, 1\}^{51}$ and we have to consider the DoE constraint $\sum_{i=1}^{51} w_i = 4$. Due to some prior knowledge, we know that $\bar{p}_1 \in [0.4, 2]$ and $\bar{p}_2 \in [3, 10]$, and consider the discretized parameter spaces D_1 for parameter p_1 and D_2 for parameter p_2 , where

$$D_1 := \{0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0\},$$

and

$$D_2 := \{3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0\}.$$

Each grid point $p^{(0)} = (p_1^{(0)}, p_2^{(0)})^T \in D_1 \times D_2$ serves as a parameter initial value of the underlying DoE problem. Subsequently, after having identified an optimal measurement selection $w^*(p^{(0)})$, the corresponding parameter initial value $p^{(0)}$ serves also as an initial value to solve the parameter estimation problem.

Figure 7.2 illustrates the deviations $\|\bar{p} - p^*(p^{(0)})\|_2$ of the resulting estimates and the true parameter values, depending on the used initial values of a measurement selection with the A-criterion and the Q-criterion, respectively. It is obvious that the estimates resulting from a measurement selection with the A-criterion very sensitively depend on the used parameter initial values. In particular, for those initial values where $p_1^{(0)}$ is close

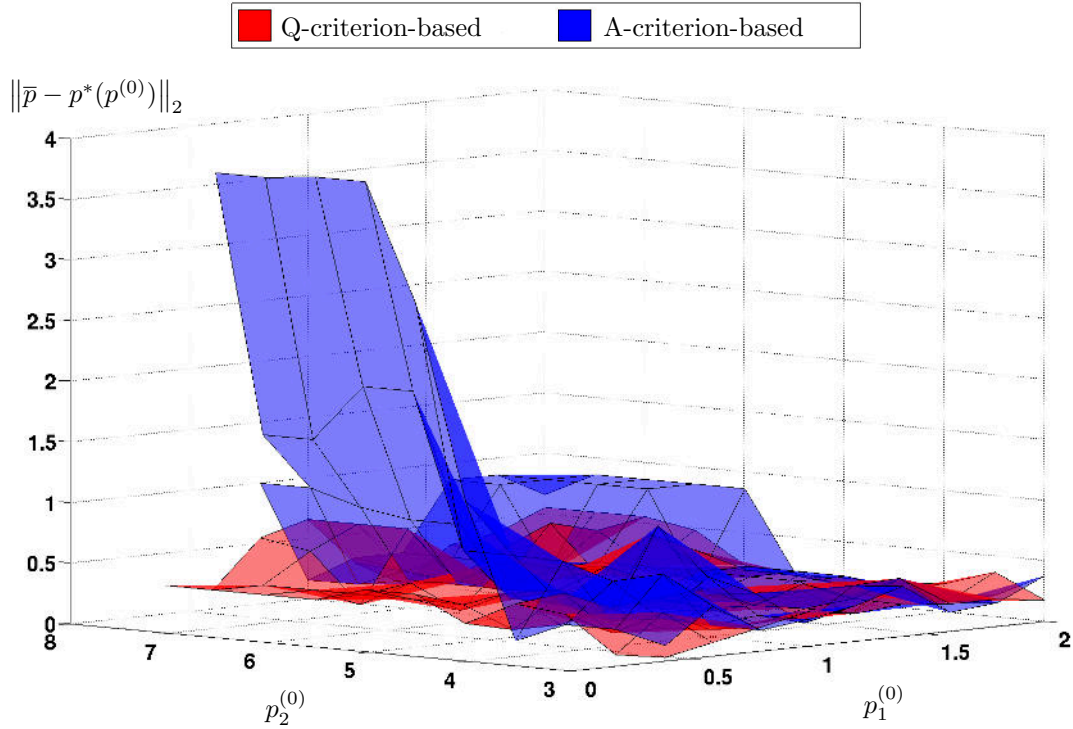


Figure 7.2: Deviations of the estimates to the true values, depending on different initial values and different DoE objective functions.

to the lower interval bound, we observe significant deviations between the estimates and the true parameters. As opposed to this, the estimates resulting from a measurement selection with the Q-criterion seem to be very robust against changed initial parameter values. Here, we have only small deviations between the estimates and the true parameter values. The reason for this behavior can be seen in Figures 7.3 and 7.4. They illustrate the sizes of estimates of the Lipschitz constants $\tilde{\kappa}$ and $\tilde{\omega}$ depending on the used initial values. Thereby, the constants are evaluated at the corresponding parameter initial values $p^{(0)}$ and the resulting design variables $w^*(p^{(0)})$. If $w^*(p^{(0)})$ is determined by using the A-criterion, both figures show much larger values of the constants than if the Q-criterion were used. This is especially the case if $p_1^{(0)}$ is close to the lower interval bound. Thus, the Q-criterion leads to an essential reduction of the nonlinearity of the considered parameter estimation problem, which has a beneficial effect on the estimates.

7.2 Design of Optimal Experiments for the Monod Model

In the second example we consider the Monod model, describing the substrate dependent growth of a microbial biomass. In literature, parameter estimations and the design of optimal experiment properties of the Monod model are discussed in e.g. Dette et al. [39],

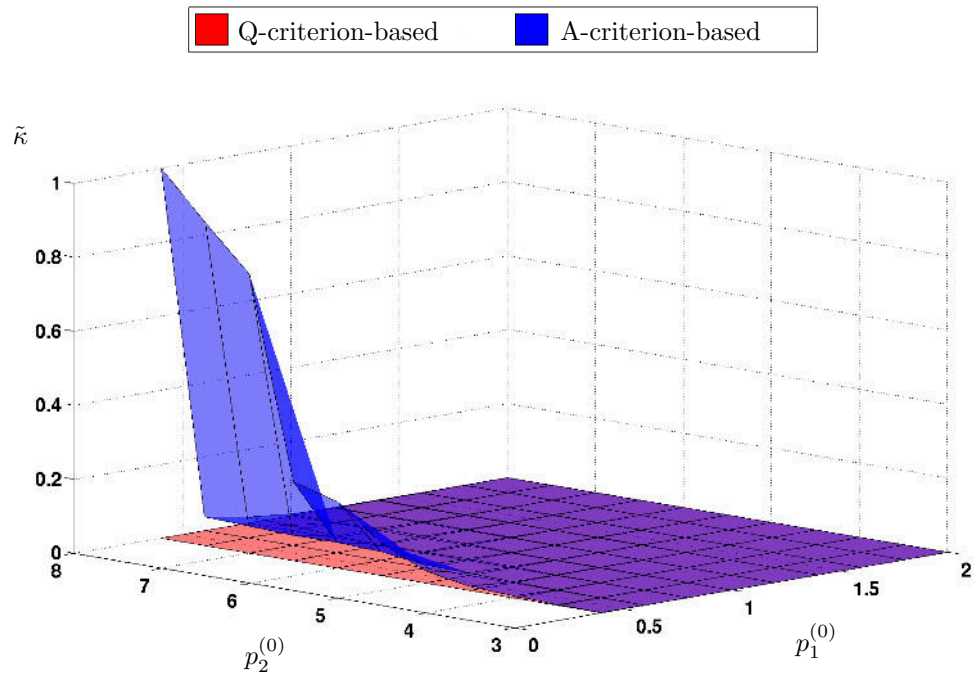


Figure 7.3: Normalized values of κ -estimates $\tilde{\kappa}$, subject to different initial values and different DoE objective functions.

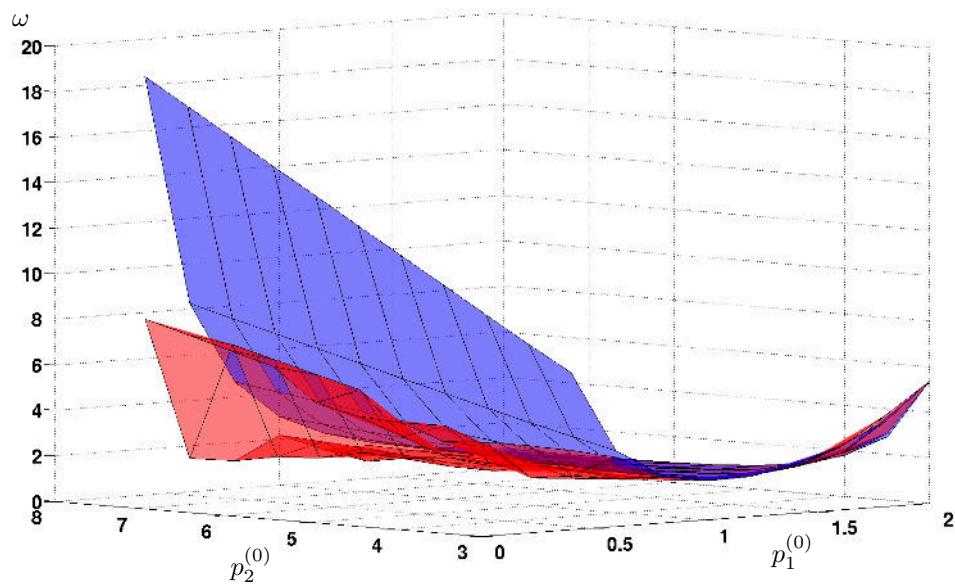


Figure 7.4: Values of ω -estimates, subject to different initial values and different DoE objective functions.

Merkel et al. [78], Ossenbruggen et al. [83], Strigul et al. [104], and Vanrolleghem et al. [107].

The Monod model can be described by a first order ordinary differential equation

$$\frac{dy(t)}{dt} = \mu(t) \cdot y(t), \quad (7.2.1)$$

where

$$\mu(t) = \mu_{max} \frac{s(t)}{s(t) + K_s}$$

with

$$s(t) = \frac{y_0 - y(t)}{Y} + s_0,$$

according to Pirt [87] and Koch [61]. The state $y(t)$ denotes the time dependent growth of a biomass concentration with the specific growth rate $\mu(t)$. The specific growth rate $\mu(t)$ consists of the maximal specific growth rate μ_{max} , the saturation constant K_s and the time dependent substrate concentration $s(t)$. The substrate concentration at time t is determined by the yield coefficient Y , the biomass concentration $y(t)$ and the initial concentrations y_0 and s_0 , respectively. The unknown parameters are the maximal specific growth rate, the saturation constant and the yield coefficient. We label the wanted parameters by

$$p := (p_1, p_2, p_3)^T := (\mu_{max}, K_s, Y)^T.$$

In order to estimate the unknown quantities, we want to use the design of optimal experiments to identify nine suitable measurement times from $t_i = i$, where $i = 0, \dots, 50$. The initial concentrations are given by $y_0 = 0.03$ and $s_0 = 1$, respectively. We use synthetic measurements with measurement errors of the order of 10% and the true parameter values are $\bar{p} := (0.25, 0.5, 0.25)^T$.

The following results are based on randomly perturbed initial parameter values for the identification of measurements by using DoE and for a subsequent estimation of the wanted parameters by using the *Gauss-Newton* method. The design variables are just given by the sampling variables $\xi := w$, with $w \in \{0, 1\}^{51}$, and since the parameter estimation should be performed by using exactly nine measurements, we have to consider the DoE constraint $\sum_{i=1}^{51} w_i = 9$. Table 7.1 shows the *Gauss-Newton* convergence properties and the resulting parameter estimates for a measurement selection using a Q-criterion and an A-criterion-based DoE. The most significant difference occurs in the necessary number of *Gauss-Newton* iterations. In case of a measurement selection by using the A-criterion, the subsequent parameter estimation takes 57 *Gauss-Newton* iterations as opposed to 7 *Gauss-Newton* iterations when solving the parameter estimation problem, where the measurements are identified with a Q-criterion-based DoE. This occurs due to the different

Table 7.1: Parameter estimation properties dependent on different DoE objective functions.

	A-criterion	Q-criterion
# <i>Gauss-Newton</i> iterations	57	7
p_1^*	0.1889	0.2636
p_2^*	0.2051	0.6445
p_3^*	0.1915	0.2321
$ \bar{p}_1 - p_1^* $	0.0611 ($\hat{=}$ 24%)	0.0136 ($\hat{=}$ 5%)
$ \bar{p}_2 - p_2^* $	0.2949 ($\hat{=}$ 41%)	0.1145 ($\hat{=}$ 23%)
$ \bar{p}_3 - p_3^* $	0.0585 ($\hat{=}$ 23%)	0.0179 ($\hat{=}$ 7%)
$\ \bar{p} - p^*\ $	0.3068	0.1462
$\frac{1}{2} \ F(p^*)\ _2^2$	0.0001	0.0002
$\tilde{\kappa}$	0.9778	0.132
$\tilde{\kappa} + \frac{1}{2}\tilde{\omega} \ \Delta p^{(0)}\ _2$	0.9805	0.1047

values of $\tilde{\kappa}$ and $\tilde{\kappa} + \frac{1}{2}\tilde{\omega} \|\Delta p^{(0)}\|_2$, respectively. The values $\tilde{\kappa}$ and $\tilde{\omega}$ are scaled estimates of the Lipschitz constants as introduced in Theorem 2.5.1 describing the *Gauss-Newton* convergence properties. In case of the A-criterion, those values are very close to 1 and consequently we have a slow *Gauss-Newton* convergence rate. On the other hand, the values are much smaller in the case of the Q-criterion, which leads to a faster convergence rate of the *Gauss-Newton* method. This verifies that the choice of the Q-criterion has an intensely beneficial effect on the *Gauss-Newton* convergence properties. The different convergence rates are illustrated in Figure 7.5. Another significant difference can be seen in the absolute deviations of the estimates from the corresponding true parameter values. In Table 7.1 it is shown that we have deviations from 23% up to 41% in the case of a measurement selection by using the A-criterion. Much better results were determined by using the Q-criterion for the design of experiment problem, where we consider parameter sensitivities up to the second order. Here, the absolute deviation of the estimates from the true parameter values is only between 5% and 23%.

Finally, we can conclude that the use of a Q-criterion-based DoE has very beneficial effects in terms of the subsequent parameter estimation. In comparison to an A-criterion-based DoE, the resulting parameter estimates are much better and the *Gauss-Newton* convergence rate can be reduced by a factor of 8.

7.3 Design of Optimal Experiments for the Verhulst-Pearl Equation

The third example is about the Verhulst-Pearl differential equation, describing the growth rate of a microbiological culture in a restricted habitat, see Kot [69] and Banks et al. [7, 8].

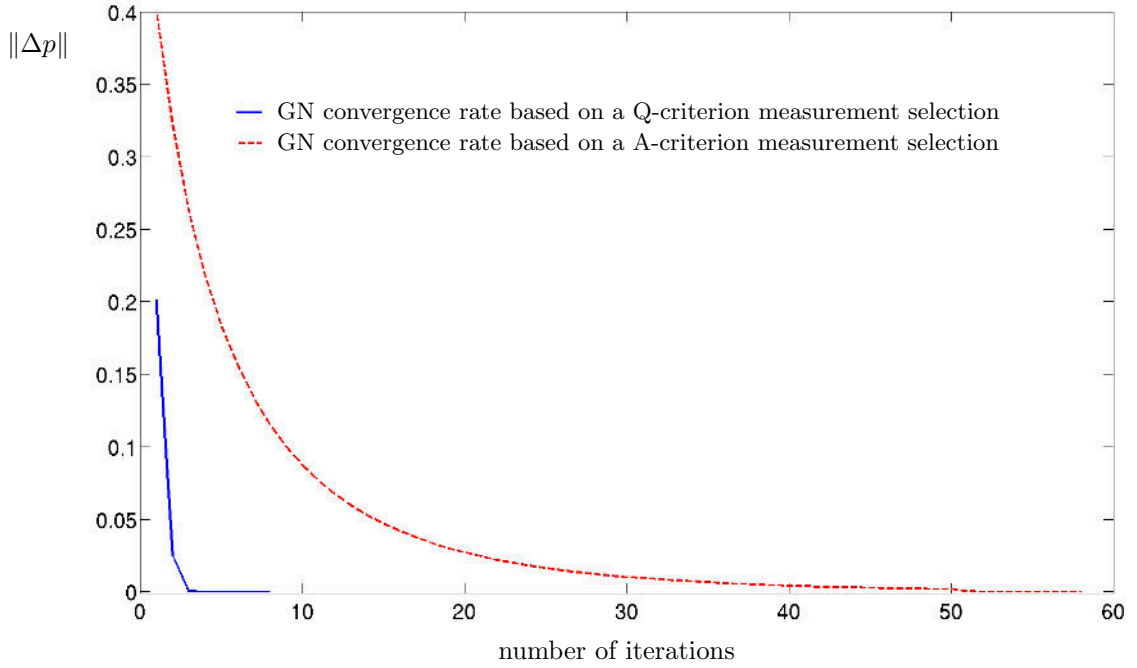


Figure 7.5: *Gauss-Newton* convergence rates based on different DoE objective functions

The dynamics of the system are given by the ordinary differential equation

$$\frac{dy(t)}{dt} = r \cdot y(t) \left(1 - \frac{y(t)}{K}\right).$$

The constant $K > 0$ describes the carrying capacity of the restricted habitat and $r > 0$ is the intrinsic growth rate of the considered microbiological culture. The solution $y(t) : \mathbb{R} \rightarrow [0, K]$ is explicitly given by

$$y(t) = \frac{K}{1 + \left(\frac{K}{y_0} - 1\right) e^{-tr}},$$

where $t \in [t_0, t_e]$ denotes the time and $y_0 = y(t_0)$ is the initial population size at time t_0 . The graph of $y(t)$ describes a sigmoid and has an inflection point at $t_W = \frac{1}{r} \ln\left(\frac{K}{y_0} - 1\right)$, with $y(t_W) = \frac{K}{2}$.

First of all, we want to consider different confidence regions to investigate the parameter sensitivities. Therefore, we assume that the unknown parameters are $p = (p_1, p_2, p_3)^T = (K, r, y_0)^T$. In order to estimate the parameters, we used synthetic measurements with perturbations of the order of 15% and the real parameter values $\bar{p} = (17.5, 0.7, 0.1)$. In Figure 7.6 the nonlinear (solid line), the linearized (dashed line) and the quadratically approximated (gray area) confidence regions for the parameters p_2 and p_3 are given.

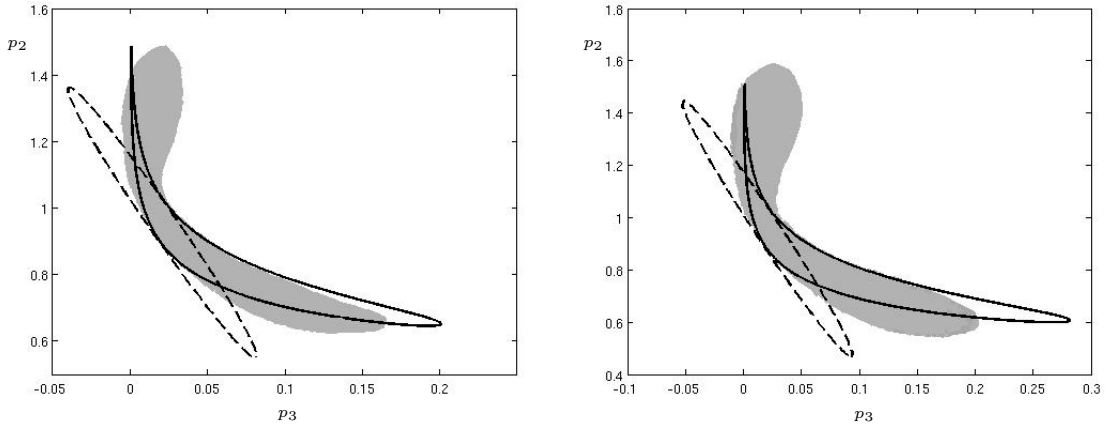


Figure 7.6: Verhulst-Pearl: Confidence regions for $\gamma_3^2(\alpha) = 7.81$ (left) and $\gamma^2(\alpha) = 11.34$ (right).

Thereby, two different probability levels are shown by means of different values of the $(1 - \alpha)$ -quantile of the χ^2 -distribution. The value $\gamma^2(\alpha) = 7.81$ corresponds to 95% confidence regions and $\gamma^2(\alpha) = 11.34$ corresponds to 99% confidence regions. The shape of the confidence regions suggests that a linear sensitivity analysis is unsatisfactory for the assessment of the statistical accuracy of the estimates.

	$[r_{min}, r_{max}]$	$[(y_0)_{min}, (y_0)_{max}]$
linearized conf. intervals	$[0.4588, 1.4548]$	$[-0.0529, 0.0943]$
quadratically approximated conf. intervals	$[0.5452, 1.5914]$	$[-0.0089, 0.1979]$
nonlinear conf. intervals	$[0.6106, 1.4865]$	$[0.0007, 0.2618]$

Table 7.2: Exact confidence intervals of $p_2 = r$ and $p_3 = x_0$.

This presumption is corroborated by Table 7.2 including the corresponding confidence intervals. It is obvious that even the statistical assessment of the third parameter—the initial population size y_0 —is inaccurate by using the linearized confidence techniques. In particular it holds that the linearized confidence interval of the third parameter does not cover the true parameter value $\bar{p}_3 = 0.1$. Here, the quadratically approximated confidence region seems to be superior.

To investigate the DoE and *Gauss-Newton* convergence properties of the Verhulst-Pearl equation, we consider the following scenario:

Let us assume that we can control the size of the initial population y_0 and the unknown parameters which have to be estimated are $p := (p_1, p_2)^T := (K, r)^T$. The main goal is to investigate the *Gauss-Newton* convergence properties when identifying a number of measurements and the initial population size by using the design of optimal experiments with uncertain initial values of the parameters. Thereby, our special focus lies on the robustness of the A-criterion and the Q-criterion with respect to uncertain input data of

the DoE problem.

Let us attend to the task of using DoE to identify seven (suitable) measurement times out of $t_i = i \cdot 0.5$, where $i = 0, \dots, 100$, and the best choice of the initial value y_0 to estimate the wanted parameters p_1 and p_2 . Therefore, the design variables are given by the sampling variables and the initial population size

$$\xi^T = (w^T, y_0),$$

and the corresponding DoE problem constraints are

$$\begin{aligned} w_i &\in \{0, 1\}, \quad i = 1, \dots, 101, \\ \sum_{i=1}^{101} w_i &= 7, \\ 10^{-4} &\leq y_0 \leq 1. \end{aligned}$$

Due to prior knowledge, we assume that the unknown parameters lie within the intervals

$$\begin{aligned} K = p_1 &\in [15, 20], \\ r = p_2 &\in [0.5, 1]. \end{aligned}$$

The *Gauss-Newton* convergence properties are illustrated in Figure 7.7, in dependence on the parameter initial values of the DoE and the parameter estimation problem, respectively. The upper diagram shows the convergence results when the measurement selection and the initial population size are determined by an A-criterion-based DoE problem, and the lower diagram is related to a Q-criterion-based DoE problem. On the vertical axes of the diagrams the discretization of parameter $p_1 = K$ from 15 to 20 in steps of 0.5 is shown and on the horizontal axes the discretization of parameter $p_2 = r$ from 0.5 to 1 in steps of 0.05 is portrayed. Each point of the parameter grid is used as an initial value to perform a DoE problem with one of the above mentioned objective functions to obtain seven suitable measurements and an initial population size y_0 . Subsequently, the same initial values and the identified design variables are used to estimate the wanted parameters by using the *Gauss-Newton* method. In case of a determination of the system settings by means of the A-criterion, the *Gauss-Newton* method shows unsatisfactory convergence properties. In Figure 7.7, the black squares represent a lack of convergence of the *Gauss-Newton* method, which is the case for approximately half of the squares where the A-criterion is used. In the center of the A-criterion diagram—where the initial parameters are close to their true values—we have more or less satisfactory results. However, in two further cases it takes up to 70 iterations until it converges. In contrast, we get very satisfactory results when using a Q-criterion-based DoE approach to identify the system settings. In almost any case it takes only about 10 iterations until it converges, and only in seven cases the *Gauss-Newton* method failed.

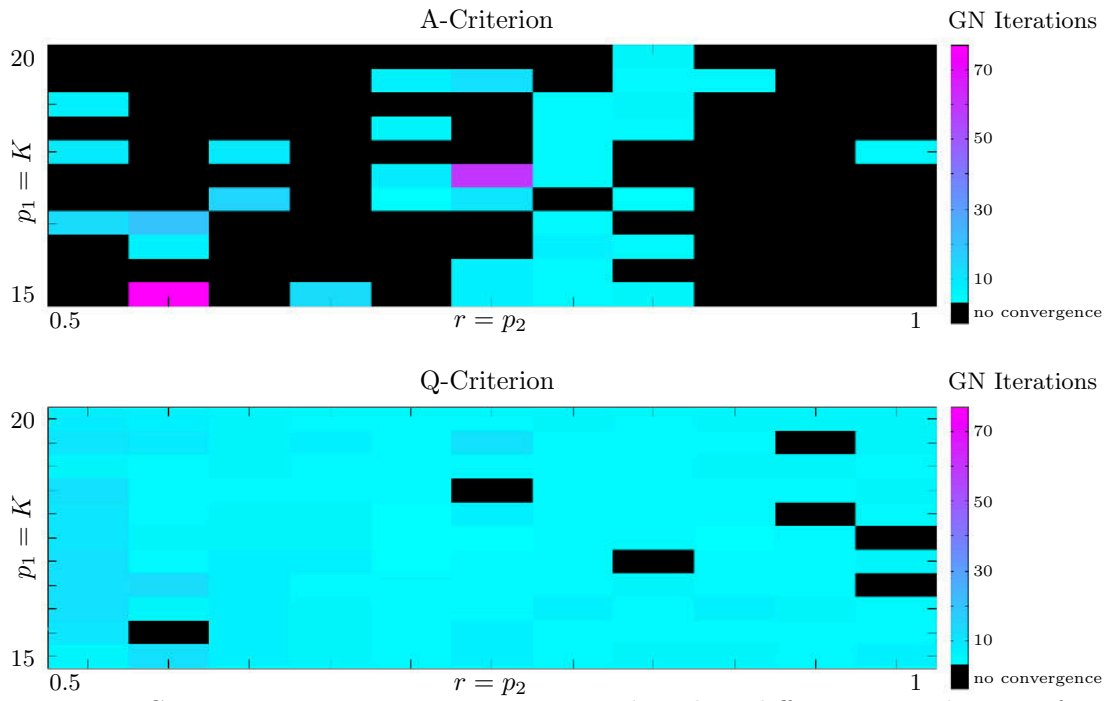


Figure 7.7: *Gauss-Newton* convergence properties based on different DoE objective functions depending on uncertain initial parameter values

This shows again the impressive advantages of a Q-criterion-based DoE approach in comparison to commonly used methods. Furthermore, the introduced approach seems to be very robust against uncertainties in the initial parameter values.

8 Conclusion

This thesis led to two main contributions: first we have developed and analyzed a quadratic approximation of confidence regions to quantify the statistical accuracy of a parameter estimate in the case of highly nonlinear model functions. Then we have contributed a new objective function to robustify the design of optimal experiments procedure. When using the introduced objective function, we not only considered parameter sensitivities up to the second order, but we also improve the *Gauss-Newton* convergence rate at the following parameter estimation.

Below, the major contents and contributions of the chapters are summarized.

After a general introduction in Chapter 1, we started this thesis with a consideration of multiple experiment parameter estimation problems for ordinary differential equations in Chapter 2. After having discussed the numerical treatment of the dynamics, we proposed a generalized *Gauss-Newton* method in order to solve the resulting finite dimensional nonlinear equality constrained optimization problem. Furthermore, we discussed the convergence properties of the *Gauss-Newton* method and we thoroughly amplified the meaning of the Lipschitz constant κ .

In this thesis, one of the major tasks was the development of a higher order sensitivity analysis to overcome the difficulties of the statistical assessment of a parameter estimate in the case of highly nonlinear model functions. Next to discussing common approaches, we constructed a quadratic approximation of the confidence region in Chapter 3. Thereby, the new region has been based on a second order representation of the parameter vector in dependence on the measurement errors. We analyzed the new confidence region and we established exact bounds for the quadratic components, which can be basically determined by solving a symmetric eigenvalue problem. In this context, a main result has been that the quadratically approximated confidence region is bounded by an expression consisting of the trace of the linear approximation of the covariance matrix as well as of the Lipschitz constants κ and ω . These constants have already been known from the local convergence theory of the generalized *Gauss-Newton* method. Considering the interpretations of ω and κ , the newly introduced confidence region is bounded by the nonlinearity of the model functions and the compatibility between the model and the used measurements, respectively. Furthermore, we computed a quadratic approximation of the covariance matrix. This has delivered another higher order method to quantify the statistical accuracy of a parameter estimate considering that the diagonal elements of the covariance matrix are the parameter variances. At the end of this chapter, we considered some illustrating examples visualizing the approximation accuracy of the newly introduced methods.

In Chapter 4, we considered the model-based design of optimal experiments, where we attended to the task of developing a new criterion to robustify the procedure. After a general introduction to the problem formulation, we defined a new objective function—the Q-criterion—for the design of optimal experiments problems, which is based on the results of the quadratic sensitivity analysis. Thereby, we paid special attention to the numerical computation of the Lipschitz constant κ . We suggested an approximation of κ which is basically obtained by the traces of symmetric matrices. Furthermore, we investigated the robustness properties of the design of optimal experiments when using the Q-criterion. It has been shown that there is a strong similarity between the Q-criterion-based and a *worst-case* approach of the design of optimal experiments, where parameter uncertainties have to be taken into account. Moreover, we have shown that the parameter estimation problem settings identified by a Q-criterion-based design of optimal experiments have very beneficial effects on the *Gauss-Newton* convergence rate. This was done by considering the relation of the Q-criterion to a chance constrained formulation of the design of optimal experiments problem.

We discussed a numerical treatment of multiple experiments parameter estimation problems in Chapter 5. Thereby, we paid special attention to the numerical and parallel computation of the *Gauss-Newton* increments and the linear approximation of the covariance matrix. Furthermore, a parallel approach to the computation of the A-criterion for the design of optimal experiments has been treated.

In Chapter 6, we discussed the derivatives which are needed for the parameter estimation and the design of optimal experiments procedure. Next to the first and the second order derivatives of the functions of the parameter estimation problem, we focused on the derivative of the introduced Q-criterion with respect to the design variables. In this context, we have shown that it basically requires the derivatives of traces for the entire computation of the derivative of the Q-criterion. Moreover, we computed the derivative of the generalized inverse of the Jacobians of the functions of the parameter estimation problem for the constrained and the unconstrained case.

In Chapter 7, we tested the properties of the newly introduced Q-criterion on several examples. Here, we especially focused on the robustness of the resulting settings of the parameter estimation problem as well as on its effects on the *Gauss-Newton* convergence properties. It has become clear that the parameter estimates resulting from the systems settings identified by a Q-criterion-based design of optimal experiments were distinctly more reliable and stable against uncertainties in the parameter initial values than when the systems settings were identified by an A-criterion-based design of optimal experiments. Furthermore, we observed that we had a much better convergence rate of the *Gauss-Newton* method when the Q-criterion was used instead of the A-criterion. This became particularly clear in the third example. Here the *Gauss-Newton* method failed in most of the cases where the A-criterion was used, however, we still had good results for the Q-criterion-based design of experiments. Thus, the good properties of the newly introduced objective function became evident.

An important direction for future work is an integration of the newly developed Q-criterion into approved design of optimal experiments software like e.g. VPLAN by Körkel [62]. Next to the computation of the needed derivatives up to the third order, it is desirable to have an adequate threshold whether the linearization techniques are sufficient or if it is advisable to use the quadratic approach. Thereby, a suitable threshold would be basically determined by the Lipschitz constants κ and ω evaluated at the current parameter guess.

List of Figures

1.1	Modeling, simulation and optimization, Körkel [62].	1
1.2	Parameter estimation and sensitivity analysis.	2
2.1	Illustration of the <i>Multiple Shooting</i> method	16
2.2	Illustration of the reflected measurements $\tilde{\eta}$, Bock et al. [22].	29
3.1	Confidence regions of example 3.5.1 with probability level $1 - \alpha = 0.95$	55
3.2	Confidence regions of example 3.5.1 with probability level $1 - \alpha = 0.995$	56
3.3	Confidence regions of example 3.5.2 with probability level $1 - \alpha = 0.95$	57
3.4	Confidence regions of example 3.5.2 with probability level $1 - \alpha = 0.995$	58
4.1	Illustration of the commonly used DoE objective functions, Körkel [62].	65
4.2	Sequential DoE and parameter estimation.	81
5.1	Strategy of a parallel increment computation.	96
5.2	Procedure of parallel computing of the covariance matrix.	103
7.1	Strategy for investigating the properties of the Q-criterion.	134
7.2	Example 1: Deviations of the estimates to the true values.	136
7.3	Example 2: Normalized values of κ -estimates $\tilde{\kappa}$	137
7.4	Example 3: Values of ω -estimates.	137
7.5	Monod model: <i>Gauss-Newton</i> convergence rates	140
7.6	Verhulst-Pearl: Confidence regions for $\gamma_3^2(\alpha) = 11.34$	141
7.7	Verhulst-Pearl: <i>Gauss-Newton</i> convergence properties	143

List of Tables

3.1	Confidence intervals of example 3.5.1 for $1 - \alpha = 0.95$ and $1 - \alpha = 0.995$.	56
3.2	Confidence intervals of example 3.5.2 for $1 - \alpha = 0.95$ and $1 - \alpha = 0.995$.	57
7.1	Monod model: Parameter estimation properties.	139
7.2	Exact confidence intervals of $p_2 = r$ and $p_3 = x_0$	141

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