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OPTIMAL MODEL-BASED DESIGN OF EXPERIMENTS IN DYNAMIC SYSTEMS: NOVEL TECHNIQUES AND UNCONVENTIONAL APPLICATIONS

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To my parents, Elio and Tiziana
To Caterina

Little by little the night turns around
Counting the leaves which tremble at dawn
Lotuses lean on each other in yearning
Over the hills a swallow is resting
Set the controls for the heart of the sun

Over the mountain
Watching the watcher
Breaking the darkness
Waking the grapevine
Knowledge of love is knowledge of shadow
Love is the shadow that ripens the wine
Set the controls for the heart of the sun
The heart of the sun
The heart of the sun

Witness the man who waves at the wall
Making the shape of his questions to Heaven
Whether the sun will fall in the evening
Will he remember the lesson of giving?
Set the controls for the heart of the sun
The heart of the sun
The heart of the sun

(from the album "A saucerful of secrets" by Pink Floyd)

Foreword

The realization of this work has involved the intellectual and financial support of many people and institutions, to whom the author is most grateful. Most of the research activity that led to the results summarized in this Thesis has been carried out at DIPIC, the Department of Chemical Engineering Principles and Practice of the University of Padova, under the supervision of Dr. Fabrizio Bezzo and Prof. Massimiliano Barolo. Part of the work has been conducted under the supervision of Prof. Sandro Macchietto, at the Department of Chemical Engineering of the Imperial College of London (London, U.K.), through the financial Grant fund EPSRC - DT/E005691/1. The realization of this study has been made possible also through the financial support of the University of Padova under Progetto di Ateneo 2007 (cod. CPDA074133): "A process systems engineering approach to the development of an artificial pancreas for subjects with type-1 diabetes mellitus".

All the material reported in this Thesis is original, unless explicit references to the authors are provided. Part of the material presented in this Thesis have been published as reported in the following.

PUBLICATIONS IN INTERNATIONAL JOURNALS

Galvanin, F., M. Barolo, S. Macchietto and F. Bezzo (2009)
Optimal design of clinical tests for the identification of physiological models of type 1 diabetes mellitus.
Ind. Eng. Chem. Res., **48**, 1989-2002.

Galvanin, F., M. Barolo and F. Bezzo (2009)
Online model-based re-design of experiments for parameter estimation in dynamic systems.
Ind. Eng. Chem. Res., **48**, 4415-4427.

Galvanin, F., M. Barolo, F. Bezzo and S. Macchietto (2009)
A backoff strategy for model-based experiment design under parametric uncertainty.
AIChE J., in press. doi:10.1002/aic.12138

PUBLICATIONS IN BOOK CHAPTERS

Galvanin, F., M. Barolo, S. Macchietto and F. Bezzo (2010)
A process systems engineering approach to the development of an artificial pancreas for subjects with type-1 diabetes mellitus.
In: Process Systems Engineering series Volume 7: Dynamic Process Modelling, Pistikopoulos et al. (Eds.), Wiley-VCH Verlag, Weinheim, in press.

PUBLICATIONS IN CONFERENCE PROCEEDINGS

Galvanin, F., M. Barolo and F. Bezzo (2008)
Towards on-line model-based design of experiments.
In: *European Symposium on Computer Aided Process Engineering – 18* (B. Braunschweig and X. Joulia, Eds.), Elsevier, Amsterdam (The Netherlands), 349-354.

Galvanin, F., M. Barolo, F. Bezzo and S. Macchietto (2009)
A backoff-based strategy to improve robustness in model-based experimental design under parametric uncertainty.
In: *Design for Energy and the Environment* , (M.M. El-Halwagi, A.A. Linninger, Eds.), CRC Press, Boca Raton FL (U.S.A.), 623-630.

Galvanin, F., M. Barolo, S. Macchietto and F. Bezzo (2009)
On the optimal design of clinical tests for the identification of physiological models of type 1 diabetes mellitus. In: *Computer-Aided Chemical Engineering 27, 10th International Symp. on Process Systems Engineering*, (R.M. Brito Alves, C.A. Oller do Nascimento, E.C. Biscaia Jr., Eds.), Elsevier, Amsterdam (The Netherlands), 183-188.

Galvanin, F., M. Barolo, S. Macchietto and F. Bezzo (2008)
Progettazione ottimale di test clinici per l'identificazione di modelli fisiologici del diabete mellito di tipo 1. Presented at *Convegno GRICU 2008* (Le Castella, KR, Italy), 14-17 September, 1377-1381.

SUBMITTED PAPERS

Galvanin, F., M. Barolo, F. Bezzo and S. Macchietto (2010)
Optimal design of clinical tests for the identification of physiological models of type 1 diabetes mellitus in the presence of model mismatch. Submitted to: *Chemical Engineering Science*.

Galvanin, F., M. Barolo, F. Bezzo (2010)
A framework for model based design of experiments in the presence of continuous measurement systems. Submitted to: 2010 IFAC International Symposium on Dynamics and Control of Process Systems (DYCOPS 2010).

The paper "Online model-based redesign of experiments for parameter estimation in dynamic systems" has been awarded as runner-up in the Process Systems Enterprise Ltd. Model-Based Innovation Prize.

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Abstract

Model-based design of experiments (MBDoE) techniques are a very useful tool for the rapid assessment and development of dynamic deterministic models, providing a significant support to the model identification task on a broad range of process engineering applications. These techniques allow to maximise the information content of an experimental trial by acting on the settings of an experiment in terms of initial conditions, profiles of the manipulated inputs and number and time location of the output measurements.

Despite their popularity, standard MBDoE techniques are still affected by some limitations. In fact, when a set of constraints is imposed on the system inputs or outputs, factors like uncertainty on prior parameter estimation and structural system/model mismatch may lead the design procedure to plan experiments that turn out, in practice, to be suboptimal (i.e. scarcely informative) and/or unfeasible (i.e. violating the constraints imposed on the system). Additionally, standard MBDoE techniques have been originally developed considering a discrete acquisition of the information. Therefore, they do not consider the possibility that the information on the system itself could be acquired very frequently if there was the possibility to record the system responses in a continuous manner.

In this Dissertation three novel MBDoE methodologies are proposed to address the above issues. First, a strategy for the online model-based redesign of experiments is developed, where the manipulated inputs are updated while an experiment is still running. Thanks to intermediate parameter estimations, the information is exploited as soon as it is generated from an experiment, with great benefit in terms of precision and accuracy of the final parameter estimate and of experimental time.

Secondly, a general methodology is proposed to formulate and solve the experiment design problem by explicitly taking into account the presence of parametric uncertainty, so as to ensure by design both feasibility and optimality of an experiment. A prediction of the system responses for the given parameter distribution is used to evaluate and update suitable backoffs from the nominal constraints, which are used in the design session in order to keep the system within a feasible region with specified probability.

Finally, a design criterion particularly suitable for systems where continuous measurements are available is proposed in order to optimise the information dynamics of the experiments since the very beginning of the trial. This approach allows tailoring the design procedure to the specificity of the measurement system.

A further contribution of this Dissertation is aimed at assessing the general applicability of both standard and advanced MBDoE techniques to the biomedical area, where unconventional

experiment design applications are faced. In particular, two identification problems are considered: one related to the optimal drug administration in cancer chemotherapy, and one related to glucose homeostasis models for subjects affected by type 1 diabetes mellitus (T1DM). Particular attention is drawn to the optimal design of clinical tests for the parametric identification of detailed physiological models of T1DM. In this latter case, advanced MBDoE techniques are used to ensure a safe and optimally informative clinical test for model identification. The practicability and effectiveness of a complex approach taking simultaneously into account the redesign-based and the backoff-based MBDoE strategies are also shown. The proposed experiment design procedure provides alternative test protocols that are sufficiently short and easy to carry out, and allow for a precise, accurate and safe estimation of the model parameters defining the metabolic portrait of a diabetic subject.

Riassunto

Le moderne tecniche di progettazione ottimale degli esperimenti basata su modello (MBDoE, *model-based design of experiments*) si sono dimostrate utili ed efficaci per sviluppare e affinare modelli matematici dinamici di tipo deterministico. Queste tecniche consentono di massimizzare il contenuto informativo di un esperimento di identificazione, determinando le condizioni sperimentali più opportune da adottare nella sperimentazione allo scopo di stimare i parametri di un modello nel modo più rapido ed efficiente possibile. Le tecniche MBDoE sono state applicate con successo in svariate applicazioni industriali. Tuttavia, nella loro formulazione standard, esse soffrono di alcune limitazioni. Infatti, quando sussistono vincoli sugli ingressi manipolabili dallo sperimentatore oppure sulle risposte del sistema, l'incertezza nell'informazione preliminare che lo sperimentatore possiede sul sistema fisico (in termini di struttura del modello e precisione nella stima dei parametri) può profondamente influenzare l'efficacia della procedura di progettazione dell'esperimento. Come conseguenza, è possibile che venga progettato un esperimento poco informativo e dunque inadeguato per stimare i parametri del modello in maniera statisticamente precisa ed accurata, o addirittura un esperimento che porta a violare i vincoli imposti sul sistema in esame. Inoltre, le tecniche MBDoE standard non considerano nella formulazione stessa del problema di progettazione la specificità e le caratteristiche del sistema di misura in termini di frequenza, precisione e accuratezza con cui le misure sono disponibili.

Nella ricerca descritta in questa Dissertazione sono sviluppate metodologie avanzate di progettazione degli esperimenti con lo scopo di superare tali limitazioni. In particolare, sono proposte tre nuove tecniche per la progettazione ottimale di esperimenti dinamici basata su modello:

1. una tecnica di progettazione in linea degli esperimenti (OMBRE, *online model-based redesign of experiments*), che consente di riprogettare un esperimento mentre questo è ancora in esecuzione;
2. una tecnica basata sul concetto di "backoff" (arretramento) dai vincoli, per gestire l'incertezza parametrica e strutturale del modello;
3. una tecnica di progettazione che consente di ottimizzare l'informazione dinamica di un esperimento (DMBDoE, *dynamic model-based design of experiments*) allo scopo di considerare la specificità del sistema di misura disponibile.

La procedura standard MBDoE per la progettazione di un esperimento è sequenziale e si articola in tre stadi successivi. Nel primo stadio l'esperimento viene progettato considerando

l’informazione preliminare disponibile in termini di struttura del modello e stima preliminare dei parametri. Il risultato della progettazione è una serie di profili ottimali delle variabili manipolabili (ingressi) e l’allocazione ottimale dei tempi di campionamento delle misure (uscite). Nel secondo stadio l’esperimento viene effettivamente condotto, impiegando le condizioni sperimentali progettate e raccogliendo le misure come da progetto. Nel terzo stadio, le misure vengono utilizzate per stimare i parametri del modello. Seguendo questa procedura, l’informazione ottenuta dall’esperimento viene sfruttata solo a conclusione dell’esperimento stesso. La tecnica OMBRE proposta consente invece di riprogettare l’esperimento, e quindi di aggiornare i profili manipolabili nel tempo, mentre l’esperimento è ancora in esecuzione, attuando stime intermedie dei parametri. In questo modo l’informazione viene sfruttata progressivamente mano a mano che l’esperimento procede. I vantaggi di questa tecnica sono molteplici. Prima di tutto, la procedura di progettazione diventa meno sensibile, rispetto alla procedura standard, alla qualità della stima preliminare dei parametri. In secondo luogo, essa consente una stima dei parametri statisticamente più soddisfacente, grazie alla possibilità di sfruttare in modo progressivo l’informazione generata dall’esperimento. Inoltre, la tecnica OMBRE consente di ridurre le dimensioni del problema di ottimizzazione, con grande beneficio in termini di robustezza computazionale.

In alcune applicazioni, risulta di importanza critica garantire la fattibilità dell’esperimento, ossia l’osservanza dei vincoli imposti sul sistema. Nella Dissertazione è proposta e illustrata una nuova procedura di progettazione degli esperimenti basata sul concetto di “backoff” (arretramento) dai vincoli, nella quale l’effetto dell’incertezza sulla stima dei parametri e/o l’inadeguatezza strutturale del modello vengono inclusi nella formulazione delle equazioni di vincolo grazie ad una simulazione stocastica. Questo approccio porta a ridurre lo spazio utile per la progettazione dell’esperimento in modo tale da assicurare che le condizioni di progettazione siano in grado di garantire non solo l’identificazione dei parametri del modello, ma anche la fattibilità dell’esperimento in presenza di incertezza strutturale e/o parametrica del modello.

Nelle tecniche standard di progettazione la formulazione del problema di ottimo prevede che le misure vengano acquisite in maniera discreta, considerando una certa distanza temporale tra misure successive. Di conseguenza, l’informazione attesa dall’esperimento viene calcolata e massimizzata durante la progettazione mediante una misura discreta dell’informazione di Fisher. Tuttavia, nella pratica, sistemi di misura di tipo continuo permetterebbero di seguire la dinamica del processo mediante misurazioni molto frequenti. Per questo motivo viene proposto un nuovo criterio di progettazione (DMBDoE), nel quale l’informazione attesa dall’esperimento viene ottimizzata in maniera continua. Il nuovo approccio consente di generalizzare l’approccio della progettazione includendo le caratteristiche del sistema di

misura (in termini di frequenza di campionamento, accuratezza e precisione delle misure) nella formulazione stessa del problema di ottimo.

Un ulteriore contributo della ricerca presentata in questa Dissertazione è l'estensione al settore biomedico di tecniche MBDoE standard ed avanzate. I sistemi fisiologici sono caratterizzati da elevata complessità, e spesso da scarsa controllabilità e scarsa osservabilità. Questi elementi rendono particolarmente lunghe e complesse le procedure di identificazione parametrica di modelli fisiologici dettagliati. L'attività di ricerca ha considerato due problemi principali inerenti l'identificazione parametrica di modelli fisiologici: il primo legato a un modello per la somministrazione ottimale di agenti chemioterapici per la cura del cancro, il secondo relativo ai modelli complessi dell'omeostasi glucidica per soggetti affetti da diabete mellito di tipo 1. In quest'ultimo caso, al quale è rivolta attenzione particolare, l'obiettivo principale è identificare il set di parametri individuali del soggetto diabetico. Ciò consente di tracciarne un ritratto metabolico, fornendo così un prezioso supporto qualora si intenda utilizzare il modello per sviluppare e verificare algoritmi avanzati per il controllo del diabete di tipo 1. Nella letteratura e nella pratica medica esistono test clinici standard, quali il test orale di tolleranza al glucosio e il test post-prandiale da carico di glucosio, per la diagnostica del diabete e l'identificazione di modelli dell'omeostasi glucidica. Tali test sono sufficientemente brevi e sicuri per il soggetto diabetico, ma si possono rivelare poco informativi quando l'obiettivo è quello di identificare i parametri di modelli complessi del diabete. L'eccitazione fornita durante questi test al sistema-soggetto, in termini di infusione di insulina e somministrazione di glucosio, può infatti essere insufficiente per stimare in maniera statisticamente soddisfacente i parametri del modello.
In questa Dissertazione è proposto l'impiego di tecniche MBDoE standard e avanzate per progettare test clinici che permettano di identificare nel modo più rapido ed efficiente possibile il set di parametri che caratterizzano un soggetto affetto da diabete, rispettando durante il test i vincoli imposti sul livello glicemico del soggetto. Partendo dai test standard per l'identificazione di modelli fisiologici del diabete, è così possibile determinare dei protocolli clinici modificati in grado di garantire test clinici altamente informativi, sicuri, poco invasivi e sufficientemente brevi. In particolare, si mostra come un test orale opportunamente modificato risulta altamente informativo per l'identificazione, sicuro per il paziente e di facile implementazione per il clinico. Inoltre, viene evidenziato come l'integrazione di tecniche avanzate di progettazione (quali OMBRE e tecniche basate sul concetto di backoff) è in grado di garantire elevata significatività e sicurezza dei test clinici anche in presenza di incertezza strutturale, oltre che parametrica, del modello. Infine, si mostra come, qualora siano disponibili misure molto frequenti della glicemia, ottimizzare mediante tecniche DMBDoE l'informazione dinamica progressivamente acquisita dal sistema

di misura durante il test consente di sviluppare protocolli clinici altamente informativi, ma di durata inferiore, minimizzando così lo stress sul soggetto diabetico.

La struttura della Dissertazione è la seguente. Il primo Capitolo illustra lo stato dell'arte delle attuali tecniche di progettazione ottimale degli esperimenti, analizzandone le limitazioni e identificando gli obiettivi della ricerca.
Il secondo Capitolo contiene la trattazione matematica necessaria per comprendere la procedure standard di progettazione degli esperimenti.
Il terzo Capitolo presenta la nuova tecnica OMBRE per la riprogettazione in linea di esperimenti dinamici. La tecnica viene applicata a due casi di studio, riguardanti un processo di fermentazione di biomassa in un reattore semicontinuo e un processo per la produzione di uretano.
Il quarto Capitolo propone e illustra il metodo basato sul concetto di "backoff" per gestire l'effetto dell'incertezza parametrica e strutturale nella formulazione stessa del problema di progettazione. L'efficacia del metodo è verificata su due casi di studio in ambito biomedico. Il primo riguarda l'ottimizzazione dell'infusione di insulina per l'identificazione di un modello dettagliato del diabete mellito di tipo 1; il secondo la somministrazione ottimale di agenti chemioterapici per la cura del cancro.
Il quinto Capitolo riguarda interamente il problema della progettazione ottimale di test clinici per l'identificazione di un modello fisiologico complesso del diabete mellito di tipo 1. La progettazione di protocolli clinici modificati avviene adottando tecniche MBDoE in presenza di elevata incertezza parametrica tra modello e soggetto diabetico.
Il sesto Capitolo affronta il problema della progettazione dei test clinici assumendo sia incertezza di modello parametrica che strutturale.
Il settimo Capitolo propone un nuovo criterio di progettazione (DMBDoE) che ottimizza l'informazione dinamica acquisibile da un esperimento. La tecnica viene applicata a un modello complesso del diabete mellito di tipo 1 e ad un processo per la fermentazione di biomassa in un reattore semicontinuo.
Conclusioni e possibili sviluppi futuri vengono descritti nella sezione conclusiva della Dissertazione.

Table of Contents

List of symbols

General symbols

A	=	Glucose amount of the meal for the Lynch-Bequette model of glucose homeostasis
c	=	Molar concentration
C_g	=	Glucose concentration in the blood
$C_{g,b}$	=	Basal glucose concentration in the blood
C_i	=	*i*-th generic constraint
c_{ij}	=	*ij*-th element of the correlation matrix for model parameters ($\mathbf{C}_\theta$)
D	=	Meal disturbance function
D_g	=	Amount of carbohydrates of a meal for HM and HWM
E	=	Expected value operator
E_a	=	Activation energy
EGP	=	Endogenous glucose production
EGP_0	=	Endogenous glucose production extrapolated to zero insulin concentration
f	=	Differential and algebraic system implicit function
f^{v1}	=	Feed molar number for the first vessel
f^{v2}	=	Feed molar number for the second vessel
f_{θ_i}	=	Reparameterising function for the *i*-th model parameter
F_{01}	=	Non-insulin dependent flux
G	=	Blood glucose concentration response of the subject
$\hat{G}$	=	Blood glucose concentration response predicted by the model
g	=	Measurements selection function
GTF	=	Global t-factor
h	=	Reaction enthalphy of reversible reaction
H	=	Threshold-based function for drug effectiveness
I	=	Insulin concentration in the accessible compartment
$\overline{I}$	=	Generic measure function of information
I_b	=	Insulin basal value
I_α	=	Global Precision Index

I_π	=	Global Accuracy Index
J	=	Objective function of the dynamic optimisation
k	=	Reaction constant
K	=	Constant prior contribution to information measurement for A-optimal MBDoE
k_{c2}	=	Steric factor for reversible reaction
k_i	=	*i*-th bolus release relaxing factor
k_{ref}	=	Steric factor
M_i	=	Molar mass of the *i*-th species
n	=	Disappearance rate of insulin
n_i	=	Molar number of the *i*-th species
n_i^0	=	Initial molar number of the *i*-th species
n_i^{v1}	=	Molar number of the *i*-th species in the first vessel
n_i^{v2}	=	Molar number of the *i*-th species in the second vessel
n_{sp}	=	Number of sampling points
n_{sw}	=	Number of switching levels
n_{up}	=	Number of updates
n_φ	=	Number of design variables
n_{φ_i}	=	Number of design variables in the *i*-th update
n_{ξ_θ}	=	Number of parameters needed to define probability density function p_θ
n_{ξ_x}	=	Number of parameters needed to define probability density function p_x
N	=	Number of experiments
N_i	=	Normal probability density function for the *i*-th parameter
N_y	=	Number of measured variables
N_{meals}	=	Number of meals
N_u	=	Number of manipulated inputs
N_w	=	Number of time invariant controls
N_x	=	Number of state variables
N_θ	=	Number of model parameters
$N_{\theta^{CM}}$	=	Number of parameters for Cobelli model
$N_{\theta^{HM}}$		Number of parameters for Hovorka model
N_λ	=	Number of eigenvalues of $\mathbf{V}_\theta$

N'	=	Number of samples representing probability p_θ
p	=	Generic probability density function
p_0	=	Generic prior probability density function
p_θ	=	Probability density function of model parameters
p_x	=	Probability density function of model responses
p_Θ	=	Probability density function of normalised model parameters
$p_{\theta\|\boldsymbol{\varphi}}$	=	Probability density function of model parameters conditioned by $\boldsymbol{\varphi}$
$p_{x\|\boldsymbol{\varphi}}$	=	Probability density function of model responses conditioned by $\boldsymbol{\varphi}$
q	=	Element of the dynamic sensitivity matrix ($\mathbf{Q}$)
q_i	=	i-th element of the dynamic sensitivity matrix ($\mathbf{Q}$)
r	=	Reaction rate
R	=	Gas constant
R_a	=	Rate of glucose appearance in plasma
R_i	=	Rate of insulin appearance in plasma
R_{θ_i}	=	Probability density function of a uniform distribution for the i-th model parameter
s_{ij}	=	ij-th element of the inverse matrix of $\boldsymbol{\Sigma}$
S_{IT}^f	=	Insulin sensitivity of distribution/transport
S_{ID}^f	=	Insulin sensitivity of disposal
S_{IE}^f	=	Insulin sensitivity of EGP
SWR	=	Sum of weighted residuals
$SSWR$	=	Sum of squared weighted residuals
t	=	Time
t'	=	t-value for Bartlett's formula (4.8)
t_f	=	Maximum experimental time
T_{g2}	=	Reference temperature for reversible reaction
t_i	=	t-value of the i-th parameter
T_{ref}	=	Reference temperature
t^{sw}	=	Switching time
t_{tot}	=	Total elapsed time
t^{up}	=	Updating time
u	=	Insulin infusion rate

u_b = Time-invariant basal insulin infusion rate

u_{bol} = Insulin bolus amount

u_d = Drug administration rate

u_s = Time-dependent insulin infusion rate

V = Reactor volume

$\bar{V}$ = Generic measure function of uncertainty

V_I = Insulin distribution volume

v_{ij} = *ij*-th element of the variance-covariance matrix $\mathbf{V}_\theta$

x = Generic state variable

X = Insulin concentration in the non accessible compartment

x^0 = Initial conditions for the generic state variable

x^{MAX} = Profile of the maximum values for the generic state variable

x^{MIN} = Profile of the minimum values for the generic state variable

y = Generic measured output

y^{CM} = Measured response from CM

y^{HM} = Measured response from HM

$\hat{y}^{CM}$ = Response predicted by CM

$\hat{y}^{HM}$ = Response predicted by HM

y_{max} = Time-invariant upper bound on the measured response

y_{min} = Time-invariant lower bound on the measured response

z = Feed rate

z_i = Piecewise constant function

Vectors and Matrices [dimension]

$\mathbf{C}$ = Set of constraint functions [N_c]

$\widetilde{\mathbf{C}}$ = Stochastic vector of constraint functions [N_c]

$\mathbf{C}_\theta$ = Correlation matrix [$N_\theta \times N_\theta$]

$\mathbf{C}_\theta^{exp}$ = Expected correlation matrix [$N_\theta \times N_\theta$]

$\mathbf{C}_\theta^{act}$ = Actual correlation matrix [$N_\theta \times N_\theta$]

$\mathbf{G}$ = Set of active constraints [N_c]

$\mathbf{H}_\theta$ = Dynamic Information matrix [$N_\theta \times N_\theta$]

$\mathbf{H}_\theta^0$ = Preliminary information matrix [$N_\theta \times N_\theta$]

$\mathbf{H}_{\theta}^{*}$	=	Dynamic Information matrix [$N_\theta \times N_\theta$] for a single experiment
$\mathbf{H}_{\theta\|k}^{*}$	=	Dynamic Information Matrix of the *k*-th experiment [$N_\theta \times N_\theta$]
$\breve{\mathbf{H}}_{\theta}^{*}$	=	Dynamic Information matrix for a single re-design in a single experiment [$N_\theta \times N_\theta$]
$\breve{\mathbf{H}}_{\theta\|k}^{*}$	=	Dynamic Information Matrix of the *k*-th re-design in a single experiment [$N_\theta \times N_\theta$]
$\mathbf{H}_{\theta}^{act}$	=	Actual dynamic information matrix [$N_\theta \times N_\theta$]
$\mathbf{H}_{\theta}^{exp}$	=	Expected dynamic information matrix [$N_\theta \times N_\theta$]
$\mathbf{I}$	=	Fisher Information Matrix [$N_\theta \times N_\theta$]
$\mathbf{L}$	=	Constant Information Matrix for OMBRE [$N_\theta \times N_\theta$]
$\mathbf{M}_k$	=	Contribution of the *k*-th sample to the overall information $\mathbf{H}_\theta$ [$N_\theta \times N_\theta$]
$\mathbf{K}$	=	Constant Information Matrix for Sequential ED [$N_\theta \times N_\theta$]
$\mathbf{y}^0$	=	Vector of initial conditions [N_y]
$\mathbf{y}$	=	Measurements vector [N_y]
$\hat{\mathbf{y}}$	=	Vector of estimated responses [N_y]
$\mathbf{P}_E$	=	Matrix of parameter estimability [$N_y n_{sp} \times N_\theta$]
$\mathbf{Q}$	=	Sensitivity matrix [$n_{sp} \times N_\theta$]
$\mathbf{Q}'$	=	Time dependent sensitivity matrix [$N_y \times N_\theta$]
$\mathbf{Q}_{i\|k}$	=	Sensitivity matrix of the *i*-th measured response in the *k*-th experiment [$n_{sp} \times N_\theta$]
$\mathbf{Q}_r$	=	Sensitivity matrix of the *r*-th response [$n_{sp} \times N_\theta$]
$\mathbf{r}$	=	Matrix of absolute residuals [$N_y \times n_{sp}$]
$\mathbf{t}^{up}$	=	Vector of updating times [n_{up}]
$\mathbf{t}^{sp}$	=	Vector of sampling points [n_{sp}]
$\mathbf{t}_{sw}$	=	Vector of switching times [n_{sw}+1]
$\mathbf{u}$	=	Vector of manipulated inputs [N_u]
$\mathbf{V}_\theta$	=	Variance-covariance matrix of model parameters [$N_\theta \times N_\theta$]
$\mathbf{V}_\theta^{exp}$	=	Expected variance-covariance matrix of model parameters [$N_\theta \times N_\theta$]
$\mathbf{V}_\theta^{act}$	=	Actual variance-covariance matrix of model parameters [$N_\theta \times N_\theta$]
$\mathbf{w}$	=	Vector of time-invariant control variables [N_w]
$\mathbf{W}$	=	Matrix of weighting factors for (2.37) [$N_\theta \times N_\theta$]
$\mathbf{W}'$	=	Matrix of weighting factors for (2.38) [$N_\theta \times N_\theta$]
$\mathbf{x}$	=	Vector of state variables [$N_x \times N_x$]

$\dot{\mathbf{x}}$	=	Vector of derivatives on state variables [N_x]
$\bar{\mathbf{x}}$	=	Vector of average responses [N_x]
$\mathbf{x}_0$	=	Vector of initial conditions for state variables [N_x]
$\mathbf{X}$	=	Matrix of stochastic simulation responses [$N' \times N_y$]
$\mathbf{X}_i$	=	Vector of responses in the *i*-th simulation run [N_x]
$\mathbf{z}_{sw}$	=	Vector of switching levels [n_{sw}]
$\mathbf{z}_\theta$	=	Vector of sensitivities of $p(y,\boldsymbol{\theta})$ [N_θ]
$\boldsymbol{\alpha}$	=	Vector of significance factors [N_c]
$\boldsymbol{\beta}$	=	Vector of backoff functions [N_c]
$\boldsymbol{\gamma}$	=	Vector of eteroschedastic factors [N_y]
$\boldsymbol{\varepsilon}$	=	Vector of measurements error [N_y]
$\boldsymbol{\varsigma}$	=	Vector of variance model parameters [N_p]
$\boldsymbol{\theta}$	=	Vector of true values of model parameters [N_θ]
$\boldsymbol{\theta}^*$	=	Vector of perturbated values for model parameters [N_θ]
$\hat{\boldsymbol{\theta}}$	=	Vector of estimated values of model parameters [N_θ]
$\tilde{\boldsymbol{\theta}}$	=	Stochastic vector of model parameters [N_θ]
$\boldsymbol{\theta}^0$	=	Vector of initial guesses of model parameters [N_θ]
$\hat{\boldsymbol{\theta}}^{CM}$	=	Vector of estimated values of model parameters for CM [$N_{\theta^{CM}}$]
$\hat{\boldsymbol{\theta}}^{HM}$	=	Vector of estimated values of model parameters for HM [$N_{\theta^{HM}}$]
$\boldsymbol{\Theta}$	=	Vector of normalised model parameters for the subject [N_θ]
$\hat{\boldsymbol{\Theta}}$	=	Vector of estimated values of normalised model parameters [N_θ]
$\boldsymbol{\Theta}_{1-4}$	=	Subset of the first four normalised model parameters of $\boldsymbol{\Theta}$ [N_θ -1]
$\boldsymbol{\kappa}$	=	Vector of confidence intervals [N_x]
$\boldsymbol{\Lambda}$	=	Vector of user-defined coefficients for (4.15) [N_c]
$\boldsymbol{\sigma}_x$	=	Vector of standard deviations on model responses [N_x]
$\boldsymbol{\Sigma}$	=	Measurement errors variance-covariance matrix [$N_y \times N_y$]
$\boldsymbol{\Sigma}_i$	=	Measurement errors variance-covariance matrix in the *i*-th experiment [$N_y \times N_y$]
$\boldsymbol{\Sigma}_\theta$	=	Prior variance-covariance matrix of model parameters [$N_\theta \times N_\theta$]
$\boldsymbol{\xi}_\theta$	=	Vector of parameters needed to define probability density function p_θ [n_{ξ_θ}]
$\boldsymbol{\xi}_x$	=	Vector of parameters needed to define probability density function p_x [n_{ξ_x}]
$\boldsymbol{\varphi}$	=	Design vector [n_φ]

$\boldsymbol{\varphi}_{\mathrm{OPT}}$ = Optimal design vector [n_φ]

$\tilde{\boldsymbol{\varphi}}$ = Stochastic design vector [n_φ]

$\boldsymbol{\varphi}_i$ = ED vector before the *i*-th update [$n_{\varphi i}$]

$\boldsymbol{\omega}$ = Vector of standard deviations of the measured responses [N_y]

Greek Letters

α = Statistical level of significance

α' = Conversion coefficient

β_i = *i*-th element of the backoff vector

Γ = Response selection function

γ_j = Eteroschedastic factor for the *j*-th measured response

δ = Dirac impulse function

ε = Small non-zero number for formula (4.44)

ε^{MM} = Bias term

ε' = Expected error for Bartlett's formula (4.8)

ε_i = *i*-th measurement error

$\varepsilon_i^{(\theta)}$ = Relative error of parameter estimate

ε_I' = Small positive tolerance number for (2.37)

ε_I'' = Small positive tolerance number for (2.38)

η = Cramer-Rao efficiency index

η^{DOE} = Design efficiency index

η_C^{DOE} = Design efficiency for anticorrelation

θ_i = *i*-th model parameter

$\tilde{\theta}_i$ = Stochastic realisation of the *i*-th model parameter

$\tilde{\theta}_{ij}$ = Stochastic realisation of the *i*-th element of the parameters vector in the *j*-th event

θ'_i = *i*-th re-parameterised model parameter

Θ_i = *i*-th normalised model parameter

$\tilde{\Theta}_i$ = Stochastic realisation of the *i*-th normalised model parameter

$\tilde{\Theta}_{ij}$ = Stochastic realisation of the *i*-th normalised parameter in the *j*-th event

ι = Small non-zero number for (4.34)

κ_i = Confidence interval of the *i*-th parameter

λ_i = *i*-th eigenvalue of the variance-covariance matrix $\mathbf{V}_\theta$

μ_i = Scaling factor for the *i*-th model parameter

ρ = Mass density

σ_θ = Standard deviation of model parameter

$\hat{\sigma}$ = Expected variance for Bartlett's formula (4.8)

$\sigma_{x,i}$ = Standard deviation of the *i*-th response

σ_y = Standard deviation of a single measured variable

$\sigma_{y_{ij}}$ = *ij*-th element of $\mathbf{\Sigma}$

τ = Experiment duration

τ^{max} = Maximum experiment duration

τ_i = Length of the *i*-th updating interval

φ_i = *i*-th element of the design vector

Φ^I = Objective function for *a-posteriori* identifiability testing

Φ^{PE} = Generic objective function for parameter estimation

Φ^{LS} = Objective function for least squares parameter estimation

Φ^{WLS} = Objective function for weighted least squares parameter estimation

Φ^{MAP} = Objective function for MAP bayesian parameter estimation

χ_{RIF} = Reference chi-square

ψ = $\mathbf{V}_\theta$ measurement function

ψ^H = Constraint on expected information

ψ_k = *k*-th measurement function of $\mathbf{V}_\theta$

ω_j = Standard deviation of the *j*-th measured response

Ω_θ = Measurement of global precision of parameters estimate

Other symbols

N = Set of probability density functions with normal distributions [N_c]

R = Set of probability density functions with uniform distribution [N_c]

T = Uncertainty domain of model parameters

Acronyms

BOM	=	Block-oriented modeling
CGM	=	Continuous glucose monitoring
CGMs	=	Continuous glucose monitoring system
CHO	=	Carbohydrates
CM	=	Cobelli model
DAEs	=	Differential and algebraic equations system
DGSM	=	Derivative-based global sensitivity measures
DMBDoE	=	Dynamic model-based design of experiments
DoE	=	Design of experiments
DOPT	=	Dynamic optimisation
DOPT-B	=	Dynamic optimisation with backoff
ED	=	Experiment design
EGP	=	Endogenous glucose production
FAST	=	Fourier amplitude sensitivity test
FIM	=	Fisher information matrix
GSA	=	Global sensitivity analysis
GTF	=	Global *t*-factor
HM	=	Hovorka model
HT	=	Human thermoregolatory
HWM	=	Hovorka-Wilinska model
IVGTT	=	Intravenous glucose tolerance test
LS	=	Least squares
MAP	=	Maximum *a-posteriori*
MBDoE	=	Model-based design of experiments
MBDoE-B	=	Model-based design of experiments with backoff
METER	=	Minimisation of the expected total error
MIMO	=	Multiple-input-multiple-output
ML	=	Maximum likelihood
MOGTT	=	Modified oral glucose tolerance test
MPGT	=	Modified postprandial glucose test
NLP	=	Non linear programming
OGTT	=	Oral glucose tolerance test
OMBRE	=	Online model-based redesign of experiments

OMBRE-B = Online model based redesign of experiments including backoff
OSS = Optimal sampling scheduling
PCA = Principal component analysis
PD = Proportional derivative
PE = Parameter estimation
PGT = Postprandial glucose test
PID = Proportional integral derivative
RSM = Response surface methods
SA = Sensitivity analysis
SGI = Structurally globally identifiable
SISO = Single-input-single-output
SNI = Structurally nonidentifiable
SQP = Sequential quadratic programming
SRQP = Sequential reduced quadratic programming
SRSM = Stochastic response surface methods
SSWR = Sum of square weighred residuals
SVD = Singular value decomposition
SWR = Sum of weighted residuals
TGA = Thermogravimetric analysis
T1DM = Type 1 diabetes mellitus
WHO = World health organisation
WLS = Weighted least squares

Chapter 1

Introduction and literature survey

The statement of physical laws, correlations and prior knowledge on a system can be exhaustively condensed in a compact form by using a mathematical model, where cause-effect relationships are represented and emphasised through analytical expressions. Intuitions and hypothesis on the ongoing phenomena must be proved in a controlled environment (i.e. the laboratory) where experiments are carried out to investigate and validate the adequacy of one or more candidate mathematical models. Data collection and model building activities can become very highly expensive tasks if the experimental settings are chosen without considering any scientific rationale. Model-based design of experiments (MBDoE) is a powerful tool to maximise the information content of the experimental trials, allowing to detect the best experimental settings to adopt in order to facilitate the model identification task. This Thesis is concerned with the development of advanced MBDoE techniques for parameter estimation. These techniques are particularly useful and effective to preserve the optimality and feasibility of the planned experiments even in the presence of model uncertainty.

1.1 Motivation and main achievements of the research project

Any scientific conclusion related to process understanding has to be proved by experimental evidence, and experimental data are usually required to get relevant information for building and developing a reliable mathematical model. Building mathematical models to represent physical phenomena from observations is, and has long been, a basic principle of the scientific research method. A mathematical model is a surrogate of information, built in an iterative fashion during the course of an experimental investigation, where *a priori* knowledge in form of physical/chemical/biological laws defines the model structure and adjustable parameters (which may have physical meaning or not) have to be estimated in the most precise and accurate way. The model identification is the process of both assessing the model structure and estimating the model parameters within the range of expected utilisation. It is natural to ask whether it is possible to plan the experiments in order to facilitate the task of estimating the parameters or to discriminate between rival model structures. Even the more sophisticated numerical techniques may fail on extracting useful information from a series of poorly designed experiments, and the result of the identification procedure can merely

become a waste of time and resources. A possible solution to overcome this issue is given by the design of experiments (DoE) techniques. These are valuable tools for the rapid assessment and development of mathematical models, allowing to increase the information content of the trials while diminishing the impact of the model identification task on the economy of the whole experimentation. When designing an experiment, decisions need to be made before data collection, and usually data collection is restricted by the available resources. Standard DoE techniques ignore that a candidate model *is* a preliminary information on the process itself: a number of experiments has to be performed in order to reach a preliminary statistical representation of a response surface linking the (measured) output variables with the (design) input variables. This procedure can be costly and very time consuming. As an evolution, model-based design of experiments techniques take the advantage of the knowledge of the structure of the underlying system, detecting a set of optimally informative experiments and minimising at the same time the required experimental effort. The MBDoE identification procedure, thanks to the model exploitation, is quick and particularly flexible and allows to manage active constraints on the system under investigation. However, conventional MBDoE techniques are still affected by some evident limitations. A structural mismatch between the system's response and the identification model combined to the initial uncertainty in the actual parameters value may lead to plan unfeasible (i.e., violating the active constraints) or sub-optimal (i.e. scarcely informative) experiments for model identification.

This Thesis shows how the above issues can be tackled through the adoption of advanced MBDoE techniques. The main contributions of this Thesis to MBDoE development are:

1. an MBDoE strategy explicitly taking into account uncertainty on both model structure and parameters;
2. an online MBDoE strategy exploiting the information as soon as it is generated from the system;
3. a MBDoE technique suitable for systems where continuous measurements are available;
4. the apply of MBDoE techniques to unconventional applications.

These newly proposed MBDoE strategies are tested and applied to different case studies, from biological to reaction systems described by deterministic dynamic models where a crucial aspect to address is the precise identification of the model parameters. In particular, in the biomedical engineering area, where complex models have been developed to simulate and analyse the behaviour of organs and metabolic systems, the identification procedure may become a critical problem and an almost impossible task if the identification tests are not properly planned. A particularly innovative contribution of this Thesis is the application of these newly developed MBDoE strategies to complex physiological models of type 1 diabetes mellitus. Advanced MBDoE techniques are exploited to design a set of clinical tests that allow estimating the model parameters in a statistically sound way, fulfilling the imposed constraints on safeness for the subject and easiness of conduction. Simulated results

demonstrate how a MBDoE approach can improve the effectiveness of clinical tests and serve as a tool to devise safer and more efficient clinical protocols.

1.2 Introduction to design of the experiments

The purpose of an experiment is to gain significant information from a system, to get useful insights on a physical phenomenon and understand its specific behaviour. The basic idea underneath DoE is that it is possible to plan a set of experimental trials in order to improve the information that can be acquired from a system by simply acting on the experimental settings. The theory about design of experiments was first proposed by Ronald A. Fisher in his celebrated book *The design of experiments* in 1935, where he put the fundamental basis of the so called *factorial design*. The goal of factorial design was to analyse the effect of each factor (i.e. design variable) in terms of variance, as well as the interactions between factors, on the system response. A full factorial design contains all the possible realisations of the factors within a design region defined by high/low levels of variability for the design variables. Fisher explained the principles of experimentation design by mean of a psycho-physical experiment, where a lady declares that by tasting a cup of tea made with milk she can discriminate whether the milk or the tea infusion was first added to the cup. He considered the problem of designing an experiment by means of which this assertion could be tested. Fisher arguely noticed that often the conclusions that can be drawn from an experiment are criticised because of incorrect treatment of the data, the purview of the statistician, the existence of faulty experimental protocols or the role of the experiment designer. All these aspects, concerning the logical structure of the experimental activity, have to be carefully considered by the designer when planning an experiment. In the text book, fundamental design concepts as randomisation, replication, orthogonality and balance of experiments are coupled with a rigorous statistical variance analysis. Other classical DoE methods were devised by Davies and coworkers (1954) that, together with Fisher (1935), applied and developed these basic design techniques in situations, such as in agriculture and industry, where no a priori mathematical models were available. A further refinement of the factorial design methodology was provided by Frank Yates aiming at choosing a specific subset of input factors realisations. This was called *fractional factorial design* and is discussed in details in the book by Box *et al.* (1978). Box and Wilson (1951) suggested the use of response surface methods (RSM) to explore the relationships between input factors and one or more responses. In RSM methods the data coming from a sequence of experimental trials are used to detect an optimal response. This is found by regressing the data collected from the experimental trials through a statistical function of the most relevant input factors (usually a polynomial) representing a response surface (Figure 1.1). An evolution of RSM is provided by stochastic response surface methods (SRMS; Isukapalli *et al.*, 1998). These methods are more efficient

to represent the variability of the system response in the presence of parametric uncertainty. According to these methods both inputs and outputs are approximated by series of random variables and the parameters of the power series of the outputs have to be estimated. The design methodology, involving a Monte Carlo simulation, is computationally less expensive for building a trustworthy response surface than RSM or factorial methods.

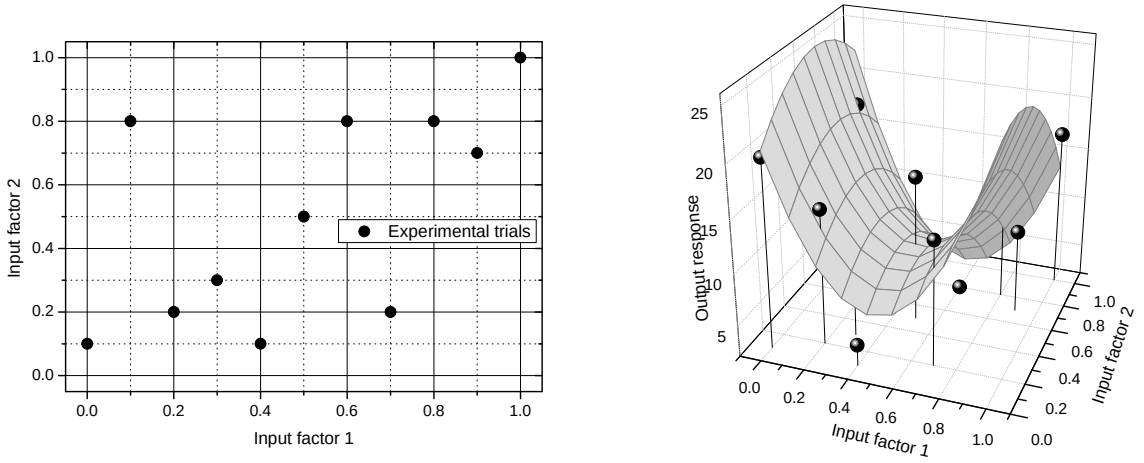


Figure 1.1 *Response surface methods (RSM) for DoE: (a) factorial design table and (b) construction of response surface .*

The above mentioned DoE methodologies are known as "black box experiment design" methods because the analysis is carried out on the set of independent variables (experimental conditions) and dependent variables (measurements) without postulating any formal relationship between them (as could be dictated by physical laws or statements), and simply by analysing the outcomes of the sequence of observations on statistical basis. Factorial methods are widely used in the DoE practice in many areas of application, including biology (Valdramidis *et al.*, 2006; Geuten *et al.*, 2007), medicine (Linusson *et al.*, 2000; Altekar *et al.*, 2007), chemistry (Liang *et al.*, 2001; Llamas-Galilea, 2009) and in mixture design (Solvason *et al.*, 2009), economics (Davis and Holt, 1993) and even political sciences (King *et al.*, 2007). A practical approach to DoE with a number of applications on different scientific areas can be found in the exhaustive text books by Anderson and McLean (1974) and Hinkelmann and Kempthorne (1994) where the goals and subtleties of experiment design are underlined and discussed. Other authoritative books on the subject are given by Box and Draper (1987), Atkinson and Donev (1992) and the more recent book by Lazic (2004). DoE methodologies represent a first bridge between the experimental world and the modeling world (Figure 1.2), and became rapidly very popular for their easiness of implementation and interpretation. The experimental activity provides the required information, in the form of collected data, in order to define candidate models, select/validate a model and, finally, to perform the parameter

identification task on the chosen model. If a model is a reliable representation of reality, it can be usefully exploited in the choice of the proper experimental settings, and thus giving a valuable support to the experiment design activity in order to increase or optimise the information content of each single trial.

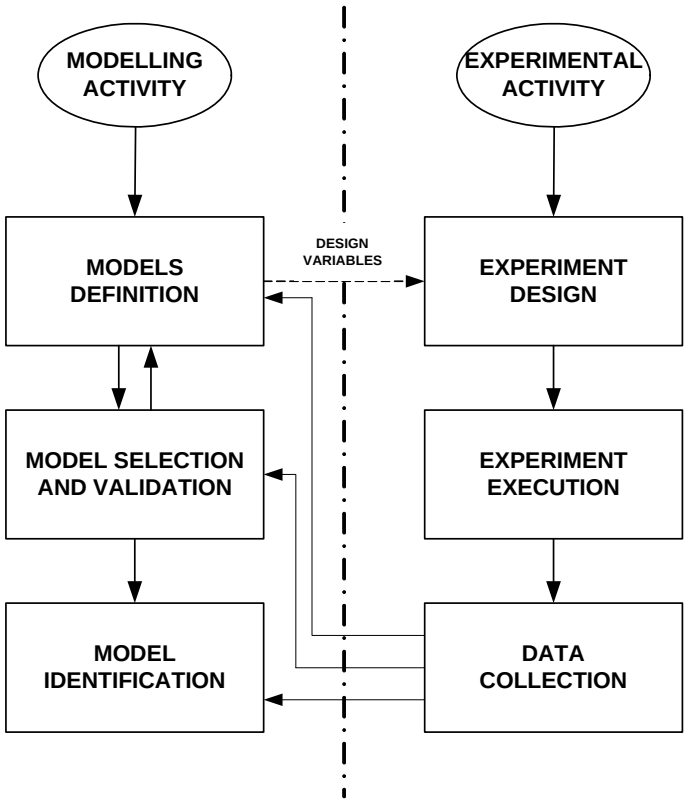


Figure 1.2 *Relationships between modelling and experimental activity.*

Black box DoE techniques are a useful tool for model development and validation, but suffers from some drawbacks. In fact, the technique allows to improve the information content of a trial, but information is built from a sequence of observations in an iterative fashion. It is literally a "data driven" design and preliminary unsuccessful experiments could result in a totally ineffective experimental campaign. Furthermore, when a high number of factors is present, the experimental effort required by these methods in order to build a first (roughly approximated) response surface is very high. Usually the statistical models provided by DOE methodologies such RSM are only a rough approximation of the reality, and an estimated optimal design point can turn, in practice, to be suboptimal because of the inadequacy of the regression model.

1.3 Representation of the information content of an experiment

Response surface methodologies, surrogate modeling (Queipo *et al.*, 2005), as well as kriging (Stein *et al.*, 1999) or meta-modeling (Simpson *et al.*, 2001), are basically regression or approximation methods where information is extracted from experimental data and condensed into a statistical or stochastic model. Unfortunately, this preliminary information is essentially a *local* information, that cannot be exploited outside the range of experimental conditions defined by the performed experiments. In stochastic models the ranges of variability for each variable are provided in the form of probability distributions. On the contrary, deterministic models are particular mathematical models in which the outcomes are precisely determined through known relationships among states and events, without any room for random variation. In such models a given input will always provide the same output. A wide class of deterministic models describes the phenomena being investigated through the statement of physical laws and correlations in the form of a system of differential and algebraic equations (DAEs). The model capability of representing the underlying phenomena in a reliable and accurate way depends on the model structure (i.e., the correlations and laws being used) and on the values of parameters that can be calibrated to match the model to a specific real system.

Experimental data are typically required both to assess the model validity and to estimate the model parameters in the range of expected utilisation. The approach of perturbing a process for system identification is a widespread and mature technique for parameter identification (Ljung, 1987), in particular for systems represented by linear models. However, in particular for nonlinear systems, the choice of the experiments to be carried out is critical to establish the most appropriate model structure and the best values of the parameters as well as to save time and effort in experimental trials. Deciding which experiment to carry out is not obvious, and there is usually a trade-off between experimental effort (in time and money) and amount and quality of data. The best experiment is the one that is most informative but, as discussed by Bard (1977), information is a crucial point and it is intrinsically related to the goal of investigation. The meaningful question to ask is not “What is the best experiment?”, but “What is the best experiment for the attainment of our goal?”. Each experiment performed can be seen as a gain of information, but only an optimally designed experiment can be deemed “the best” in the sense of being optimally informative for the attainment of the following goals:

- to discriminate among possible rival models, so that the information collected can be used to change, improve or reject a model structure (*design of experiments for model discrimination*);
- to estimate the unknown parameters of the model with a desired level of precision (*design of experiments for parameter estimation*).

The model identification procedure aims at both detecting the model structure and estimating the set of model parameters. Systematic procedures for model identification have been recently proposed in literature by Asprey and Macchietto (2000), Blau *et al.* (2008) and Kreutz and Timmer (2009) and are briefly illustrated in §1.7.

Fisher (1935) was the first to think about information in analytical terms, measuring the quantity of information supplied by an experiment with respect to the particular values to which the variance refers. It is possible to gain information only by decreasing uncertainty, but the relationship between these two dual intuitive notions cannot be explained in frequentist[1] terms but only in a Bayesian fashion (Chaloner and Verdinelli, 1995) introducing probabilistic assumptions. Shannon (1948) showed that, if $\boldsymbol{\theta}$ is a N_θ-dimensional random vector of model parameters with associated probability density function $p(\boldsymbol{\theta})$, the unique suitable measure of uncertainty $\bar{V}$ associated with $p(\boldsymbol{\theta})$ is given by

$$\bar{V}\left(p\right) = -E\left(\log p\right) = -\int p\left(\boldsymbol{\theta}\right)\log p\left(\boldsymbol{\theta}\right)d\boldsymbol{\theta} \tag{1.1}$$

where E denote the expectation operator. The more disperse the distribution of $\boldsymbol{\theta}$, the more uncertain is the value any specific realisation of $\boldsymbol{\theta}$ will assume. According to Lindley (1956), if $p_0(\boldsymbol{\theta})$ and $p^*(\boldsymbol{\theta})$ are, respectively, the prior density and the posterior density of $\boldsymbol{\theta}$, the amount of information I that is gained by an experiment is

$$\bar{I} = \bar{V}\left(p_0\right) - \bar{V}\left(p^*\right) \tag{1.2}$$

and it equals the reduction in uncertainty from the prior to the posterior distributions. The goal of an optimal design technique is to find the experiment that maximises I. Since $\bar{V}\left(p_0\right)$ is unaffected by the experiment, the design procedure look for the experiment that minimises $\bar{V}\left(p^*\right)$. The design methodologies differ basically by the way in which this measure of uncertainty is evaluated and by the particular form of the information metric function. This quantity can be evaluated recursively from data adopting a regression model (DoE) or be calculated directly by using a deterministic model (MBDoE). The differences between the two experiment design approaches in terms of information fluxes are highlighted in Figure 1.3.

As can be seen in Figure 1.3a, in the black box DoE the information flux coming from experimental data is progressively used to build a regression model (i.e. a statistical model providing a response surface) representing the variability of the system as the number of performed experiments is sufficiently large to cover the overall design space. A significant

[1] Bayesian and frequentist are the two major currents in statistics. In the frequentist school, the probability of an event is related to its relative frequency over time. In the Bayesian school a prior probability of an event is assigned and updated in the light of the new relevant data.

experimental effort may be required in this first step of the design procedure to build a reliable regression model, and the optimal design settings can be gathered only when a consistent response surface is represented.

In the MBDoE strategy (Figure 1.3b) the procedure starts designing a first experiment based on the prior knowledge on the model. After that, information is extracted from the data collected after an experiment is performed, thanks to an intermediate parameter estimation session. The model thus updated is ready to be used in the subsequent optimisation where the expected information is maximised and where the contribution of performed experiments to the overall information is taken into account. The information is maximised from the very beginning of the design procedure, thanks to the information coming from the model. While a large number of experiments is needed by DoE to perform a statistically satisfactory representation of the behaviour of the system, MBDoE techniques aim at minimising the number of experiments while maximising the information content of each single trial.

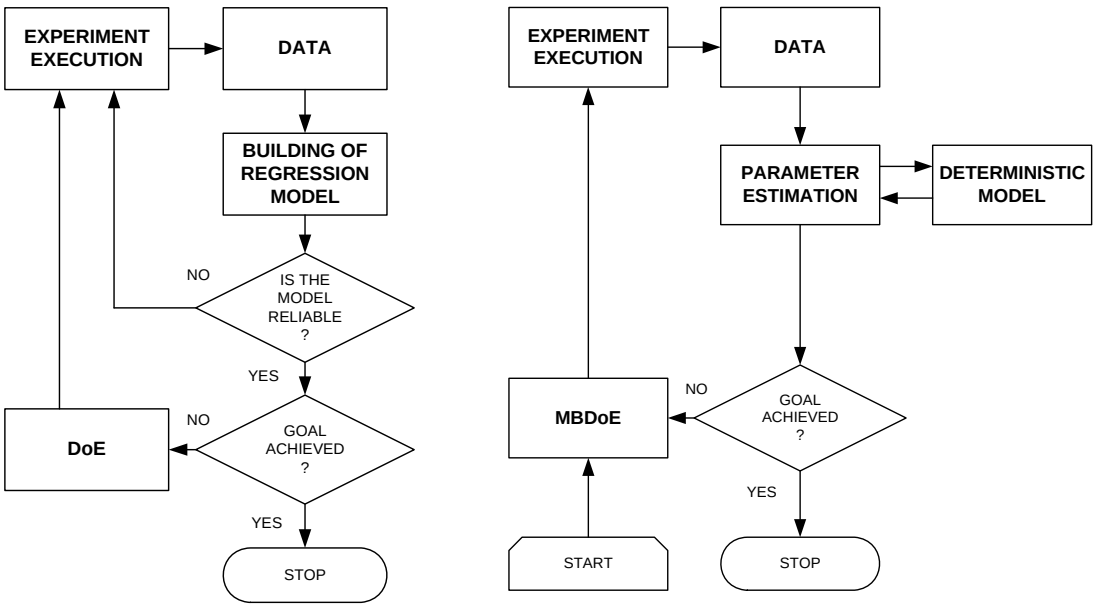


Figure 1.3 *(a) Black box design of experiment (DoE) and (b) model based design of experiments (MBDoE): differences in terms of information fluxes.*

As discussed by Kreutz and Timmer (2009) the two design approaches can be usefully integrated in a model building procedure. In particular, when no preliminary information on the undergoing phenomenon is available, a regression model built using DoE techniques can provide a significant support for the development of a deterministic model, eventually suitable for MBDoE. In both DoE and MBDoE procedures the goal determining the stopping rule can be: *i*) the attainment of a desired level of precision on parameter estimation; *ii*) the

attainment of a desired model accuracy; *iii*) the exploitation of the maximum experimental budget (i.e. the experimental effort in terms of time, work and analytical resources that can be invested to carry on the identification procedure).

1.4 Model-based design of experiments: a review

A mathematical model of a process reflects the actual knowledge of the experimenter on the underlying system and can be used to predict the information content of an experiment. In the model based design of experiments approach the systems of differential and algebraic equations, including expressions related to constraints on the system, can be embedded into a deterministic optimisation framework where the objective function being minimised is a particular metric of the overall uncertainty, usually expressed by a variance-covariance matrix. These particular design techniques have been initially applied to steady state models both in the linear and nonlinear forms with respect to model parameters and the applications reported in the literature cover a large number of applications from science to social disciplines. Box and Lucas (1959) were the first to apply MBDoE strategies to reacting systems in order to estimate the kinetic parameters of simple models. In this study the determinant of a function of the sensitivity matrices was chosen as a suitable design criterion. Kiefer (1959) was one of the first to introduce the so called "alphabetic criteria" (A-, D-, E-optimal among others) as design metrics of the variance-covariance matrix. Other pioneristic studies on MBDoE for parameter estimation are the ones by Draper and Hunter (1966) and by Kittrell *et al.* (1966). Hunter and Reiner (1965) and Atkinson and Fedorov (1975) were the first to develop model-based experimental design criteria for model discrimination based on the distinct predictions between candidate models. While these first studies adopted a frequentist approach, Box and Hill (1967) and Hsiang and Reilly (1971) used a bayesian description, where the concept of entropy was exploited as a measure of the uncertainty on discriminating between candidate models. Buzzi-Ferraris and Forzatti (1983) formulated an MBDoE criterion for model discrimination taking into account the relative variability on the predicted responses of the models. The same authors also extended the design criteria to multiresponse systems (Buzzi-Ferraris and Forzatti, 1984).

The works by White (1975) showed how results from linear design could usefully be extended to design experiments for parameter estimation adopting nonlinear models, while Fedorov (1972) discussed the optimal design of regression experiments basing on a measure of the expected information. Pritchard and Bacon (1975) developed new design criteria based on several metrics of the variance-covariance matrix of model parameters in order to decrease the degree of correlation among parameters. Bard (1977) applied optimal design criteria based on the maximisation of a metric of the Fisher information matrix (FIM) to nonlinear parameter estimation problems. The detailed review of Mehra (1974) covers the most relevant

contributions to the subject of optimal input design for parameter identification of dynamic systems. Optimal input studies have been also discussed by Goodwin and Payne (1973; 1977) by applying optimal model-based design criteria in the frequency domain to single-input-single-output systems, while Kevitzky (1975) applied an MBDoE strategy to linear discrete-time dynamic models. These preliminary studies are mainly related to the field of signal theory where stochastic models are used in the identification procedure. In the automation science, when the model itself is adopted for control purposes or embedded in a control algorithm, the recursive identification of model parameters may play a crucial role. This particular topic about model identification is known as *identification for control* (Gevers, 2005). Ljung and Gevers (1986) discovered that the adoption of model based design techniques can lead to substantial benefits when a closed loop identification procedure is carried out. More recently Hjalmarsson *et al.* (1996) found that for model-based control design a closed-loop identification gives a better performance. Furthermore, Jansson (2004) compared standard techniques for model identification in open and closed loop with MBDoE techniques, and the results underlined significant benefits of adopting appropriate input designs. Micchi and Pannocchia (2008) stressed out the importance of designing appropriate input signals for model identification in multivariable ill-conditioned systems. The authors compared the performance of random open-loop and closed-loop generated signals suitable for model predictive control.

As discussed by Shirt *et al.* (1994) in a survey article, the extension of the MBDoE methodology to deterministic dynamic models has been a slow process, mainly because of the computational effort required by the optimisation steps when a differential system is involved in the calculation and the manipulated input variables being optimised are defined by dynamic profiles. Cobelli and Tomaseth (1986) studied the problem of optimal input design for the identification of simple models of glucose homeostasis; for the first time on this specific topic the input design was based on a FIM metric. Espie and Macchietto (1989) were the first to formulate the model-based design problem as an optimal control problem and proposed a robust algorithm for both model discrimination and improvement of parameter precision. The deterministic dynamic optimisation framework for the solution of resulting numerical optimisation problem was solved by the Reduced-Space Successive Quadratic Programming (SRQPD) optimisation technique developed by Chen *et al.* (1988). Munack and Posten (1989) demonstrated and confirmed that the same MBDoE approach could be useful to address the identifiability issues related to the parameter estimation of a simple Monod model. These latter studies were the first ones dealing with the problem of optimal design of dynamic experiments in nonlinear dynamic models described by DAEs.

Throughout the years different contributions to MBDoE techniques for the identification of dynamic systems have covered different scientific areas, but the studies mainly focused on three fundamental aspects:

1. the application of MBDoE to specific and/or novel case studies;
2. the formulation of advanced MBDoE techniques and tools to overcome some major limitations of the standard design methodology;
3. the development of novel robust optimisation algorithms and numerical tools to improve the computational efficiency of MBDoE.

The three different aspects on MBDoE investigation are detailed in the following paragraphs. A recent survey article on MBDoE can be found in Franceschini and Macchietto (2008) and thus only the major contributions are recalled in this Thesis. An exhaustive text book on the subject is the one by Pukelsheim (1993).

1.4.1 Applications of model-based experiment design

Applications of MBDoE techniques cover a large variety of fields, starting from industrial engineering to chemistry, biology and bioengineering. A partial list of references is presented in Table 1.1 and the major contributions are briefly discussed in the following lines.

The design of dynamic experiments is particularly appropriate in the biological field where experimental data generation is generally very expensive and time-consuming. On the wake of the first MBDoE applications, Baltes *et al.* (1994) and Versyck *et al.* (1998) extended the studies on fermentation processes by Munack and Posten (1989) to models of unstructured microbial growth, demonstrating the benefits of adopting an MBDoE approach if compared with the standard "black box" design procedures. The study by Bernaerts and Van Impe (2004) concerns with the optimal design of dynamic experiments for the estimation of parameters of microbial growth kinetics models at sub-optimal temperature. The authors also investigated the effect of temperature constraints on the information that can be gathered from the experiments. Donckels *et al.* (2009) adopted MBDoE strategies to find the optimal sampling scheduling (OSS) both for estimating the model parameters and for discriminating among rival models with reference to enzymatic reactions, while Gadkar *et al.* (2004) discussed an iterative approach to model identification of biological networks. Martinez *et al.* (2009) used a MBDoE strategy to design dynamic experiments for identifying the set of parameters of a bioprocess for penicillin production. The authors applied global sensitivity analysis (GSA) to screen out potential identifiability issues and discussed the effect of model imperfection on the effectiveness of the design. Balsa-Canto *et al.* (2007; 2008) considered the problem of designing optimal dynamic experiments for the identification of a set of kinetic parameters of models of thermal degradation for the food industry in predictive microbiology. A recent review on the issues and fundamental concepts for designing experiments in system biology is provided by Kreutz and Timmer (2009).

A different and interesting MBDoE application is the one investigated by Emery *et al.* (1998). The authors discussed several model-based design strategies to improve the estimation of thermal properties in heating systems. In subsequent papers, Emery *et al.* (2000; 2001)

designed a set of experiments for estimating conductivity and contact resistance when surface convective coefficients are uncertain and discussed the important relationships between information, sampling rates and models for parameter estimation (Emery *et al.*, 2002).

Table 1.1 *Some applications of model-based design of experiments.*

Area	Contribution	Reference
Biological processes	Models for microbial growth	Baltes *et al.* (1994)
	Haldane growth model	Versick *et al.* (1998)
	Baranyi bacterial growth model	Grijspeerdt and Valrolleghem (1999)
	Cellular growth model	Gadkar *et al.* (2004)
	Model for biodiesel process	Franceschini and Macchietto (2007)
	Model of thermal degradation	Balsa-Canto and Rodriguez-Fernandez (2007)
	Model for penicillin production	Martinez *et al.* (2009)
	Enzymatic fermentation model	Donckels *et al.* (2009)
Thermal systems	Conductivity parameter estimation	Emery (1998)
	Conductivity under uncertainty	Emery *et al.* (2000, 2002)
Energy systems	Polymer-electrolyte-membrane fuel cells	Meiler *et al.* (2009)
Chemical systems	Kinetic model of coal pyrolysis	Lohmann *et al.* (1992)
	Nitrification model	Ossenbruggen *et al.* (1996)
	Diffusion in benzene-toluene system	Bardow *et al.* (2003)
	Alkaline hydrolysis of *n*-amylacetate	Issanchou *et al.* (2005)
	Catalytic decomposition of NH_3 on Ru	Prasad and Vlachos (2008)
	Catalytic SO_2 oxydation	Schöneberger *et al.* (2009)
	Kinetics of solid thermal decomposition	Dirion *et al.* (2008)
	Protein ion-exchange equilibrium	Barz *et al.* (2009)
	Mass transfer through porous membranes	Zhang *et al.* (2009)
Materials science	Elastic constants estimation from plate vibration measurements	Frederiksen (1998)
Cristallisation processes	Crystal growth parameters estimation	Chung *et al.* (2000)
	Industrial cristallisator	Chen *et al.* (2004)
Physiological systems	Optimal blood sampling scheduling	DiStefano et al. (1981,1982)
		Fedorov and Leonov (1997)
	Identification of statistical models for optimal dose-finding	Dragalin *et al.* (2006)
		Dette et al. (2008)
	Identifiability of models for mammalian cell cultures	Sidoli *et al.* (2005)
		Kontoravdi *et al.* (2005)
	OSS for pharmacokinetic experiments	Kalicka and Bochen (2006)
	Pharmacokinetic population analysis	Foracchia *et al.* (2004)
	Transdermal diffusion model	Schittkowski (2008)
	Pharmacokinetic and pharmacodynamic	Nyberg *et al.* (2009)
	Identification of models for type 2 diabetes	Silber *et al.* (2009)

In chemical technology, MBDoE techniques received a particular attention, quickly becoming a well consolidated tool to investigate and elucidate different reaction patterns and to improve the estimation of kinetic constants. Starting from the earlier works by Bock (1983), Lohmann *et al.* (1992) developed an MBDoE strategy suitable for the identification of reacting systems. The authors in particular analysed a decomposition model of coal pyrolysis. Bardow *et al.* (2003) focused their attention on the optimal design of diffusion experiments for the binary mixture benzene-toluene using Raman spectroscopy. Ossenbruggen *et al.* (1996) applied a D-

optimal design to a two-step nitrification model, while Issanchou *et al.* (2005) investigated the alkaline hydrolysis of *n*-amylacetate. Franceschini and Macchietto (2007) focused on the application of MBDoE techniques for the identification of parameters in a biodiesel production process. The authors in a following study also proposed novel design techniques to decrease the level of correlation among parameters (Franceschini and Macchietto, 2008). Prasad and Vlachos (2008) adopted MBDoE strategies to estimate the parameters of microkinetic models. The authors analysed the catalytic decomposition of ammonia on ruthenium. Schöneberger *et al.* (2009) performed a model-based experimental analysis of a fixed-bed reactor for catalytic SO_2 oxydation. A sequential A-optimal design was used to estimate the kinetic constants of the model, adopting a stochastic search algorithm within the constrained optimal design framework.

Reverte *et al.* (2007) and Dirion *et al.* (2008) focused their research on determining the parameters and structure of kinetic models of solid thermal decomposition with thermogravimetric analysis (TGA) instruments. In this latter study the authors computed the optimal programmed temperature profile (as applied to the thermobalance) to use during the thermogravimetric experiment in order to identify the set of parameters in a statistically reliable way. Barz *et al.* (2009) recently applied MBDoE techniques for the determination of protein ion-exchange equilibrium parameters. The authors investigated different design configurations considering uncertainties on the manipulated inputs and practical restrictions on the experiments to be carried out. With reference to materials science, Frederiksen (1998) made use of model-based design methodologies to estimate the elastic constants from plate vibration measurements. The author also investigated the effect of the measurements error on the quality of the final estimate. Chung *et al.* (2000) applied MBDoE techniques for the estimation of nucleation and growth parameters in a batch crystallisation process. An industrial process of crystallisation of ammonium sulphate was also investigated by Chen *et al*. (2004), where an MBDoE approach was exploited within a model building strategy.

Recently a larger number of MBDoE applications have been directed to the identification of physiological models. These models are usually structurally complex and their dynamics are usually difficult to identify with standard techniques. Furthermore, as a result of ethical and practical restrictions imposed on medical measurements, the optimal design, sample scheduling and planning of biomedical experiments have become important issues for the development of novel experimental protocols. The study by Sidoli *et al.* (2005) underlined the problem of global estimability of the kinetic parameters of a large scale kinetic model for mammalian cell cultures. Kontoravdi *et al.* (2005) made the use of global sensitivity analysis (GSA) techniques to determine the relevant subsets of model parameters for which a MBDoE identification task can be carried out. In this preliminary study the authors studied a complex dynamic model of monoclonal antibody-producing mammalian cell cultures. Following the pioneeristic works by DiStefano (1981; 1982) on blood sampling scheduling for the

identification of physiological models, Kalicka and Bochen (2006) focused their research on the optimal sampling scheduling in pharmacokinetic and physiologic experiments. Dragalin *et al.* (2006) proposed an adaptive sequential design for dose-finding where the parameters of a probabilistic model are estimated based on efficacy-toxicity response observations. Dette *et al.* (2008) developed robust optimal designs that take into account a set of potential dose-response profiles within classes of models commonly used in drug development practice.
Schittkowski (2008) considered a model of transdermal diffusion for developing new drugs and application devices, developing specific numerical tools and software for the optimal design of experiments for parameter estimation. Foracchia *et al.* (2004) developed a software (POPED) for optimal design of experiments with reference to large scale population kinetics. Nyberg *et al.* (2009) used optimal design techniques to improve or optimise population pharmacokinetic and pharmacodynamic studies. Silber *et al.* (2009) adopted a similar approach to improve the effectiveness of intravenous glucose tolerance tests (IVGTT) for studies on type 2 diabetes. The authors utilised the POPED software to increase the information content of population tests, basing on the computation of the FIM for the entire population. The benefits of adopting such an approach come from the fact that the information matrix is directly evaluated from a large set of data.

1.4.2 Development of advanced MBDoE techniques

MBDoE techniques are flexible tools for the identification of deterministic dynamic models, particularly useful to detect the optimally informative experimental conditions to carry out during the experimental activity. A powerful feature of these techniques is that they allow to take into account a set of active constraints on the physical system being studied. These constraints can be enforced on both state and design variables, and their existence is intrinsically related to the system under investigation. An ideal experiment, if properly designed with MBDoE methodologies, should be:

1. optimally informative (i.e. providing the maximum information);
2. feasible (i.e. the constraints on the system must be satisfied).

Unfortunately, at least in their standard formulations, MBDoE techniques cannot ensure that these requirements are always met simultaneously. As discussed by Ford *et al.* (1989), since the design methodology is model-based, both model mismatch (i.e., the behaviour of the system can be structurally different from the model representation) and parametric mismatch (the actual values of model parameters can be very different from the proper set of parameters describing the system) may affect the effectiveness of the whole design procedure. In particular, the scarce preliminary information on the system (in terms of model structure and values of model parameters) can lead the procedure to predict inconsistent values of the expected information. The expected information (usually evaluated by a particular metric of the Fisher information matrix, expressing the chosen design criteria) may be significantly

different from the actual information acquired by the experiment. The final result can be a sub-optimal designed experiment (scarcely informative) or, in the worst case, an unfeasible experiment, where the constraints imposed on the system turn, in practice, to be violated. A further limitation of the technique is given by the fact that often the classical design criteria could be insufficient to decrease the uncertainty of the inference region in a satisfactory way. The criteria should be tailored on the specificity of the given parametric model, in order to investigate different directions and sources of variability.

When a standard MBDoE approach is attempted, assuming that no model discrimination is required beforehand, three consecutive steps are needed to determine the model parameters:

1. the design of a new set of experiments, based on current knowledge (model structure and parameters, statistics from prior experiments) and on the maximization of some scalar value associated to the dynamic FIM;
2. the execution of the designed experiment and collection of new data;
3. the estimation of new model parameters and statistical assessment.

A scheme of a standard MBDoE procedure is shown in Figure 1.4.

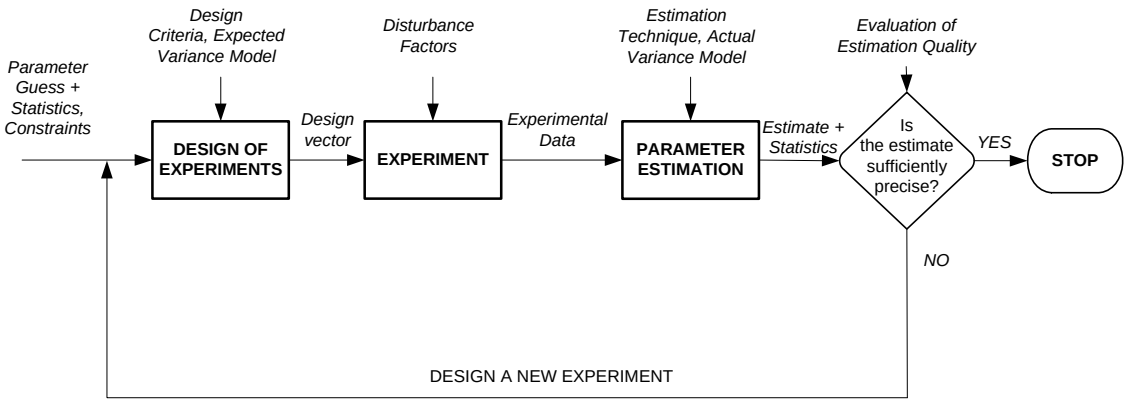


Figure 1.4 *Standard procedure for model-based design of experiments.*

The sequential iteration of steps 1, 2, and 3 leads to a progressive reduction in the uncertainty region of model parameters, thanks to the new information obtained from experimental data. The way in which these design activities are managed and linked together define the so called "topology" of the design procedure and is usually fixed, in the sense that the three operations are generally carried out in a strictly sequential way. However, note that, if multiple equipments are available, there is no reason to think that the experiments should be planned and performed in a sequential way. Other topologies could be more efficient in terms of design effectiveness and resource utilisation. On this perspective, additional degrees of freedom are available to the experimenter, regarding the management of elapsed time and allocation decisions (which equipment can be used to perform a specific experiment). These aspects, defining the overall experimental structure, can be investigated by design and eventually embodied within a dynamic optimisation framework.

In a similar fashion, there is no apparent reason to perform a parameter estimation and an experiment design session only when a single trial has already concluded. Information could be acquired and exploited as soon as it is generated by the experiment.

Advanced MBDoE techniques have been developed throughout the years to overcome the above mentioned limitations of the original methodology and to extend MBDoE applicability to large and complex systems. The contributions include:

1. the development of novel design criteria;
2. model transformation for MBDoE;
3. the modification of MBDoE topology.

A list of the major contributions to the development of advanced MBDoE strategies is shown in Table 1.2, and briefly detailed in the following lines.

Table 1.2 *Several contributions to the development of advanced MBDoE strategies.*

Topic	Contribution	Reference
Development of novel design criteria	Integration of alphabetic design criteria	Versyck and Van Impe (1998)
	Curvature-based MBDoE criteria	Benabbas *et al.* (2005)
	Robust MBDoE criteria	Asprey and Macchietto (2002)
		Körkel *et al.* (2004)
		Bruwer and MacGregor (2006)
		Rojas *et al.* (2007)
		Chu and Hahn (2008)
	METER design criterion	Bardow (2008)
	AC-optimal design criteria	Franceschini and Macchietto (2008)
	A-optimal oriented MBDoE	Schittkowski (2007)
	SV-optimal design criterion	Galvanin *et al.* (2007)
	P-optimal design criterion	Zhang and Edgar (2009)
	Criterion including posterior covariance matrix of differences between model predictions	Schwaab *et al.* (2008b)
	Derivative-free MAP derived MBDoE	Heine *et al.* (2008)
Model transformation for MBDoE	Incremental identification techniques	Bardow and Marquardt (2004) Bardow *et al.* (2005) Brendel *et al.* (2006)
	Design using hybrid function approximations	Chen and Wang (2004)
	BOM identification technique	Rollins and Larson (2006)
	Multiple reparameterisations	Schwaab *et al.* (2007, 2008a)
Modification of MBDoE topology	Adaptive input design	Lindquist and Hjalmarsson (2001)
	Optimal adaptive input design	Stigter *et al.* (2008)

Versyck and Van Impe (1998) proposed an innovative MBDoE design criterion incorporating the classic alphabetic design criteria (Kiefer, 1954) within a single objective function, where the designer, thanks to proper weighting factors, could choose to favour one design metric instead of another. Robust techniques for optimal experimental design have been proposed in literature (Asprey and Macchietto, 2002) to preserve the optimality of the design in the presence of parametric uncertainty, solving a max-min optimisation problem ("worst case approach") or performing a dynamic optimisation over all the predicted uncertainty region of model parameters ("expected value approach"). Both criteria were applied to a semi-

continuous bioreactor model. A robust design approach was also followed by Körkel *et al.* (2004) studying the reaction of urethane. Benabbas *et al.* (2005) proposed an original design method based on the evaluation of the second order sensitivities and taking into account the curvature of the inference regions. The authors demonstrated the benefits of adopting a curvature-based MBDoE with reference to the bioreactor model previously discussed by Asprey and Macchietto (2002). Bruwer and MacGregor (2006) proposed a robust design technique for model identification based on the D-optimal criterion, investigating the impact on design effectiveness of highly correlated sequences of manipulated inputs. Rojas *et al.* (2007) proposed a min-max approach on the frequency domain to solve the robust optimal design problems with simple constraints on the manipulated inputs. Interestingly, the authors also compare different design criteria linking robust control techniques (Hjalmarsson, 2005) and standard experimental design procedure. Chu and Hahn (2008) proposed a technique to integrate optimal parameters selection with experimental design under parametric uncertainty for nonlinear dynamic systems. The robust design was performed by adopting a hybrid method combining a genetic algorithm and a stochastic approximation technique. A different design metric (METER) suitable for ill-posed problems was proposed by Bardow (2008) where the optimal design settings are obtained by minimising the expected total error on model responses.

Complementary numerical tools have been developed for preliminary model investigation and analysis. Local sensitivity analysis (Saltelli and Tarantola, 2002), global sensitivity analysis (Sobol, 2001; Kucherenko et al., 2009; Kiparissides, 2009) and bootstrapping methods (Joshi *et al.*, 2006) can be useful for both investigating particular sources of variability of the system in terms of design variables and to tackle potential identifiability issues of candidate models (see §1.5). Recently Schuurman (2007) adopted a design approach based on local sensitivity analysis to detect the best operating conditions for transient experiments, with the purpose of estimating a set of kinetic parameters for temporal analysis of products (TAP). Sin *et al.* (2009) used both input propagation analysis and sensitivity analysis to screen out the effect of parameters and experimental conditions on the uncertainty of the outputs. The study focused on a mechanistic model describing a batch cultivation for antibiotic production.

Principal component analysis (PCA) techniques (Vajda *et al.*, 1985) are valuable tools for investigating the correlation between parameters and the joint effect of the parameters on the expected information. Franceschini and Macchietto (2008) developed several anti correlation (AC) criteria with the purpose of decreasing the level of correlation among parameters in a biodiesel model. These criteria are based on PCA of the correlation matrix of model parameters. Zhang and Edgar (2009) proposed a generalised MBDoE criterion (termed "P-optimal") introducing PCA into the analysis of the sensitivity matrix and of the information matrix. Interestingly, the authors found that the new criterion is more efficient for complex systems and less sensitive to initial parameters values.

Schittkowski (2007) proposed a promising algorithm where an A-optimal design criteria is used to evaluate the performance of the sequential identification procedure, i.e. assessing the identifiability of model parameters. In the algorithm a parameter elimination step, based on the singular values of the posterior covariance matrix of model parameters, is used to decrease the size of the information matrix in the design optimisation. Schwaab *et al.* (2008) adopted a sequential design of experiments to discriminate among rival models taking into account the posterior covariance matrix of differences between model responses in the formulation of the design criteria. The model discrimination power is enhanced in comparison to the standard criteria for model discrimination initially proposed by Hunter and Reiner (1965) and Buzzi-Ferraris *et al.* (1984), where posterior covariance contribution was neglected. The new strategy allows increasing the capability of model discrimination, simultaneously leading to improved parameter estimates. Heine *et al.* (2008) proposed a novel derivative-free MBDoE approach for the calculation of the planned experiment's information content. The authors found that the new approach yields the same result as the calculation with the FIM if the mathematical model is linear in the model parameters.

Advanced MBDoE techniques have been recently formulated to modify, reduce or transform the candidate model in order to facilitate the MBDoE identification procedure. Incremental identification techniques (Bardow and Marquardt, 2004; Bardow *et al.*, 2005; Brendel *et al.*, 2006) are particularly suitable for kinetic model identification and allow decomposing the whole identification problem into a set of minor sub-problems. Each sub-problem is focused on the evaluation of a specific set of variables (including reaction fluxes, reaction stochiometry, reaction rates and kinetic laws). One drawback of the methodology is that it requires an adequate amount of data to overcome the bias predictions between distinct submodels. A problem decomposition approach to model identification was also followed by Rollins and Larson (2006). The authors adopted a block oriented modeling (BOM) approach to build a "gray-box" model from data coming from a highly nonlinear complex model of the human thermoregulatory (HT) system. The BOM identification method is able to predict HT response and is suitable for managing physically interpretable model structures and coefficients, and thus providing a precious support for both model discrimination and parameter identification. Chen and Wang (2004) proposed a sequential MBDoE strategy based on hybrid function approximations where the simulated profiles of a batch reactors are converted into a set of function coefficients covering the whole design space. Here an optimal search strategy is carried out and coupled with an uncertainty analysis. The authors call their approach "non model based experimental design" because the deterministic model is basically approximated by a class of stochastic functions. Sjöblom and Creaser (2008) proposed a PCA model, built from a sensitivity analysis of a first principle model, for experimental screening and microkinetic modeling. The new technique is particularly suitable when the number of model parameters is very large, allowing for the reduction of the size of the uncertainty space

investigated by design. The authors stressed out the computational benefits of adopting a Jacobian based design instead of the usual design, based on the maximisation of the information matrix. Schwaab et al. (2008a, 2008b) discussed the problem of eliminating the degree of correlation among parameters by considering different parameterisations of the initial dynamic model. The authors propose a two-step parameter estimation procedure in order to minimize both parameter correlations and relative errors through a proper manipulation of the reference temperatures in reaction kinetics problems.

Several works investigated the possibility to change or modify the topology of the design procedure. When multiple equipments are available Galvanin *et al.* (2007) noticed that designing and performing the experiments in a parallel way may be beneficial in terms of time, resources utilisation and amount of acquired information. To this purpose, several design topologies (parallel, sequential-parallel) are compared with the standard sequential approach and critically discussed. The authors proposed a modified design criteria (SV-optimal), particularly suitable for parallel experiment design, based on the singular values decomposition of the variance-covariance matrix of model parameters. Adaptive input design studies have been proposed (Lindquist and Hjalmarsson, 2001), where the information is exploited as soon as it is generated from the experiment to update the manipulated input variables. Stigter *et al.* (2006) proposed a first example of optimal adaptive input design, where the optimisation of dynamic inputs is carried out "online", and the information is exploited to improve the model as soon as it is generated by the experiment. In the study only the manipulated inputs are taken into account, ignoring the possibility to determine by design the optimal allocation of sampling points and the optimal values of time invariant inputs.

1.4.3 Development of robust optimisation algorithms for MBDoE

From the algorithmic point of view, a MBDoE evaluation requires two basic computational elements to be carried out:

- a DAEs integrator for the solution of the system of differential and algebraic equations;
- an optimiser for the solution of the optimal nonlinear programming problem.

These two elements are entirely involved in the numerical solution of the MBDoE problem. For this reason the computational effort required by MBDoE techniques can be significant, expecially when complex models (defined by a large number of states and parameters) are involved in the optimisation framework. Throughout the years, research efforts were dedicated to improve the efficiency of the algorithms and tools for the numerical solution of the design optimisation problem. The key issues regarding the development of a stable and robust algorithm for MBDoE are basically:

1. the numerical treatment of discontinuities affecting both the design objective function and the manipulated dynamic profiles;
2. improvements on the optimisation strategy (local optima are always present);

3. increment of the computational speed.

Throughout the years process modelling environments and numerical software have been proposed and developed to solve optimal design problems. While black box DOE can be easily implemented by anyone using commercial packages with an user friendly interface (Minitab, 2000), MBDoE can be carried out only by using some specific software. To the writer's best knowledge, MBDoE calculations involving dynamic nonlinear differential systems can be carried out by using the gPROMS® modelling environment (PSE, 2004), suitable for multi-purpose optimisations, VPLAN® (Körkel *et al*., 2002), or the more recent EFCOSS (Bischof *et al.*, 2003). A key feature of software for MBDoE is the interface to different optimisation and DAEs integration algorithms.

The development of the gPROMS® software followed some recent advancements on both the hardware technology and the formulation of dynamic optimisation algorithms suitable for the implementation. Several contributions have been essential for the development of a dedicated MBDoE solver within the gPROMS® modelling environment. First of all, the study by Vassiliadis *et al.* (1994), who analysed a class of constrained dynamic optimisation problems involving DAE systems. Here a control vector parametrization (CVP) approach was used to convert the above problem to a finite dimensional NLP problem. In the study a dedicated DAEs solver (DASOLV; Jarvis and Pantelides, 1992), particularly suitable for treating discontinuities, was coupled with the SRQPD code developed by Chen *et al.* (1989). The same optimisation approach, adopting multistage sensitivity evaluation, was successfully adopted in a widespread number of MBDoE applications. Keeping and Pantelides (1995) showed a significant speed-up over the single processor-based calculations using parallelisation of the sensitivity evaluations for mixed systems of DAEs. Further improvements on the stability of algorithms for sensitivities evaluation were carried out by Vassiliadis *et al.* (1999), who demonstrated its effectiveness by analysing standard optimal control problems of chemical engineering.

A new software capable of solving large-scale optimisation problems (EFCOSS) has been recently developed by Bischof *et al.* (2003). The modular structure of EFCOSS allows easy extension to user-defined objective functions (hence addressing advanced MBDoE problems) and has been succesfully tested by Rasch *et al*. (2009) to solve the problem of optimal design of diffusion experiments in liquids as previously studied by Bardow *et al.* (2005).

As underlined by Banga and Seider (1996) the NLPs arising from CVP application for solving MBDoE optimisation are usually multimodal. Therefore, deterministic gradient-based local optimisation techniques may converge to local minima. Global optimality cannot be guaranteed, but in many practical cases a stochastic optimisation approach (Banga *et al.*, 2005) can provide an efficient solution in a reasonable time. The studies of Bauer *et al.* (1999) presented a specific sequential procedure for optimal model-based experimental design for chemical processes discussing the optimization problem and the sequential quadratic

programming (SQP) method used for the numerical solution. The benefits of adopting such an approach are demonstrated by an example represented by a stiff set of equations describing the reaction of urethane. Multiple shooting optimisation techniques (Bock et al., 2003) can provide substantial benefit to the robustness of a constrained optimal control problem. With those techniques the infinite dimensional optimisation problem is reduced to a finite dimensional problem where the control vector is approximated on every subinterval of a suitably chosen mesh. In a following study, Leineweber *et al.* (2003) developed an improved optimisation procedure through a simultaneous solution strategy based on multiple shooting and reduced SQP. Rustem *et al.* (2003) proposed a semi-infinite programming algorithm to solve the global optimisation design and the feasibility problem (i.e. constraints satisfaction) in parallel, with great benefits in terms of computational time saving; in this case the robust constrained MBDoE problem was solved with only constraints on the design variables. Schwaab *et al.* (2008) proposed a hybrid optimisation framework exploiting a stochastic search algorithm (particle swarm optimisation) for solving nonlinear optimisation problems arising from parameter estimation and MBDoE. Recently, theoretical and algorithmic advances on the field of deterministic global optimisation (Floudas and Pardalos, 2003) for several classes of mathematical problems demonstrates a clear evolution and new possibilities to solve previously intractable problems arising from diverse scientific areas.

1.5 Observability and identifiability of nonlinear parametric models

When analysing a MIMO system, some questions arise about

1. the possibility to move the state of the system from an initial state to a final state manipulating the inputs in a finite time interval;
2. the possibility to identify the current state of the system (once $\mathbf{u}(t)$ and $\mathbf{w}$ are fixed and known) by using only the outputs.

These dual aspects deal with the properties of *controllability* and *observability* of the system, respectively. The first aspect is crucial to ensure the applicability and the feasibility of design, and is the expected answer to the question of whether is possible to excite the system in order to obtain a desired trajectory or not. The second aspect is crucial for model identification. If a system is observable, and its states can be uniquely defined by a finite set of meaningful parameters, the problem is to achieve a statistically meaningful estimate of these parameters. Once a candidate model is considered, a critical aspect to address is the one of *parametric identifiability*. The goal of every model building strategy is to tailor the model to the specificity of the phenomena being studied, and a fundamental problem is to investigate whether unknown parameters in a given model structure can be *uniquely* recovered from experimental data. The concept of identifiability can be introduced in several ways and several identifiability definitions have been proposed in literature. First of all, as devised by

Davidescu and Jørgensen (2009), a fundamental distinction has to be done between *a priori identifiability* (or structural identifiability testing) and *a posteriori identifiability* (based on collected experimental information).

A priori identifiability (Bellman and Ästrom, 1970; Lecourtier and Walter, 1981) aims at verifying if, under ideal conditions of noise-free observations and absence of external disturbances, the unknown parameters of a postulated model can be estimated from a designed MIMO experiment. Let us consider a generic multiple-input-multiple-output (MIMO) system that can be described by a nonlinear parametric model with a given structure $M(\boldsymbol{\theta})$:

$$M\left(\boldsymbol{\theta}\right):\begin{cases} f\left(\dot{\mathbf{x}}\left(t\right),\mathbf{x}\left(t\right),\mathbf{u}\left(t\right),\mathbf{w},\boldsymbol{\theta}\right)=0 \\ \hat{\mathbf{y}}=g\left(\mathbf{x}\left(t\right)\right) \end{cases} \tag{1.3}$$

where $\boldsymbol{\theta}\in\Re^{N_\theta}$ is the set of unknown parameters to be estimated, $\mathbf{x}(t)\in\Re^{N_s}$ is the vector of time-dependent state variables, $\mathbf{u}(t)\in\Re^{N_u}$ and $\mathbf{w}\in\Re^{N_w}$ are, respectively, the time-dependent and time-invariant control variables (manipulated inputs), $\hat{\mathbf{y}}\in\Re^{M}$ is the vector of output responses predicted by the model and t is the time. A definition for *a priori* structural identifiability is given in the following lines.

Definition (Structural Identifiability): if the equality of the model inputs ($\mathbf{u}(t)$ and $\mathbf{w}$) and outputs ($\hat{\mathbf{y}}$) for two distinct set of parameters $\boldsymbol{\theta}$ and $\boldsymbol{\theta}^*$ is denoted by $M\left(\boldsymbol{\theta}\right)\approx M\left(\boldsymbol{\theta}^*\right)$, the parameter $\theta_i\in\boldsymbol{\theta}$ is *a priori* structurally globally identifiable (SGI) if for almost any $\boldsymbol{\theta}^*$

$$M\left(\boldsymbol{\theta}\right)\approx M\left(\boldsymbol{\theta}^*\right)\Rightarrow\theta_i=\theta_i^* \tag{1.4}$$

and it is structurally locally identifiable (SLI) if, for almost any $\boldsymbol{\theta}^*$, there exists a neighbourhood $v(\boldsymbol{\theta}^*)$ such that (4) is still verified (Lecourtier and Walter, 1981).

Local identifiability is a necessary condition for global identifiability, and a model is said to be SGI if (4) is verified for the entire parametric set. A parameter that is not SLI is structurally nonidentifiable (SNI) and a model is said to be SNI if any of its parameters is SNI. To test the identifiability of non linear parametric models, a local study may be misleading while a global identifiability test should be carried out. A method testing the global identifiability is the one proposed by Pohnjanpalo (1978), basing on the analysis of the series expansion of the output function, evaluated at time $t = 0$. A infinite set of equation is built called “exhaustive summary”

$$\frac{\mathrm{d}^k \hat{\mathbf{y}}}{\mathrm{d}t^k} = \alpha_k \left(t_0 \right) \qquad k = 0, 1, 2 \ldots \quad , \tag{1.5}$$

where the α_k are observational parameters given by the coefficients of the powers series of the output function. Identifiability is assessed by determining the number of solutions for the given parametric set (Walter and Pronzato, 1996). An interesting feature of this identifiability test is given by the fact that the exhaustive summary allows devising alternative parameterisations in order to preserve the model identifiability.

When the model is nonidentifiable, the identifiability analysis can be a very difficult task because the infinite set of equations of the exhaustive summary should be solved. The only way to tackle the problem is to find a finite set of equations containing all the information of the exhaustive summary. Ljung and Glad (1994) proposed a method and an explicit algorithm based on differential algebra, demonstrating how the testing of global structural identifiability can be reduced to the question of whether the given model structure can be rearranged as a linear regression. The authors also analysed the condition of "persistent excitation" for the input, that can be tested explicitly in a similar fashion, basically showing how identifiability and experiment design are highly correlated tasks. A new improved differential algebra algorithm based on the Buchberger algorithm (Buchberger, 1988) was proposed by Saccomani *et al.* (1997) where the differential ring $R(\boldsymbol{\theta})[\mathbf{x}, \hat{\mathbf{y}}, \mathbf{u}, \mathbf{w}]$ is chosen instead of the $R[\mathbf{x}, \hat{\mathbf{y}}, \mathbf{u}, \mathbf{w}, \boldsymbol{\theta}]$ differential ring chosen by Ljung and Glad (1994). In this way, once the characteristic set is obtained, their coefficients are polynomials in $\boldsymbol{\theta}$, allowing for a significant reduction in the number of variables needed for the evaluation of the exhaustive summary of the model, thus making the whole algorithm more robust and computationally efficient. Bellu *et al.* (2005) also developed a specific software tool (named DAISY) to test global identifiability of biological and physiological systems. As discussed by Saccomani *et al.* (1997) *a-priori* identifiability is a necessary condition (not sufficient) to guarantee successful parameter estimation from real data (*a-posteriori* identifiability) and, for structurally complex and large non linear dynamic models, the *a-priori* identifiability testing could become an almost impossible task because of the computational complexity.

Global and local sensitivity analysis are widely used tools to assess the *a-posteriori* identifiability of large non linear dynamic models (Brun *et al.*, 2002; Kontoravdi *et al.*, 2005). Asprey and Macchietto (2000) proposed an optimisation-based approach to test identifiability where the distance Φ^I between two parameter vectors $\boldsymbol{\theta}$ and $\boldsymbol{\theta}^*$ providing the same model output is maximised:

$$\Phi^I = \max_{\boldsymbol{\theta}, \boldsymbol{\theta}^* \in \Re^{N\theta}} \left(\boldsymbol{\theta} - \boldsymbol{\theta}^* \right)^T \mathbf{W} \left(\boldsymbol{\theta} - \boldsymbol{\theta}^* \right) \tag{1.6}$$

where **W** is a $N_\theta \times N_\theta$ weighting matrix. If this distance is arbitrarily small the model can be deemed globally identifiable. The optimisation algorithm can be constrained defining a validity domain for model parameters. Sidoli *et al.* (2005) developed a "perturbation algorithm" coupling the previously mentioned optimisation-based approach to test identifiability with a multi-local sensitivity analysis. The algorithm was successfully tested on a large-scale, dynamic, and highly non linear biological process model consisting of 27 inputs, 32 outputs, and more than 350 parameters.

Söderström and Stoica (1979) observed that the concept of model identifiability does not refer only to an intrinsic property of the model structure, but also to the identification procedure and the experimental conditions. The quality of the chosen parameter estimator (least squares, maximum likelihood, Bayesian estimator) may play a crucial role on estimating the model parameters from the data with acceptable statistical precision. Moreover, the information content of the experimental runs can by enriched by adding more measured variables to increase the observability of the system, and the input design can be carried out by adopting black box DoE or MBDoE techniques.

As discussed by Hochwald and Nehorai (1997), there is an important relationship between regularity of the FIM, usually adopted to evaluate the expected information, and the identifiability of parametric models. For linear models this relationship is explicitly defined by the Rothenberg theorem, stating that, under some preliminary assumptions, a parameter θ is locally identifiable if (and only if) the Fisher information matrix calculated at θ is not singular. This significant result can be extended to non linear dynamic models once a local approximation of the dynamic behaviour is provided. This aspect will be discussed in detail in Chapter 2.

To briefly summarise, the main advantage of assessing *a-priori* structural identifiability adopting differential algebra or series expansion methods is that they provide a global identifiability test. The main drawback is that these methods are computationally expensive. On the other hand, *a-posteriory* identifiability can be assessed by methods based on sensitivity analysis and perturbation study that tend to be more applicable, even if they require a considerable computational effort if large systems are considered.

1.6 Identifying physiological models: the need for MBDoE

What characterises physiology is *complexity* (Carson and Cobelli, 2001). Complexity usually refers to the fact that the elements of the physiological system (at the level of molecule, cell, organ and organism) are firmly interlinked following hierarchic schemes and are affected by nonlinear, stochastic and time-varying effects. Complexity also arises when observing within an organism several control mechanisms (for example feedback loops) that are carried out without an (apparent) direct response of a change in physiological variables.

Other peculiar features of a physiological system are:

1. *poor observability*: it is often very difficult to measure directly (in vivo) the quantities of interest and only indirect measures are available (implying the need to infer the value of the quantity of interest by using a specific model);
2. *poor controllability*: it is notoriously difficult for the clinician to reach a tight control of a physiological system, where severe constraints are imposed to keep the safety and the functional behaviour of the system itself.

Physiological models have been proposed in physiology and medicine studies to analyse and represent the behaviour of organs and metabolic systems. Being a representation of a complex reality, these mathematical models involve some degree of approximation. As a result, these models exhibit a structural complexity in the form of mathematical expressions, and usually contain a large number of parameters. The risk of over-parameterisation (i.e. the model is built by using too many unknown parameters) is always present, and usually leads to the unidentifiability of the candidate model (as described in the previous paragraph). A crucial issue for the use of a physiological model is the identification of model parameters for individual subjects. This may be a very challenging task, particularly for detailed physiological models, where identifying individual subject parameters from limited data may be extremely difficult. Advanced MBDoE techniques can provide a solution to tackle the identifiability issue of detailed physiological models. From a modelling point of view, this issue is very similar to the one that is faced by process engineers when they need to estimate the parameters of complex dynamic models by carrying out dynamic experiments in a chemical or biochemical process system. The problem of properly designing an identification test can be formulated as an optimal control problem, where the experiment decision variables are (for example) time varying and time invariant inputs, sampling times of response variables, experiment initial conditions and duration. This leads to an optimal MBDoE problem for parameter identification in a dynamic system where constraints are present both in the inputs (manipulated quantities) and in the outputs (measured responses). The existence of constraints on the system is related to the fact that the test must be safe for the subject but sufficiently short and easy to carry out.

Let us take a physiological model of type 1 diabetes mellitus as an example. MBDoE techniques can be adopted to optimally design an “experiment” (or a series of experiments) on a diabetic subject in order to develop an improved set of clinical tests from which the parameters of a dynamic model can be estimated with a higher degree of precision than it has been possible so far. Modified test protocols can be specifically designed to tailor a model to each individual patient, maximising the amount of information acquired from the tests and thus providing a valid alternative to the commonly adopted identification tests.

It must be stressed out the importance of the availability of a physiological model tailored to an individual subject. The model, thus identified, can provide substantial benefits both to the

clinician (who could devise customised care solutions for the subject) and to the engineer (who could design and test specifically tailored conventional and/or advanced control techniques).

1.7 Thesis overview

If the goal of every experimental activity is to learn and understand the underlying phenomena in a controlled environment, the goal of every model building activity is to achieve a substantially adequate model to be used for process design, analysis, control and optimisation. A systematic model based procedure for model building has been proposed by Asprey and Macchietto (2000) to support the development and statistical verification of dynamic process models for both linear and nonlinear dynamic systems described by DAEs (Figure 1.5).

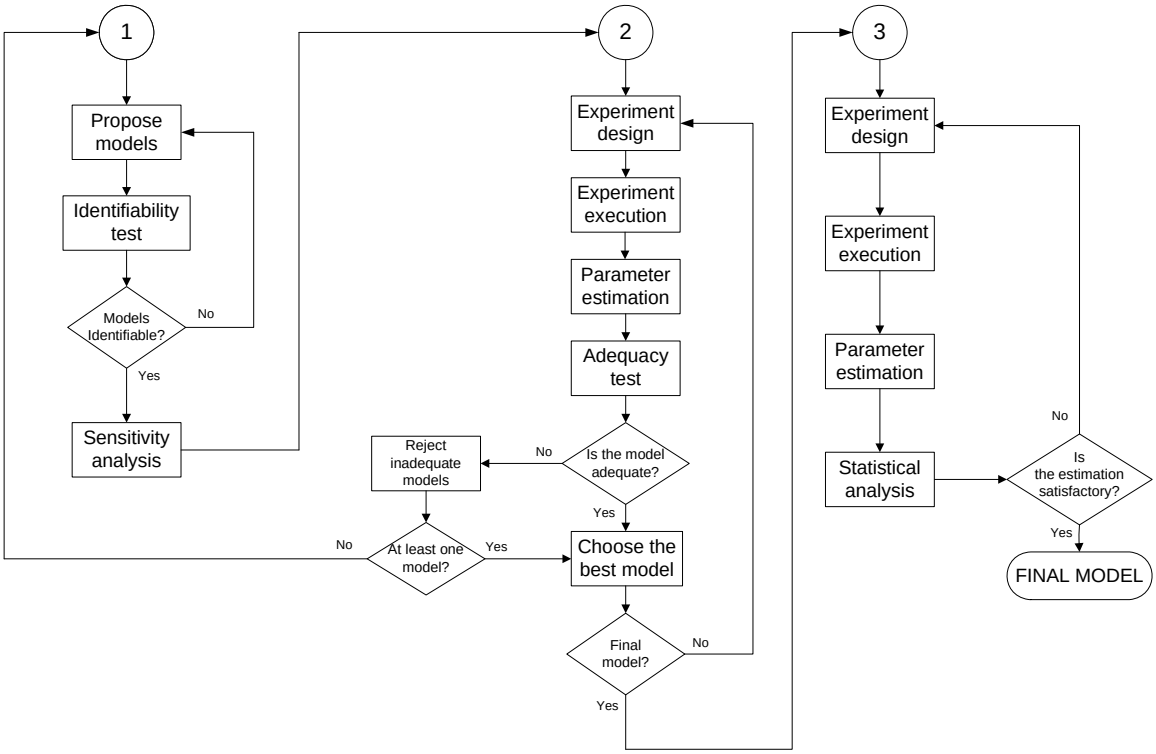


Figure 1.5 *Model building strategy (based on the scheme reported in Asprey and Macchietto (2000)).*

The procedure is articulated into three phases:

1. preliminary analysis, including identifiability testing on candidate models;
2. model-based design of experiments to discriminate among rival models;
3. model-based design of experiments for improving parameter estimation.

In the preliminary analysis candidate models are proposed and analysed. In particular, an identifiability test is carried out to check whether is possible to uniquely estimate the set of

model parameters from experimental data. In the second phase experiments are designed and performed to discriminate among possible rival models. Inadequate models are rejected (usually basing on lack-of-fit tests) and the best model is chosen as the ultimate model to complete the identification procedure in the final phase, where experiments are designed to improve the parameter estimation until a statistically sound parameter estimation is achieved. This Thesis is focused on the first and third phases of the model building procedure, where identifiability analysis is carried out and advanced MBDoE techniques are specifically developed for improving the parameter estimation and the identifiability of the model. In this study it is assumed that no design for model discrimination is required and that the selected model is an appropriate representation of the phenomenon. However, the impact of both structural model mismatch and parametric mismatch on the effectiveness of design will be investigated and discussed. Note from the general model building flowchart of Figure 4 that the identifiability attribute is a necessary condition for any MBDoE strategy in order to carry out both model discrimination and parameter estimation. The importance of the preliminary model analysis must not be underestimated, since both identifiability issues and structural inadequacy of the model may affect the effectiveness of the whole MBDoE procedure.

A basic roadmap to this Thesis is shown in Figure 1.6. Chapter 2 overviews the mathematical background of MBDoE methodologies and the principal techniques for parameter estimation. In particular the mathematical modeling of the key activities involved in the design procedure (experiment design, experiment execution with data acquisition, parameter estimation) will be illustrated in a comprehensive manner. Particular attention will be drawn on the mathematical description of the following novel MBDoE techniques:

1. online model-based redesign of experiments (OMBRE);
2. backoff strategy for MBDoE under parametric uncertainty;
3. MBDoE strategy for systems where continuous measurements are available.

Chapter 3 illustrates the applications of the novel OMBRE technique. This advanced MBDoE technique is capable of exploiting the information as soon as it is generated from the experiments, performing one or more redesign while the experiment is still running. The effectiveness of this design technique on estimating the parameters of nonlinear dynamic models will be discussed and assessed by means of two examples: a biological process (biomass fermentation in a fed-batch reactor) and a chemical process (synthesis of urethane). Chapter 4 presents a novel backoff strategy for MBDoE under parametric uncertainty. This advanced MBDoE technique allows to take into account parametric uncertainty, as well as external disturbances, in the design procedure. The purpose is dual: *i*) preserving the optimality of design (i.e., the maximisation of information); *ii*) ensuring the feasibility of the planned experiment (i.e., the satisfaction of the superimposed constraints). The novel design strategy is applied to two distinct case studies related to physiological models identification: a

basic model for studying the optimal insulin infusion rate for subjects affected by type 1 diabetes mellitus and a model for finding the optimal chemotherapeutic drugs administration for cancer treatment.

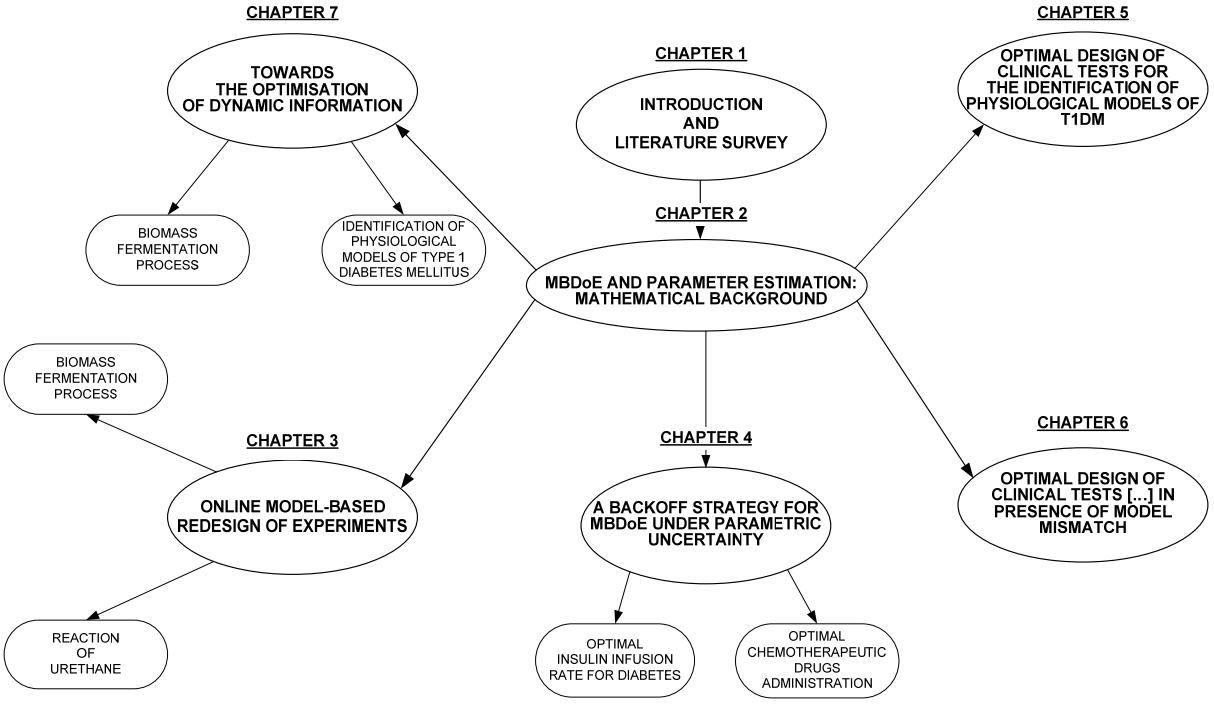


Figure 1.6 *Thesis roadmap.*

Chapter 5 faces the problem of designing optimally informative clinical tests for the identification of physiological models of type 1 diabetes mellitus. The effectiveness of adopting MBDoE strategies for designing modified test protocols is demonstrated by analysing a complex model of glucose homeostasis. Chapter 6 shows how the problem of parameter identification of complex models of type 1 diabetes can be succesfully tackled, by using advanced MBDoE techniques, even when a structural mismatch between the identification model and the subject is present. In particular, the benefits coming from the integration of OMBRE and backoff based design techniques will be discussed. Chapter 7 focuses on the possibility to optimise the dynamic information adopting MBDoE techniques. In particular, it is shown how it can be possible to tailor the design strategy to the specificity of the measurement system. Here a new MBDoE methodology, suitable when continuous measurements are available, will be proposed. In the chapter, similarities between OMBRE and model-based predictive control strategies will be underlined and novel directions for future research on MBDoE will be outlined. Some final remarks will conclude the Thesis.

Chapter 2

MBDoE for parameter estimation: mathematical background

In a standard MBDoE procedure a sequence of three key activities (design of the experiment, experiment execution, parameter estimation) must be carried out to estimate the set of parameters of a dynamic model. The scope of this Chapter is to overview the mathematical and statistical background required to understand in a comprehensive way the basic features of the MBDoE procedure for parameter estimation, where each key activity is characterised by a precise mathematical formulation.

2.1 Model-based experimental design framework

As briefly anticipated in §1.4.2, three key activities are required by a standard MBDoE procedure to design an experiment for parameter identification (Figure 2.1):

1. the design of the experiment, based on the preliminary knowledge about the system;
2. the execution of the experiment (at the experimental conditions planned by design);
3. the estimation of the model parameters.

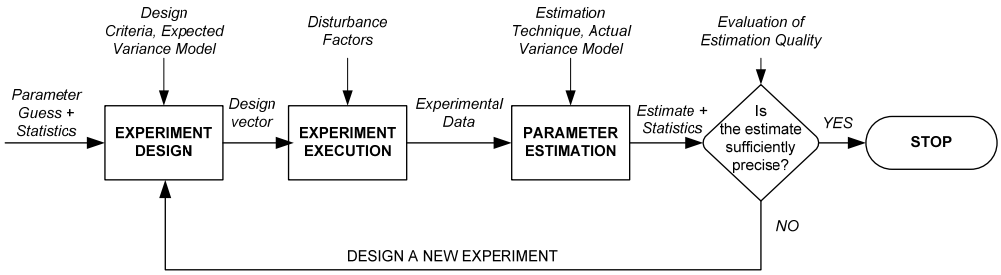


Figure 2.1 *MBDoE for parameter estimation: standard procedure.*

In the design of experiment activity, a representation of information as predicted by the model is required to perform an optimisation by acting on the experimental settings. Preliminary information on the set of model parameters, or information coming from already performed experiments, can be included in the design activity. Some preliminary hypothesis on the distribution and entity of measurement errors must be made, at least at the very beginning of the procedure, if no information on the measurement system is available. It is possible to

decrease the expected uncertainty region of model parameters only by maximising a measure of the information predicted by the model, usually known as the "expected information". The result of the optimisation run will be a set of dynamic profiles on manipulated inputs and sampling scheduling that will be adopted in the successive key activity, the experiment execution. Together with the optimal settings, a set of *a-priori* statistics will be evaluated from the estimation of the expected information (i.e. the prediction of the model of the information that will be gathered from the experimental data).

The experiment is the core of the entire design procedure, and represents the fundamental source of information coming from the physical system for model identification and validation. Information comes from experimental data collected during the experiment performed at the planned conditions[1]. The measured responses represent a local behaviour of the physical system (i.e., the behaviour of the system for the given set of experimental conditions), which is suitable for estimating precisely the set of parameters of the dynamic model. A particular attention should be made during the experimental activity to reduce and/or cancel any form of disturbance that cannot be directly controlled by the experimenter, because this would lead to a loss of information during the experiment.

The parameter estimation activity may be erroneously seen as a mere mechanical subroutine where the input is the data collected by the experiment and the output is a number representing the estimate, but that would be misleading. Parameter estimation is a mathematical procedure where useful information is extracted from experimental data, and the choice of a different estimation technique (i.e., of the mathematical form of the estimator mapping from the space of the observations to the space of the model parameters) may have a dramatic impact on both the precision of the final estimate and the model prediction of the physical system behaviour. An effective estimator should be able to discriminate between the intrinsic information contained within the experimental data and all the disturbances and measurements error that could mask some relevant dynamics of the experiment. The intrinsic information of the data as extracted by the parameter estimation activity represents the "actual information", i.e. the true information provided by the experiment which is directly used for improving parameter estimation.

If the experiments are sufficiently informative, the iterative execution of the three key activities in sequence will lead to a progressive reduction of the uncertainty region of model parameters. In the MBDoE procedure the goal providing the "stopping rule" for the iterative procedure can be: *i*) the attainment of a desired level of precision on parameter estimation; *ii*) the attainment of a desired model accuracy; *iii*) the attainment of the maximum experimental

[1] It must be pointed out that information, in the form of collected samples, is not an intrinsic feature of the series of collected data itself, but is strictly related to the goal of investigation. Experiments should be planned by MBDoE techniques for improving parameter estimation, to accept/reject a given model structure or to discriminate among rival models, and the mathematical formulation of the design of the experiment needs to be managed accordingly.

budget. Note that a critical factor is the assessment of MBDoE effectiveness, usually based on the statistical evaluation of the following factors:

1. the ability of the model to fit the measures responses;
2. the parameter estimation in terms of accuracy (i.e. asymptotic convergence to a constant value, representing the "true" vector of model parameters which is obviously unknown);
3. the parameter estimation in terms of precision (i.e. confidence of the estimate, related to the variance-covariance of model parameters).

The availability of a model is crucial for both predicting the information content of the trials and extracting useful information from collected data. A key-feature of the MBDoE design methodology is the fact that the experiment design key activity is model-based. In the following, we will refer to the model, whose parameters need to be estimated with the maximum degree of precision as the "identification model". As anticipated in §1.5, a large class of dynamic deterministic models can be represented by systems of differential and algebraic equations (DAEs):

$$\begin{cases} \mathbf{f}(\dot{\mathbf{x}}(t), \mathbf{x}(t), \mathbf{u}(t), \mathbf{w}, \hat{\boldsymbol{\theta}}, t) = 0 \\ \hat{\mathbf{y}}(t) = \mathbf{h}(\mathbf{x}(t)) \end{cases} \tag{2.1}$$

where $\boldsymbol{\theta} \in \Re^{N_\theta}$ is the set of unknown parameters to be estimated, $\mathbf{x}(t) \in \Re^{N_x}$ is the vector of time-dependent state variables, $\mathbf{u}(t) \in \Re^{N_u}$ and $\mathbf{w} \in \Re^{N_w}$ are, respectively, the time-dependent and time-invariant control variables (manipulated inputs), $\hat{\mathbf{y}} \in \Re^{N_y}$ is the vector of output responses predicted by the model and t is the time. A set of initial conditions (i.e. conditions of the state variables at $t = t_0$) is required to solve the system:

$$\begin{cases} \mathbf{f}(\dot{\mathbf{x}}(t_0), \mathbf{x}(t_0), \mathbf{u}(t_0), \mathbf{w}, \hat{\boldsymbol{\theta}}, t_0) = 0 \\ \hat{\mathbf{y}}(t_0) = \mathbf{h}(\mathbf{x}(t_0)) \end{cases} \tag{2.2}$$

The simulation of the physical system along a given experimental horizon requires the solution of the (2.1) system in terms of trajectories $\mathbf{x}(t)$ and $\hat{\mathbf{y}}(t)$ given the initial conditions (2.2), the time-invariant inputs $\mathbf{w}$, the profiles of manipulated inputs $\mathbf{u}(t)$ and the values of model parameters in $\boldsymbol{\theta}$.

Some preliminary hypothese have to be made on the model and the physical system. In fact, the whole identification procedure can be carried out if and only if:

- the identification model is an adequate representation of the system (i.e. no model discrimination step is required beforehand);
- the parameters of the identification model can uniquely be estimated from experimental data (i.e., the model is SGI, see §1.5).

Furthermore, here it is assumed that the physical system can be controlled in a perfect way (i.e. that during the experiment execution it is possible to manipulate the input variables exactly as predicted during the experiment design key activity).

2.2 Key activity 1: experiment design

A fundamental point in the design of experiment theory is the evaluation of expected information, i.e. the information foreseen by the identification model. The importance of the mathematical formulation of the expected information cannot be overestimated, because the result of the experimental design optimisation is a set of experimental settings aiming at maximising a particular measure of it.

2.2.1 Evaluation of the expected information: Fisher information

Information can be usefully evaluated from the Fisher information matrix (FIM). It is well known in literature (Soderstrom and Stoica, 1977) that the FIM $\mathbf{I}(\boldsymbol{\theta})$ is a way of measuring the amount of information that an observable random variable y carries about an unknown parameter vector $\boldsymbol{\theta}$

$$\mathbf{I}(\boldsymbol{\theta}) = \left[E\left(\frac{\partial \log p(y,\boldsymbol{\theta})}{\partial \theta_i} \frac{\partial \log p(y,\boldsymbol{\theta})}{\partial \theta_j} \right) \right]_{i,j=1\ldots N_\theta}, \tag{2.3}$$

where the likelihood function of $\boldsymbol{\theta}$, $L(\boldsymbol{\theta}) = p(y,\boldsymbol{\theta})$, has to be defined. The likelihood function describes the joint probability of the samples conditional to the value of $\boldsymbol{\theta}$. In this equation E denotes the expectation operator and $\mathbf{I}$, which is always a semi-positive definite matrix, is evaluated at a fixed value $\boldsymbol{\theta}$ of model parameters. It is possible to define the N_θ-dimensional vector of sensitivities for $p(y,\boldsymbol{\theta})$:

$$\mathbf{z}_\theta = \left. \frac{\partial \log p(y,\boldsymbol{\theta})}{\partial \theta_i} \right|_{i=1\ldots N_\theta}, \tag{2.4}$$

and it results $\mathbf{I}(\boldsymbol{\theta}) = E\mathbf{z}_\theta \mathbf{z}_\theta^T \geq 0$. The FIM represents the variance of the sensitivities $\mathbf{z}_\theta$, which is the relevant information that can be obtained from the model by exciting the system at some specific experimental conditions. Note that (2.3) is a general expression where the information evaluation is not explicitly related to a specific probability density function used to define the likelihood. For a single-input-single-output (SISO) system, if $p(y,\boldsymbol{\theta})$ comes from a multivariate normal distribution, the FIM can be written as

$$\mathbf{I}(\boldsymbol{\theta}) = \left[\frac{1}{\sigma_y^2} \frac{\partial y}{\partial \theta_i}^T \frac{\partial y}{\partial \theta_j} \right]_{i,j=1\ldots N_\theta} \quad , \tag{2.5}$$

where σ_y^2 is the variance of y. For multi-input-multi-output (MIMO) dynamic systems the FIM expression can be written as

$$\mathbf{I}(\boldsymbol{\theta}, t) = \left[\mathbf{Q}'^T(t) \boldsymbol{\Sigma}^{-1} \mathbf{Q}'(t) \right] \quad , \tag{2.6}$$

where $\mathbf{Q}'$ is the $N_y \times N_\theta$ dynamic sensitivity matrix, whose elements are expressed by

$$q'_{ij} = \frac{\partial y_i}{\partial \theta_j} \qquad i = 1\ldots N_y,\ j = 1\ldots N_\theta \tag{2.7}$$

and $\boldsymbol{\Sigma}$ is the $N_y \times N_y$ dimensional matrix of measurements errors. Note that equations (2.3-2.7) are evaluated at given values of the manipulated inputs, and that a norm (for instance Euclidean or Frobenius norm) or a measurement function ψ of $\mathbf{I}(\boldsymbol{\theta}, t)$ represents a dynamic form of the FIM, and thus can be useful to define a time-dependent profile of the expected information (see §2.5).

2.2.2 Design vector and dynamic information matrix

It is useful to group all the experiment design variables defining the experimental settings (as represented in the identification model) in a single vector known as the *design vector* $\boldsymbol{\varphi} \in \Re^{n_\varphi}$:

$$\boldsymbol{\varphi} = \left\{ \mathbf{y}_0, \mathbf{u}(t), \mathbf{w}, \mathbf{t}^{sp}, \tau \right\} \quad . \tag{2.8}$$

In the expression (2.8) of the design vector:

- $\mathbf{y}_0$ is the set of initial conditions of the measured variables[2];
- $\mathbf{u}(t)$ is the set of time-dependent manipulated inputs;
- $\mathbf{w}$ is the set of time-invariant inputs;
- $\mathbf{t}^{sp} = \left[t_1 \quad \ldots \quad t_{n_{sp}} \right]^T$ is the vector of n_{sp} sampling times, defining the set of time instants at which the output variables are sampled;
- τ is the duration of an experiment.

[2] The initial conditions that can be designed are all and only those on the measurable set of variables; in principle, this may not be necessarily true (measurable initial conditions could refer to states that are not measurable during the experiment or, *vice-versa*, some measurable outputs might not be measured at the beginning). However, as this does not affect the generality of the approach, it was decided not to complicate the notation further.

Note that, interestingly, the optimal allocation of samples expressed by $\mathbf{t}^{sp}$ is a design variables itself, because the information contained within each single samples is entirely related to the dynamics of the system. The set of time-dependent manipulated inputs $\mathbf{u}(t)$ is usually approximated adopting control vector parameterisation techniques (Vassiliadis *et al.*, 1994). These profiles can be approximated by piecewise constant, piecewise linear, or polynomial functions over a predefined number of intervals. As an example, adopting a piecewise constant function for a time-dependent manipulated input, the variables that need to be optimised are

1. the $(n_{sw} - 1)$ times at which a given manipulated input changes in value (usually known as "switching times"); these time instants are collected in the $\mathbf{t}_{sw}$ vector of switching times, characteristic of each control variable;
2. the n_{sw} time invariant values (usually known as "switching levels") that the manipulated input assumes before and after each switching time; these values are collected in the $\mathbf{z}_{sw}$ vector of switching levels, characteristic for each control variable.

The variables to be optimised are grouped in the following design vector

$$\boldsymbol{\varphi} = \left\{ \mathbf{y}_0, \mathbf{z}_{sw,u_1}, ..., \mathbf{z}_{sw,u_{N_u}}, \mathbf{t}_{sw,u_1}, ..., \mathbf{t}_{sw,u_{N_u}}, \mathbf{w}, \mathbf{t}^{sp}, \tau \right\} \quad . \tag{2.9}$$

As can be recognised, a large-scale optimisation problem is obtained as the number of switching intervals grows.

In the hypothesis of validity of (2.6), Zullo (1991) proposed a discrete dynamic form for the FIM, particularly suitable for solving optimal design problems in dynamic systems where a discrete sampling of the measured variables is carried out. This *dynamic information matrix* $\mathbf{H}_\theta$ for a sequence of N experiments takes the form:

$$\mathbf{H}_\theta(\boldsymbol{\theta}, \boldsymbol{\varphi}) = \sum_{k=1}^{N} \sum_{i=1}^{N_y} \sum_{j=1}^{N_y} s_{ij|k} \mathbf{Q}_{i|k}^T \mathbf{Q}_{j|k} + \mathbf{H}_\theta^0 \quad , \tag{2.10}$$

where $\mathbf{Q}_{i|k}$ is the $n_{sp} \times N_\theta$ dynamic sensitivity matrix of the i-th measured response in the k-th experiment, whose elements (for the k-th experiment) are represented by

$$\mathbf{Q}_i = \left[\frac{\partial \hat{y}_{il}}{\partial \theta_m} \right] \qquad l = 1, ..., n_{sp} \qquad m = 1, ..., N_\theta \tag{2.11}$$

$s_{ij|k}$ is the ij-th element of the $N_y \times N_y$ inverse matrix of measurements error in the k-th experiment, and $\mathbf{H}_\theta^0$ is the prior dynamic information matrix, taking into account the statistical information about the parametric system before each trial is carried out. For instance, when the prior information can be expressed by simple bounds of variability for

model parameters, a N_θ-dimensional hyper-rectangular region of variability can be built assuming a uniform distribution for the model parameters. In that case, being

$$\mathbf{H}_\theta^0 = \left[\boldsymbol{\Sigma}_\theta\right]^{-1} \tag{2.12}$$

the preliminary dynamic information matrix, together with $\boldsymbol{\Sigma}_\theta$, the preliminary variance-covariance matrix of model parameters, assumes a diagonal form. If no preliminary information is available at all, the $\mathbf{H}_\theta^0$ term of (2.10) can be neglected.
The variance-covariance matrix of model parameters $\mathbf{V}_\theta$ is the inverse matrix of $\mathbf{H}_\theta$, and, for a single experiment, is expressed as:

$$\mathbf{V}_\theta\left(\boldsymbol{\theta},\boldsymbol{\varphi}\right) = \left[\boldsymbol{\Sigma}_\theta^{-1} + \mathbf{H}_\theta\left(\boldsymbol{\theta},\boldsymbol{\varphi}\right)\right]^{-1} = \left[\boldsymbol{\Sigma}_\theta^{-1} + \sum_{i=1}^{N_y}\sum_{j=1}^{N_y} s_{ij}\mathbf{Q}_i^T\mathbf{Q}_j\right]^{-1}. \tag{2.13}$$

The scope of the design procedure is to minimise some metric ψ of $\mathbf{V}_\theta$ by acting on the elements of the design vector (2.8). The different mathematical formulations of ψ define the design criteria and are discussed in the following Section.

2.2.3 Design criteria

The maximisation of the expected information predicted by the identification model is carried out by minimising a metric ψ of the variance-covariance matrix of model parameters by acting on the elements of the design vector:

$$\boldsymbol{\varphi}_{\mathrm{OPT}} = \arg\min\left\{\psi\left[\mathbf{V}_\theta\left(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi}\right)\right]\right\}. \tag{2.14}$$

During the optimisation, the set of model parameters is kept fixed at the current estimated value $\hat{\boldsymbol{\theta}}$. The most commonly used design criteria are the so called "alphabetic criteria" (Kiefer, 1959):

1. A-optimal: minimising the trace of $\mathbf{V}_\theta$, $\psi = tr\left(\mathbf{V}_\theta\right)$;
2. E-optimal: minimising the largest eigenvalue of $\mathbf{V}_\theta$, $\psi = \max_{k=1\ldots N_\theta} \lambda_k\left(\mathbf{V}_\theta\right)$;
3. D-optimal: minimising the determinant of $\mathbf{V}_\theta$, $\psi = \det\left(\mathbf{V}_\theta\right)$;

The geometrical interpretation of the alphabetic design criteria, with reference to a two parameters problem, is illustrated in Figure 2.2.

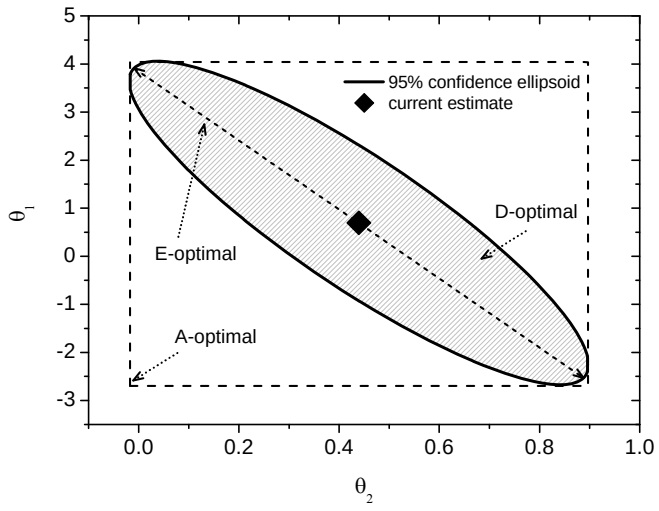


Figure 2.2 *Geometric interpretation of the alphabetic design criteria.*

Considering linear confidence regions, an A-optimal design aims at decreasing the hyper-rectangular enclosing the confidence ellipsoid, while a D-optimal design aims at decreasing the volume of the confidence ellipsoid. The maximum eigenvalue of the variance-covariance matrix of model parameters defines the major axis of the ellipsoid (related to the principal direction of variability of the ellipsoid) being minimised by the E-optimal design criterion. Note that, since $\mathbf{V}_\theta$ is a positive definite symmetrical matrix, these criteria are highly correlated (the determinant of $\mathbf{V}_\theta$ is the product of all its eigenvalues and the trace is the sum of the eigenvalues of $\mathbf{V}_\theta$). Whilst the E-optimal criterion acts on a single principal component of $\mathbf{V}_\theta$, the other two criteria aims at minimising a global measure of uncertainty. A modification of the E-optimal criterion was proposed by Mehra (1974)

$$\psi = \frac{\max\limits_{k=1\ldots N_\theta} \lambda_k\left(\mathbf{V}_\theta\right)}{\min\limits_{k=1\ldots N_\theta} \lambda_k\left(\mathbf{V}_\theta\right)} \quad , \tag{2.15}$$

where the ratio between the largest and the smallest eigenvalue of $\mathbf{V}_\theta$ (condition number) is minimised. This criterion acts on the shape of the uncertainty region (for a two parameters system $\psi = 1$ and the uncertainty region has a perfectly circular shape).

Alternative design criteria have been proposed in literature exploiting a singular value decomposition (SVD) of $\mathbf{V}_\theta$. Investigating different directions of variability through SVD it is possible to deliver a vector of experimental conditions producing information that is as different as possible (orthogonal) from the other ones. In mathematical terms, that means that the information content of matrix $\mathbf{H}_\theta$ is split into its singular values identified by its N_θ eigenvalues λ_i. The SV-optimal criterion (Galvanin *et al.*, 2007), particularly suitable for planning parallel experiments to be carried out, aims at maximising the information linked to

the N_λ largest singular values of $\mathbf{V}_\theta$. Thus, the overall optimisation problem is split into N_λ separate optimisation problems, where the k-th measure ψ_k is defined as:

$$\psi_k = \lambda_k(\mathbf{V}_\theta) \qquad k = 1,...,N_\lambda \le N_\theta \qquad \lambda_1 > \lambda_2 > ... > \lambda_N \quad . \tag{2.16}$$

In other words, it is possible to optimise the information within the largest N_λ eigenvalues, each requiring the solution of a distinct optimal design problem.

As illustrated in Figure 2.3, here SV-optimal design allows compressing the confidence ellipsoid of the parameters to be estimated by minimising its axes in a selective way. Although the relative size of the axes (i.e. the relative magnitude of the eigenvalues) does depend on the model being analysed, it is quite significantly affected by the variance-covariance matrix of the measurements $\mathbf{\Sigma}$. Large values of the matrix elements (i.e. measurement uncertainty) amplify the difference between the eigenvalues.

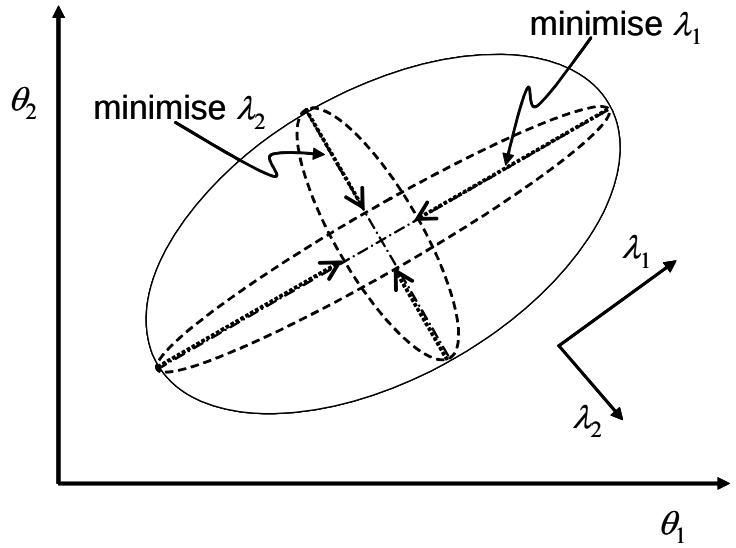


Figure 2.3 *Geometrical interpretation of SV-optimality.*

Zhang and Edgar (2008) introduced a design criterion (termed P-optimal) where a principal component analysis (PCA) of the dynamic information matrix allows to automatically choose the most informative directions of information to exploit during the design optimisation. As interestingly underlined by the authors, the P-optimal criterion can be usefully adopted both to decrease the dimension of the optimisation problem (a subset of the overall principal components can be used to describe the information) and to avoid ill-conditioning on $\mathbf{H}_\theta$. The singularity of the dynamic information matrix may arise:

1. from an over-parameterisation of the model (the model is described by a large number of parameters and some of them have a limited impact on the predictions of the measured responses, i.e. a low sensitivity);

2. from a high correlation between model parameters;
3. from an erroneous scaling of the sensitivities (2.13); usually the parameters of a model should be normalised in order to get a significant expression for $\mathbf{H}_\theta$;
4. when the design variables are not sufficient to excite the system and gain relevant information;
5. from structural unidentifiability of the model in the region investigated by the design procedure (in the design space the model is not SGI).

It is possible to evaluate the expected correlation among model parameters from $\mathbf{V}_\theta$ through the correlation matrix $\mathbf{C}_\theta$, whose elements (correlation coefficients) have the form:

$$c_{ij} = \frac{v_{ij}}{\sqrt{v_{ii}}\sqrt{v_{jj}}} \quad , \tag{2.17}$$

where the v_{ij}'s are the elements of the variance-covariance matrix $\mathbf{V}_\theta$ of model parameters. When the elements outside the principal diagonal are close to unity the model parameters are expected to be highly correlated, and the design could turn in practice to be unsuccessful, because correlation tends to decrease the expected information as provided by $\mathbf{H}_\theta$, and to restrict the capability of MBDoE on reducing the expected uncertainty region of model parameters. This may cause instability on the overall optimisation procedure and sub-optimal (scarcely informative) experiments to be planned.

Several design criteria have been proposed in the literature, following the pioneristic work by Pritchard and Bacon (1978), to decrease the level of correlation among the model parameters directly acting on some metric of $\mathbf{C}_\theta$. The authors proposed the following design criterion

$$\varphi = \arg\min \left[\sum_{\substack{i,j \\ i \neq j}} \frac{c_{ij}^2}{\left(N_\theta^2 - N_\theta\right)} \right]^{1/2} \tag{2.18}$$

where the square root of the correlation coefficients between pair of parameters is minimised.

Walter and Pronzato (1997) analysed parameter estimation problems using linear confidence regions and underlined that a high correlation results in a rotation of the principal axes of the confidence ellipsoid (Figure 2.4). However, as argued by Franceschini (2007) a confidence ellipsoid which is parallel to the axes is not a sufficient condition to ensure the absence of correlations. Franceschini and Macchietto (2008) recently proposed some anti-correlation design criteria (PAC, ACE and E-AC design criteria). While the PAC criterion aims at minimising specific metric of $\mathbf{C}$, the ACE criterion minimises some metric of $\mathbf{C}_\theta$ taking into account additional constraints on the eigenvalues of the information matrix and thus ensuring a minimum information level for the experiment. The E-AC criterion does exactly the

opposite: it minimises some metric of $\mathbf{V}_\theta$ by superimposing a constraint on the minimum reduction of the elements of $\mathbf{C}_\theta$. In this way the experimenter can choose an acceptable degree of correlation between the model parameters and additional constraints can be set on the elements of $\mathbf{V}_\theta$.

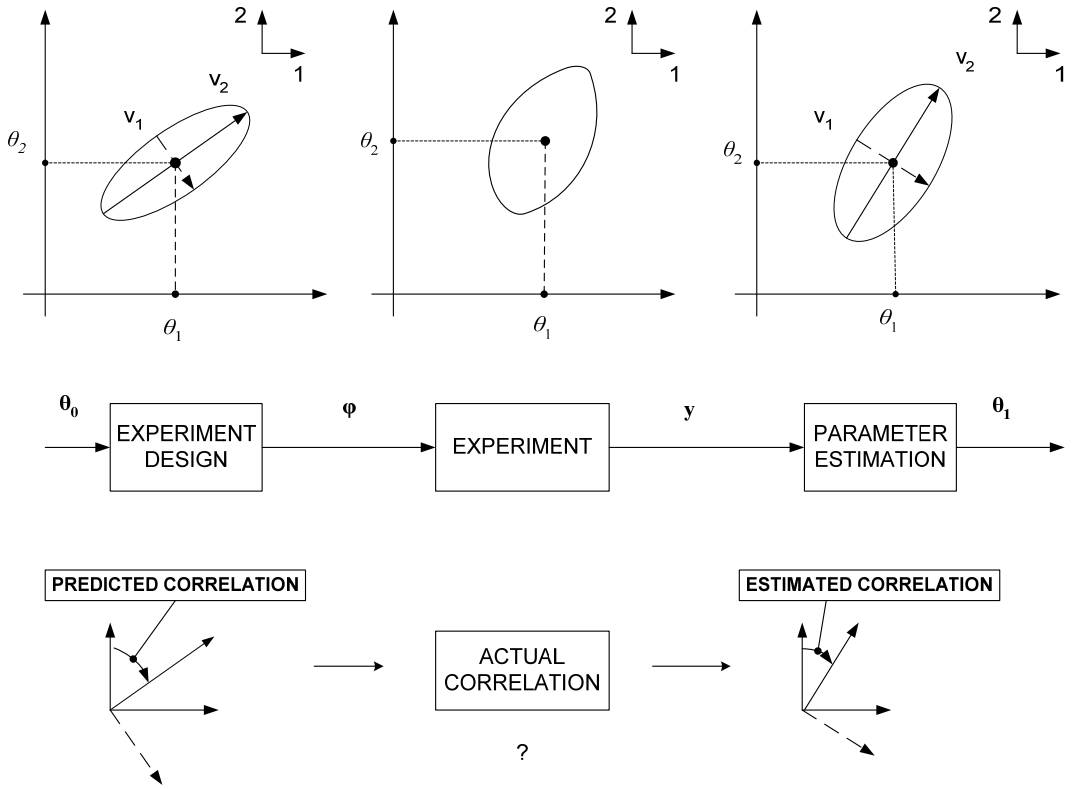


Figure 2.4 *Relationship between uncertainty and correlation during a standard MBDoE procedure (v_1 and v_2 are the principal axes of the confidence ellipsoid).*

It must be pointed out that, as discussed by Rooney and Biegler (2001), a non-linear analysis of the confidence region should be carried out to describe the uncertainty region in a detailed and reliable way. In fact, if the model parameters have a physical meaning, once the experiment is performed the system would provide the real correlation between physical factors affecting the system responses. However, the actual correlation of the system can only be evaluated *a-posteriori*, i.e. after a parameter estimation session is carried out. The mismatch between expected and actual information, which is always present in an MBDoE procedure and deeply affects the design efficiency (see §2.6), turns out to be a mismatch between the expected and the actual correlation foreseen by the identification model.

For some systems it may be very difficult (perhaps impossible) to provide sufficient excitation patterns to gain significant information from an experimental trial in such a way as to estimate the model parameters in a statistically satisfactory way. A typical example can be provided by closed batch reactive systems, where the goal is to estimate a set of kinetic

parameters. The possibility to manipulate the temperature during the trials can be severely limited by the experimental budget, and the management of the other design variables (initial conditions, the set of sampling times and duration of the experiment) could be not sufficent to estimate the kinetic parameters in a statistically sound way. In such a case, the experiment needs to be enriched (for example by adding extra measured variables, or adding a tracer), otherwise a standard MBDoE strategy could be totally ineffective to improve the information content of the experiment.

The calculation of dynamic sensitivities is a fundamental step for evaluating the dynamic information matrix, and their representation (see §2.5.2) may be crucial to avoid singularity issues affecting $\mathbf{H}_\theta$ during the design procedure.

2.3 Key activity 2: experiment execution

The information level of an experiment is firmly related to the measurements nature (what to measure), to the measurements quality (how to measure), and to the measurements frequency (when to measure). In principle, each measurement contains some "information" that can be extracted during the parameter estimation session. For parameter estimation purposes, an "ideal" set of measured responses from a single experiment should be:

- accessible to the set (or to a subset) of model parameters (i.e., the experiment eventually helps decreasing the overall parameter variability, or the variability of a subset of parameters; Krishnan *et al.*, 1992);
- as free as possible from the effect of undesired disturbances (it is particularly important to avoid disturbances not enclosed in the model representation);
- as clean as possible from measurements errors that are random and/or systematic (these are related both to the experimental apparatus and experimenter's skills and experience);
- free from cross-correlation between measurement errors (i.e., covariance matrix of measurement errors nearly diagonal).

A set of variables are chosen as measured variables according to:

- the availability (i.e. the experimental budget) and the features of the measurement system;
- the observability of the system, which is an intrinsic characteristic of the system itself.

In the experimental practice it is possible to measure the control variables ($\mathbf{u}(t)$ e $\mathbf{w}$) and the set of system responses ($\mathbf{y}$) in each performed experiment. The MBDoE procedure is built in order to improve the parameter estimation by exploiting the information within the $\mathbf{y}$ set of measured responses. According to that, in the parameter estimation task only the set of responses of the experimental system will be exploited and compared with the ones predicted by the model.

If the experimenter is able to minimise all the disturbance in the system that cannot be represented by the model, and under the assumption that only measurement errors affects the

system responses, the set of measurements **y** for a single experiment can be expressed in vectorial form by:

$$\mathbf{y}(t_i) = \hat{\mathbf{y}}(t_i) + \boldsymbol{\varepsilon}(t_i) \qquad i = 1 \ldots n_{sp} \tag{2.19}$$

where $\boldsymbol{\varepsilon}$ is the N_y-dimensional vector of measurements errors, whose probability distribution $p(\boldsymbol{\varsigma})$ is usually defined by a set of distribution parameters $\boldsymbol{\varsigma}$. For instance, assuming a multivariate normal distribution for $\boldsymbol{\varepsilon}$, it is generally assumed that

$$E\left[\varepsilon_i\right] = 0 \qquad i = 1 \ldots N_y \tag{2.20}$$

and the variance-covariance of measurements errors is given by the $N_y \times N_y$ matrix:

$$\boldsymbol{\Sigma} = \begin{bmatrix} \sigma_{y_1}^{\ 2} & \sigma_{y_{12}}^{\ 2} & \cdots & \sigma_{y_{1,N_y}}^{\ 2} \\ \sigma_{y_{21}}^{\ 2} & \sigma_{y_2}^{\ 2} & \cdots & \\ \vdots & \vdots & \ddots & \\ \sigma_{y_{N_y,1}}^{\ 2} & & & \sigma_{y_{N_y}}^{\ 2} \end{bmatrix} . \tag{2.21}$$

Thus, $\boldsymbol{\varsigma} = \left\{0, \boldsymbol{\Sigma}\right\}$ and the measurements errors have zero mean and variance-covariance given by $\boldsymbol{\Sigma}$ (i.e. only white noise corrupts the measurements), which is not necessarily constant between consecutive experiments. The values outside the diagonal of $\boldsymbol{\Sigma}$ represents the correlation between the measurement errors of the N_y measured responses in the given experiment. The features of the measurement system define $\boldsymbol{\varepsilon}$, and in the experimental practice the elements of $\boldsymbol{\varsigma}$ can be estimated by repeated trials at fixed experimental conditions. A variance model can be useful in some circumstances to define or identify the distribution of the measurements errors. The model should describe and condensate all the features of the measurements system for the given experimental protocol. In the hypothesis of uncorrelated measurements errors it is assumed that, for a single experiment, the estimated variance of the measurements errors can be represented by a functional relationship of the form

$$\sigma^2_{\ y_j} = \omega_j^{\ 2} \left(\hat{y}_j^2\right)^{\frac{\gamma_j}{2}} \tag{2.22}$$

where $\hat{y}_j$ is the j-th system response as predicted by the model, ω_j is the standard deviation of the j-th measured response while γ_j is the eteroschedastic factor. The parameters γ_j e ω_j define the chosen variance model (Table 2.1). A series of experiments can be planned and performed to estimate the parameters of the variance model or these parameters can be pre-set by the experimenter basing on the actual knowledge of the measurement system.

Table 2.1 *Variance model parameters.*

Expected variance model	γ	ω
Constant variance	0	Fixed *a-priori* or estimated
Constant relative variance	1	Fixed *a-priori* or estimated
Heteroschedastic	Fixed *a-priori* or estimated	Fixed *a-priori* or estimated

2.4 Key activity 3: parameter estimation

The goals of the parameter estimation task are:

1. to achieve a statistically sound parameter estimation (i.e., providing a precise and accurate estimation of model parameters)
2. to maximise the capability of the model to predict the measured responses (i.e., providing a satisfactory fitting of the measured responses).

An estimator can be defined as a statistic (i.e. a function of the observable data **y**) in the form:

$$\hat{\boldsymbol{\theta}} = \Phi^{PE}\left(\mathbf{y}\right) : \Re^{N_y} \rightarrow \Re^{N_\theta} \tag{2.23}$$

where $\hat{\boldsymbol{\theta}}$ is the parameters estimate (i.e. the result of the application of the estimator). An efficient estimator should provide:

1. an estimate that is as close as possible to the "true" value of the model parameters describing the system in a reliable way;
2. an estimate with the minimum dispersion around the estimated value (i.e., minimum variance).

The first feature is concerned with the accuracy of the estimate, while the second is related to the precision of the estimate. The first feature is quite difficult to get, since the true value of model parameters is obviously unknown, and a weaker assumption should be made on the estimator concerning the asymptotic convergence to a possible value of the parameters $\boldsymbol{\theta} \in \Re^{N_\theta}$ as the number of samples tends to infinity:

$$\lim_{n_{sp}\rightarrow\infty} E\left[\Phi^{PE}\left(\mathbf{y}\right)\right] = \boldsymbol{\theta} \ . \tag{2.24}$$

An estimator such that (2.24) is satisfied is said to be *unbiased*. Unbiased estimators are particularly important in the parameter estimation theory for their properties and their efficiency deeply influencse the whole MBDoE procedure. For unbiased estimators a lower bound on the variance-covariance of model parameters is defined by the Cramer-Rao Theorem:

$$\mathbf{V}_\theta(\boldsymbol{\theta}) - \mathbf{I}(\boldsymbol{\theta})^{-1} \geq 0 \quad , \tag{2.25}$$

where **I** is the Fisher information matrix defined by (2.3). The (2.25) expression provides an upper limit (known as Cramer-Rao Limit) on the precision provided by the estimator which is independent by the particular form of the estimation criterion.
The ideal result of the estimation run should be a vector having the minimum variance (i.e. a precise parameter estimate) but providing at the same time the minimum deviation of the predicted responses $\hat{\mathbf{y}}$ from the measured ones **y**. This can be obtained by minimising the elements of the $N_y \times n_{sp}$ matrix of absolute residuals **r**, whose elements take the form

$$r_{ij} = \left\| y_i(t_j) - \hat{y}_i(t_j) \right\| \qquad i = 1 \ldots N_y,\ j = 1 \ldots n_{sp}. \tag{2.26}$$

Several estimators can be used to estimate the set of model parameters of a dynamic model, but the most frequently used are:

1. least squares (LS);
2. weighted least squares (WLS);
3. maximum likelihood (ML);
4. Bayesian.

The simplest estimators are the LS estimator

$$\Phi^{LS}(\mathbf{y}) = \sum_{i=1}^{N} \left[(\mathbf{y}_i - \hat{\mathbf{y}}_i)^T (\mathbf{y}_i - \hat{\mathbf{y}}_i) \right] \quad , \tag{2.27}$$

or the WLS estimator, where the variance-covariance matrix of measurements errors has to be provided for each experimental trial:

$$\Phi^{WLS}(\mathbf{y}, \boldsymbol{\Sigma}_1, \ldots, \boldsymbol{\Sigma}_N) = \sum_{i=1}^{N} \left[(\mathbf{y}_i - \hat{\mathbf{y}}_i)^T \boldsymbol{\Sigma}_i^{-1} (\mathbf{y}_i - \hat{\mathbf{y}}_i) \right]. \tag{2.28}$$

LS or WLS only provide an estimate $\hat{\boldsymbol{\theta}}$ of model parameters but no *a-posteriori* statistics concerning the precision of the estimate are provided by the estimators. A maximum likelihood approach is much more suitable in an MBDoE procedure, and provides a conditioned probability distribution of the final estimate. It then becomes possible to extract the useful information from the data evaluating the *a-posteriori* variance-covariance matrix of model parameters. When the measurements errors can be considered normally distributed, a maximum likelihood estimator can be expressed as (Bard, 1974):

$$\Phi^{ML}\left(\mathbf{y},\boldsymbol{\Sigma}_1,...,\boldsymbol{\Sigma}_N\right)=L\left(\boldsymbol{\theta},\boldsymbol{\Sigma}_1,...,\boldsymbol{\Sigma}_N\right)=$$
$$2\pi^{\frac{N_y}{2}}\prod_{i=1}^{N}\left|\boldsymbol{\Sigma}_i\right|^{-\frac{1}{2}}\exp\left\{-\frac{1}{2}\sum_{i=1}^{N}\left[\left(\mathbf{y}_i-\hat{\mathbf{y}}_i\right)^T\boldsymbol{\Sigma}_i^{-1}\left(\mathbf{y}_i-\hat{\mathbf{y}}_i\right)\right]\right\}, \tag{2.29}$$

where $\boldsymbol{\Sigma}_i$ is the variance-covariance matrix of measurements errors in the i-th experiment.
It is possible to estimate simultaneously $\hat{\boldsymbol{\theta}}$ and $\boldsymbol{\Sigma}_i$ adopting two different strategies:

- starting from an initial guess for the $\boldsymbol{\Sigma}_i$ the maximisation of the (2.29) is carried out by acting on the elements of $\hat{\boldsymbol{\theta}}$; the variance-covariance of residuals allows for the re-estimate of the elements of $\boldsymbol{\Sigma}_i$;
- a variance model in the form (2.22) is adopted and the maximisation of the (2.29) is carried out estimating both parameters $\boldsymbol{\omega},\boldsymbol{\gamma}$ of the variance model and $\hat{\boldsymbol{\theta}}$.

A much more efficient estimation can be provided by Bayesian estimators, where *a-priori* information on the parametric system can be enclosed and exploited in the optimisation. The most commonly used Bayesian estimators are the minimum variance and the maximum-*a-posteriori* (MAP) estimators, here briefly presented. The maximum-a-posteriori (MAP) estimator, in the hypothesis of gaussian measurements errors and gaussian distribution of model parameters can be expressed as

$$\Phi^{MAP}\left(\mathbf{y},\boldsymbol{\Sigma}_\theta,\boldsymbol{\Sigma}_1,...,\boldsymbol{\Sigma}_2\right)=\frac{1}{\sqrt{\left(2\pi\right)^{N_\theta}\left|\Sigma_\theta\right|}}\exp\left[-\frac{1}{2}\left(\hat{\boldsymbol{\theta}}-\boldsymbol{\theta}_0\right)^T\boldsymbol{\Sigma}_\theta\left(\hat{\boldsymbol{\theta}}-\boldsymbol{\theta}_0\right)\right]\cdot$$
$$\frac{1}{\sqrt{\left(2\pi\right)^{N_y}\left|\Sigma_y\right|}}\exp\left[-\frac{1}{2}\sum_{i=1}^{N}\left[\left(\mathbf{y}_i-\hat{\mathbf{y}}_i\right)^T\boldsymbol{\Sigma}_i^{-1}\left(\mathbf{y}_i-\hat{\mathbf{y}}_i\right)\right]\right], \tag{2.30}$$

and the estimator aims at minimising both the vector of residuals and the variance-covariance of model parameters. Note that a prior parameter estimation ($\boldsymbol{\theta}_0$) with related statistics (given by $\boldsymbol{\Sigma}_\theta$, the prior variance-covariance matrix of model parameters), together with the $\boldsymbol{\Sigma}_i$ are required by the estimator to estimate the model parameters. It is well known in the literature (Sorenson, 1980) that a MAP estimator, if compared with a ML estimator, usually improves the precision of the final parameter estimate, at the cost of a slightly worse fitting of experimental data. Moreover, in some specific problems (Pillonetto *et al.*, 2003) it is known to prevent numerical identifiability issues arising from the usage of ML estimators. The main drawback of the MAP estimator is that its performance is greatly influenced by the prior information on model parameters and by the chosen reparameterisation (§2.5.2).
When an ML or MAP estimators is used, the following elements are required to solve the parameter estimation problem:

- a model in the (2.1) form with the initial conditions (2.2);

- an initial guess on the parameter $\hat{\boldsymbol{\theta}}_0$, eventually described by *a-priori* statistics (given by $\boldsymbol{\Sigma}_\theta$) describing the preliminary uncertainty region of model parameters;
- a set of design vectors defining the experimental settings of the *N* experiments performed;
- a **y** set of collected data for each performed experiment;
- information on the measurement system (expressed through $\boldsymbol{\Sigma}$); if no information on the measurement system is available, the use of a variance model in the (2.22) form, whose variance parameters need to be estimated, is greatly suggested;

The results from the parameter estimation session are:

- the parameters estimate $\hat{\boldsymbol{\theta}}$;
- some *a-posteriori* statistics defining the confidence of the estimate;
- (if required) the estimated parameters for the variance model.

From the computational point of view, a parameter estimation session is a nonlinear problem requiring a DAEs solver to integrate the (2.1) model equations and a robust optimiser able to avoid local minima during the minimisation procedure (this being a critical point that may compromise the effectiveness of the entire MBDoE procedure). It is very important to perform statistical tests for assessing the quality of the estimates in terms of: *i*) fitting of the observed data; *ii*) precision of parameter estimation (defined by the actual information on the parametric system). Moreover, preliminary assumptions on the behaviour of the measurements errors have been made during the experimental design and parameter estimation key activities. These assumptions should be confirmed by the experimental trials and validated through statistical assessment.

In this dissertation, the ML estimator (exploiting different variance models) has been used to perform all the parameter estimation sessions, and providing a final estimate and related statistics in the assumption of normally distributed measurements errors.

2.4.1 Quality assessment of the estimates

A satisfactory parameter estimate should have two main features (Emery, 2001):

1. accuracy, i.e. closeness to true value (which is unknown): the values of the parameter set should capture the information embedded in the measurements rejecting the effect of noise and disturbances;
2. precision, i.e. minimal uncertainty: the parameter set should be confined into a restricted confidence region.

The precision of the estimate is strictly related to the uncertainty region described by the variance-covariance matrix $\mathbf{V}_\theta$. The confidence intervals of the estimates provide a significant support to understand whether the parameters are well estimated or not. Confidence intervals are usually evaluated by the following expression:

$$\kappa_i = t\left(\frac{1-\alpha}{2}, n_{sp}NM - N_\theta\right)\sqrt{v_{ii}} \qquad i = 1\ldots N_\theta \quad , \tag{2.31}$$

where t is the upper $(1 - \alpha)/2$ critical value for a t-distribution with $\left(n_{sp}MN - N_\theta\right)$ degrees of freedom. Approximately, for a $(1 - \alpha) = 95\%$ confidence level it is

$$\kappa_i^{95\%} = 2\sqrt{v_{ii}} \qquad i = 1\ldots N_\theta \quad , \tag{2.32}$$

and the confidence intervals are directly estimated from the diagonal elements of $\mathbf{V}_\theta$. If the parameters are assumed to be normally distributed, it is possible to carry on a t-test, once the variance-covariance matrix of model parameters $\mathbf{V}_\theta$ is known. The t-values are evaluated as

$$t_i = \frac{\hat{\theta}_i}{\sqrt{v_{ii}}} \qquad i = 1\ldots N_\theta \quad , \tag{2.33}$$

where v_{ii} is the i-th diagonal element of $\mathbf{V}_\theta$. The t-values are a common choice to measure the confidence of the model parameters with respect to the estimate, and during the test they should be compared to a reference t-value, usually given by a Student t-distribution with $\left(n_{sp}MN - N_\theta\right)$ degrees of freedom. If the t-value of a given parameter is higher than the reference t-value, the estimate is satisfactory. Very high t-values usually mean that the parameters are estimated with a high confidence. Note that using (2.31-2.33) no information about the covariance of the parametric system is exploited. For such systems where a high correlation between model parameters is present, a multivariate normal analysis is recommended, and a Hotelling t^2-test should be performed to assess the quality of the estimates.

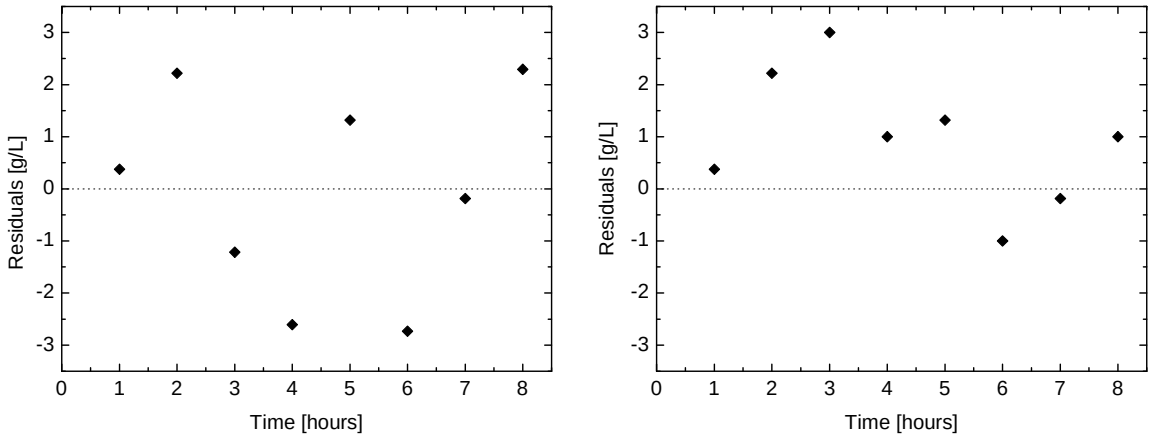
To verify that a proper minimisation of the residuals is realised through the parameter estimation procedure (*lack-of-fit* test) a χ^2-test can be performed considering the sum of weighted residuals

$$SWR = \sum_{i=1}^{N}\left[\left(\mathbf{y}_i - \hat{\mathbf{y}}_i\right)\boldsymbol{\Sigma}_i^{-1}\left(\mathbf{y}_i - \hat{\mathbf{y}}_i\right)\right] \quad . \tag{2.34}$$

In this test the SWR is compared with a reference χ^2 distribution with $\left(n_{sp}MN - N_\theta\right)$ degrees of freedom and, if

$$SWR < \chi_{RIF} \quad , \tag{2.35}$$

then the fitting of the experimental data is efficient and the model can be considered as a reliable representation of the physical system. However, a particular attention should be made on the distribution of the residuals (2.27) in time. For the assumptions made in §2.3, it must be verified that all the hyphothese done on the variance of the measurements errors are satisfied. The assumption of gaussian distribution of measurements errors in both the design procedure and the experiment should be confirmed by the distribution of the residuals by what is known as a "whiteness test".



(a) *(b)*

Figure 2.5 *Distribution of residuals in the case of (a) whiteness test passed and (b) whiteness test failed.*

In the whiteness test the normality assumption is assessed by verifying that the residuals are randomly distributed and follow a normal distribution with zero mean and variance-covariance given by $\boldsymbol{\Sigma}$. Let us consider a series of biomass concentration measurements in a single response bioreactor where the measurements errors have been considered normally distributed with zero mean and standard deviation σ_y = 2 g/L. After the experiment execution a parameter estimation session is carried out and the residuals are analysed. As illustrated in Figure 2.5a the residuals are randomly distributed around the mean of 0.005 g/L and with standard deviation of 2 g/L (the entire set of data points is within the ±4 g/L range, usually describing the 95% of variability of the samples), and the normality assumption on the measurements errors is well approximated by the distribution of residuals. Figure 2.5b shows a case where the residuals are not randomly distributed and the normality assumption is not satisfied (the mean of the residuals is 1 g/L and the standard deviation is 1.3 g/L). In this case, either the chosen identification model could be an inadequate representation of the physical system, or the parameters could be poorly estimated, or a structural model mismatch may be present (i.e. the physical system should be described by a model whose mathematical structure is different from the one of the identification model).

2.5 Preliminary analysis of the model

In §1.5 the concept of parametric identifiability was introduced and the problem of *a-priori* testing of the structural global identifiability of a model was discussed. The *a-priori* identifiability testing is usually performed within a subset of the possible experimental conditions investigated by design and is computationally expensive to perform in complex nonlinear dynamic models. Alternative methods can be used to assess the *a-posteriori* identifiability of dynamic models:

1. *a-posteriori* identifiability testing;
2. sensitivity analysis;
3. information and correlation analysis.

These methods can be used to verify if it is possible to estimate the set of model parameters from experimental data starting from prior (limited) knowledge on the parametric system.

2.5.1 A-posteriori identifiability

An optimisation-based procedure for assessing *a-posteriori* identifiability during the design procedure is here presented following the original definition provided by Asprey and Macchietto (2000).

Definition (*a-posteriori identifiability*): a model with predicted response given by $\hat{\mathbf{y}}(\boldsymbol{\theta},\boldsymbol{\varphi},t)$ is globally identifiable if, for every design vector $\boldsymbol{\varphi} \in \Re^{n_\varphi}$ and for each parametric set $\boldsymbol{\theta} \in \boldsymbol{\Theta}$ and $\boldsymbol{\theta}^* \in \boldsymbol{\Theta}$, in a time horizon $t \in [0,\tau]$ the following condition is met:

$$\Phi^I = \max_{\boldsymbol{\theta}\in\boldsymbol{\Theta},\, \boldsymbol{\theta}^*\in\boldsymbol{\Theta}^*} (\boldsymbol{\theta}-\boldsymbol{\theta}^*)^T \mathbf{W} (\boldsymbol{\theta}-\boldsymbol{\theta}^*) < \varepsilon_I' \tag{2.36}$$

under the condition

$$\int_0^t \left(\hat{\mathbf{y}}(\boldsymbol{\varphi},\boldsymbol{\theta}) - \hat{\mathbf{y}}(\boldsymbol{\varphi},\boldsymbol{\theta}^*)\right)^T \mathbf{W}' \left(\hat{\mathbf{y}}(\boldsymbol{\varphi},\boldsymbol{\theta}) - \hat{\mathbf{y}}(\boldsymbol{\varphi},\boldsymbol{\theta}^*)\right) dt < \varepsilon_I'' \tag{2.37}$$

(ε_I' and ε_I'' are small positive numbers and $\mathbf{W}$ and $\mathbf{W}'$ are proper weighting matrices). Basically the model is identifiable if each distinct parametric set will provide a distinct model response. If distinct sets of model parameters define exactly the same dynamic response, it will be impossible to discriminate between the two set by using only the system measurements and the model is not uniquely identifiable.

Note that the assessment of *a-posteriori* identifiability requires the evaluation of (2.36) and (2.37) for each possible realisation of $\boldsymbol{\varphi} \in \Re^{n_\varphi}$. In practice, in order to reduce the

computational burden, this identifiability testing is carried out only locally (i.e. around a fixed set of experimental conditions) once a preliminary design vector has been identified by maximising a measure of the expected information.

2.5.2 Sensitivity analysis

Sensitivity analysis is the study of how the variation in the output of the model can be apportioned, qualitatively or quantitatively, to different sources of variation, and of how the information depends upon the information fed in it (Saltelli *et al.*, 2000). Local and global sensitivity analysis techniques have been proposed in the literature for the attainment of the following goals:

1. to screen out the most influential parameters affecting the system responses;
2. to analyse the information behaviour for a given set of experimental conditions.

This second point is of particular interest and it is intrinsically related to the formulation of the dynamic information matrix in (2.13) for the optimal design of the experiment. Thus, it is very important to verify the impact of a change in the estimated values of model parameters $\hat{\boldsymbol{\theta}}$ on the system responses $\hat{\mathbf{y}}$. The $N_y \times N_\theta$ matrix of local sensitivities (i.e. sensitivities evaluated at $\hat{\boldsymbol{\theta}}$) is

$$\mathbf{Q}(t) = \begin{bmatrix} q_{1,1}(t) & \cdots & q_{1,N_\theta}(t) \\ \vdots & \ddots & \vdots \\ q_{N_y,1}(t) & \cdots & q_{N_y,N_\theta}(t) \end{bmatrix} = \begin{bmatrix} \dfrac{\partial \hat{y}_1(t)}{\partial \theta_1} & \cdots & \dfrac{\partial \hat{y}_1(t)}{\partial \theta_{N_\theta}} \\ \vdots & \ddots & \vdots \\ \dfrac{\partial \hat{y}_{N_y}(t)}{\partial \theta_1} & \cdots & \dfrac{\partial \hat{y}_{N_y}(t)}{\partial \theta_{N_\theta}} \end{bmatrix} . \tag{2.38}$$

In the design of experiment activity the sensitivity matrix in the (2.38) form is evaluated for the *r*-th measured response at each sampling time through the $n_{sp} \times N_\theta$ dimensional matrix $\mathbf{Q}_r$

$$\mathbf{Q}_r = \begin{bmatrix} \left.\dfrac{\partial y_r}{\partial \theta_1}\right|_{t_1} & \cdots & \left.\dfrac{\partial y_r}{\partial \theta_{N_P}}\right|_{t_1} \\ \vdots & \ddots & \vdots \\ \left.\dfrac{\partial y_r}{\partial \theta_1}\right|_{t_{n_{sp}}} & \cdots & \left.\dfrac{\partial y_r}{\partial \theta_{N_P}}\right|_{t_{n_{sp}}} \end{bmatrix} . \tag{2.39}$$

The analysis of the time profiles of the (2.38) sensitivities highlights the dynamic behaviour of the parametric system and may provide useful insights on the optimal allocation of sampling points for a given measured response. As an example, Figure 2.5 shows the sensitivity profiles of a four-parameter model with a single measured output. A peak is present around t = 10 hours for q_{11} and q_{14}. In that point the measurements can provide useful information for estimating θ_1 and θ_4. On the contrary, poor information can be gathered by the experimental measurements (at the current experimental settings) on θ_2 (the sensitivity q_{12} is close to zero).

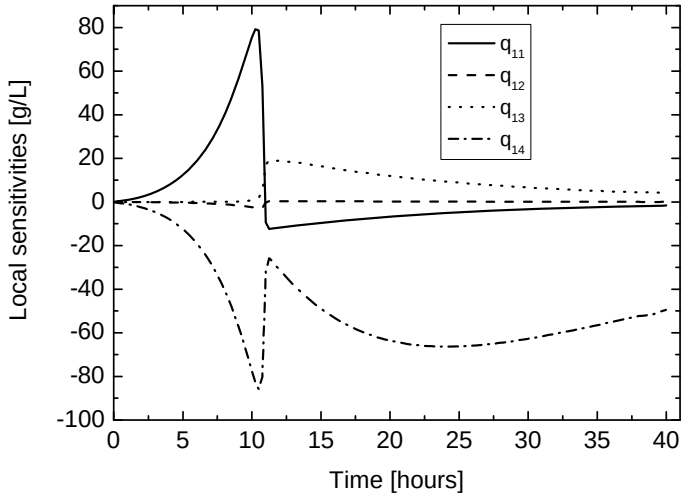


Figure 2.5 *Profiles of dynamic sensitivities as elements of (2.39) for a single response model.*

Based on the evaluation of local sensitivities, it is possibile to define the $\left(N_y n_{sp} \times N_\theta\right)$ matrix of parameters estimability (Shaw, 1999), whose rank needs to be evaluated:

$$\mathbf{P}_E = \begin{bmatrix} \left.\frac{\partial \hat{y}_1}{\partial \theta_1}\right|_{t=t_1} & \cdots & \left.\frac{\partial \hat{y}_1}{\partial \theta_{N_\theta}}\right|_{t=t_1} \\ \vdots & \ddots & \vdots \\ \left.\frac{\partial \hat{y}_{N_y}}{\partial \theta_1}\right|_{t=t_1} & \cdots & \left.\frac{\partial \hat{y}_{N_y}}{\partial \theta_{N_\theta}}\right|_{t=t_1} \\ \left.\frac{\partial \hat{y}_1}{\partial \theta_1}\right|_{t=t_{n_{sp}}} & \cdots & \left.\frac{\partial \hat{y}_1}{\partial \theta_{N_\theta}}\right|_{t=t_{n_{sp}}} \\ \vdots & \ddots & \vdots \\ \left.\frac{\partial \hat{y}_{N_y}}{\partial \theta_1}\right|_{t=t_{n_{sp}}} & \cdots & \left.\frac{\partial \hat{y}_{N_y}}{\partial \theta_{N_\theta}}\right|_{t=t_{n_{sp}}} \end{bmatrix} . \tag{2.40}$$

If *rank* ($\mathbf{P}_E$) < N_θ, the sensitivity coefficients are not independent, and it is not possibile to estimate the entire parametric set from the measured responses.

The mathematical formulation of the elements of the sensitivity matrices is a central point to evaluate the expected information. As the sensitivities tend to zero, the information matrix may become singular and numerical problems affect the consistency of the whole design procedure. There are several ways to modify the evaluation of the expected information by acting on the sensitivity elements of (2.38) in order to increase the design effectiveness:

1. reparameterisation;
2. scaling of parameters;
3. scaling of sensitivities.

When a reparameterisation is carried out a set of functions combining two ore more parameters is defined in order to create a modified set of parameters being estimated. For the *i*-th model parameter, it will be

$$\theta_i' = f_{\theta_i}\left(\theta_1,...,\theta_{N_\theta}\right) \tag{2.41}$$

and the new sensitivity coefficients will be related to the elements in (2.38) through the following relationship:

$$q_i = \frac{\partial \hat{y}}{\partial \theta_i} = \frac{\partial f_{\theta_i}}{\partial \theta_i} + \frac{\partial}{\partial \theta_i} f_{\theta_i} \cdot \frac{\partial \hat{y}}{\partial \theta_i'} = \frac{\partial f_{\theta_i}}{\partial \theta_i} + \frac{\partial}{\partial \theta_i} f_{\theta_i} . q_i' \ . \tag{2.42}$$

The benefits from adopting such an approach come in the design step, where a new dynamic information matrix in the form (2.10) can be formulated by using the sensitivities of the reparameterised system.

The scaling of model parameters is required to facilitate the numerical solution of the parameter estimation and design step. The scaling is carried out by dividing each element of $\hat{\boldsymbol{\theta}}$ by a scaling factor μ

$$\Theta_i = \frac{\hat{\theta}_i}{\mu_i} \qquad\qquad i = 1 \ldots N_\theta \tag{2.43}$$

and considering the new "scaled" parametric set $\boldsymbol{\Theta} = \left[\Theta_1 \quad ... \quad \Theta_{N_\theta}\right]$. When the parameters are divided by their nominal value (i.e. the value adopted in the current design activity) a normalisation procedure is carried out and the sensitivities measure how a relative variation on the current values of model parameters may affect the predicted response. In this way each element of the entire set of sensitivities can be compared to each other.

Finally, the sensitivity elements can be directly divided by a factor to reduce the difference in magnitude of the sensitivities in time. For instance, it may be useful to divide each element of the sensitivity matrix for the maximum value that the elements will assume during the experimental time. This would keep the design step less sensitive to the difference on the dynamics of the single elements of the sensitivity matrix.
These different definition of local sensitivities will produce a different formulation of the dynamic information matrix, whose metric is maximised during the design step.

2.5.3 Information and correlation analysis

A dynamic sensitivity matrix in the (2.38) form usually contains $N_y \times N_\theta$ elements whose profiles should be analysed to assess the amount of information that can be gathered by the measured responses. However, for complex multi-response systems with a large number of model parameters, the experimenter is left with a large amount of data to analyse. As presented in literature, a multivariate statistical analysis of the entire set of sensitivities can be carried out by adopting PCA methods (Sjöblom and Creaser; 2008) to extract useful information about the local variability of the parametric system.
A more direct way to measure the information in time of the dynamic system is to evaluate a metric of the FIM in the dynamic form (2.6); the metric function can be the one used in alphabetic (A-, D-, E-optimal) or modified (P-, SV-, AC-optimal) design criteria. As an example it is considered a single response model with $N_\theta = 5$. The information coming from the sensitivity profiles can be usefully summarised by considering the trace of the FIM (Figure 2.6).

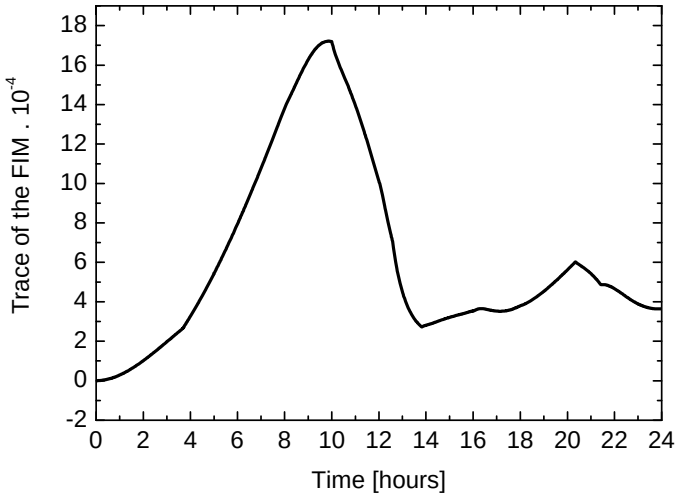
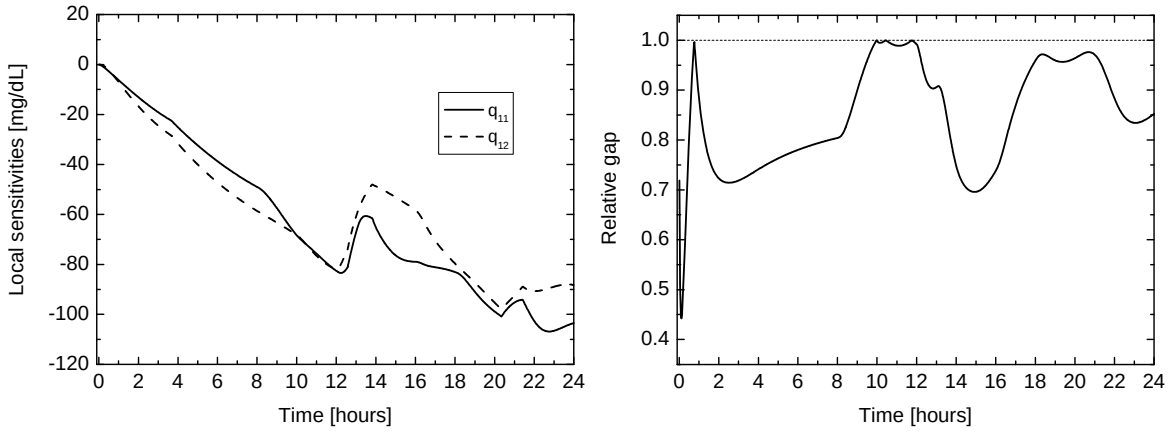


Figure 2.6 *Trace of the Fisher information matrix as given by (2.6).*

Figure 2.7a shows the high correlation between the sensitivities q_{11} and q_{12}. For $10 < t < 12$ hours the profiles are nearly coincident. Figure 2.7b shows the relative difference between the

two profiles. As the curve approaches unity the profiles overlap and, adopting the current experimental settings, if samples are acquired in that specific time frame, it is not possible to discriminate between θ_1 and θ_2 during the parameter estimation session.



(a) *(b)*

Figure 2.7 *(a) Profiles of dynamic sensitivities as elements of (2.39) and (b) relative gap between dynamic sensitivities q_{11} and q_{12} (upper correlation limit is represented by the broken line).*

Both correlation and anticorrelation between dynamic sensitivities deeply affect the effectiveness of the design procedure, and a design is much more efficient if it maximises the gap between sensitivities minimising at the same time their correlation. Numerical issues arise in the evaluation of the variance-covariance matrix (2.13): as the minors of information matrix becomes nearly singular no matrix inversion can be possible. As a result, no design based on anti-correlation criteria (acting on $\mathbf{C}_\theta$) must be carried out.

Singularity of the FIM in proximity of the "true" parametric set defining the physical system is strictly related to the identifiability of the model. Rothenberg (1971) was the first to approach the problem of identifiability of parametric models by considering the non-singularity of the FIM evaluated at the true value of the parametric set. A more generalised identifiability criterion was proposed by Bowden (1973). The interesting feature of these identifiability strategies is that it is always possible to evaluate the FIM before the experiment is executed, and thus they will provide a valuable support to experiment design. In particular, they are very useful to detect alternative parameterisations and a suitable range of experimental conditions to be used as "initial guess" in the design optimisation. The drawback is that their validity is local, i.e. it is restricted to the true value of model parameters, which is obviously unknown at the very beginning of the MBDoE procedure. However, it is possible to estimate the FIM within a prescribed region of variability of model parameters, and detect the experimental settings that would produce the singularity of the FIM. Afterwards, these experimental settings will be excluded by the design optimisation.

2.6 Experiment design efficiency

In the experiment design key activity a measure of expected information is maximised and, after each experiment is performed, a parameter estimation is carried out to exploit the information content of the available data. If a ML or MAP estimator is attempted, the parameter estimation will provide the actual information on the parametric system, in terms of *a-posteriori* statistics, as evaluated by the variance-covariance matrix of model parameters. A MBDoE procedure is efficient if $\psi\left(\mathbf{V}_\theta^{exp}\right)$ (the metric of the variance-covariance of model parameters which is optimised by design) is exactly $\psi\left(\mathbf{V}_\theta^{act}\right)$ (i.e. the metric of the variance-covariance of model parameters provided by the parameter estimation). In that case no information mismatch between the expected and the actual information is present, and the experiment would provide exactly the amount of information foreseen by experiment design. For a single iteration of the MBDoE procedure (involving the parameter estimation with the data coming from a single planned experiment) it is possible to define an experiment design efficiency:

$$\eta^{DOE} = \frac{\psi\left(\mathbf{V}_\theta^{exp}\right)}{\psi\left(\mathbf{V}_\theta^{act}\right)} \tag{2.44}$$

by comparing the measure of the actual uncertainty (represented by $\mathbf{V}_\theta^{act}$) as provided by the parameter estimation session, with the measure of the expected information predicted by design (represented by $\mathbf{V}_\theta^{exp}$). A similar relationship can be defined for the efficiency of experiment design on decreasing the degree of correlation between parameters:

$$\eta_C^{DOE} = \frac{\psi\left(\mathbf{C}_\theta^{exp}\right)}{\psi\left(\mathbf{C}_\theta^{act}\right)} \quad , \tag{2.45}$$

where $\mathbf{C}_\theta^{exp}$ is the correlation matrix predicted by design and $\mathbf{C}_\theta^{exp}$ is the correlation matrix as evaluated by parameter estimation. The assessment of (2.45) is particularly useful when anti-correlation design criteria are adopted. Note that these efficiency indices can be evaluated only *a-posteriori*, i.e. after each experiment is executed. However, they can be useful for monitoring the effectiveness of a MBDoE procedure when several experiments are planned and performed in sequence. As the number of experiments increases, the improvement on parameter estimation should provide a significant enhancement on the representation of the expected information. As a result, during a standard MBDoE procedure the (2.45) design efficiency should increase with the number of performed experiments.

Chapter 3

Online model-based redesign of experiments for parameter estimation in dynamic systems*

In this Chapter, a novel and general strategy for the online model-based redesign of experiments (OMBRE) is proposed to exploit the information as soon as it is generated from the execution of an experiment. Intermediate parameter estimations are carried out while the experiment is running, and, by exploiting the information obtained, the experiment is partially redesigned before its termination, with the purpose of updating the experimental settings in order to generate more valuable information for subsequent analysis. This enables to reduce the number of experimental trials that are needed to reach a statistically sound estimation of the model parameters, and results in a reduction of experimental time, raw materials needs, number of samples to be analysed, control effort, and labour. Two simulated case studies of increasing level of complexity are used to demonstrate the benefits of the proposed approach with respect to a state-of-the-art sequential model-based experiment design approach.

3.1 Background and motivation

In the standard experiment design methodology (cfr. §2.1), an experiment is designed on the basis of the parameter estimates available before the experiment is started, i.e. when the information coming from that experiment (in the form of measured outputs) is null. The information collected from the execution of the experiment is analysed only at the end of the experiment itself, and can be used to design the next experiment. This means that, to design an experiment, the designer completely disregards the progressive increase in the information content resulting from the progress of that experiment. This may be very costly in terms of time and resources (labour, raw materials, energy, equipment availability), as several experiments may be needed to reach a sound estimation of the model parameters. In principle, it may be convenient to exploit the information as soon as it is generated from the execution of an experiment. As discussed by Mehra (1974) and Keviczky (1975), the idea of an online input design is not new, although the applicability of such techniques was initially developed

* Portions of this Chapter have been published in Galvanin *et al.* (2008) and Galvanin *et al.* (2009a).

for simple non-physical models only. Adaptive input design techniques have been discussed and applied to linear stochastic control systems (Lindquist and Hjalmarsson, 2001; Hjalmarsson, 2001). More recently, Stigter *et al.* (2006) extended to ODE systems an adaptive technique for the optimal design of inputs. According to this technique, the optimal input design problem is solved over a preset time horizon after which a new measurement is obtained and, accordingly, new parameters are estimated, and the procedure is repeated until the end of the experiment. The authors showed that this technique was able to improve the results with respect to an input design that used a random binary sequence to excite the system. However, only the optimal design of inputs was considered in that paper; furthermore, no discussion on the improvement (if any) over a standard optimal experiment design technique was reported. Thus, a more general technique taking into account the whole experiment design variables as expressed by the design vector (§2.2.2) is required. A new advanced design strategy for Online Model-Based Redesign of Experiments (OMBRE) is here presented to exploit the information as soon as it is generated from the execution of an experiment. Instead of an input redesign, a whole experiment redesign is proposed. The net result of this strategy is that much more information can be collected from a single experiment, significantly reducing the costs associated with the parameter estimation job. The advantages of this approach over state-of-the-art model-based experiment design techniques are discussed using two simulated case studies of increasing complexity.

3.2 Problem definition

According to most of the optimal experiment design procedures, the experiment design phase, the complete experiment execution phase and the parameter estimation phase are carried out in a strictly sequential way. Figure 3.1 shows the relationship between the key activities involved during a classical sequential experiment design session for parameter estimation purposes. Using available prior information on the parameter set, an experiment design is carried out making use of the process model. As a result, experimental settings are defined in terms of optimal initial conditions, control variable profiles, and measurement sample scheduling. These settings are passed to the control system, and the experiment is carried out with the prescribed manipulated input profiles, providing a set of actual (i.e., experimental) measurements at the assigned sampling times. These measurements represent a data set that, at the end of the experiment, can be used for parameter estimation. The newly estimated model parameters can be exploited for a subsequent experiment design, so that the cycle can be iterated. Note that both the experiment design task and the parameter estimation task can be formulated as constrained optimisation problems (Pistikopoulous, 1995), and in a typical session of experimental design/parameter estimation the optimisation routines are invoked off-line. The experiment design task can be carried out adopting classical alphabetic criteria

(A-, D-, E-optimal design; Pukelsheim, 1993), or modified criteria (SV-optimal or P-optimal designs; Galvanin *et al.*, 2007; Zhang and Edgar, 2008), or methods to decrease the degree of correlation among parameters (Pritchard and Bacon, 1978; Franceschini and Macchietto, 2008).

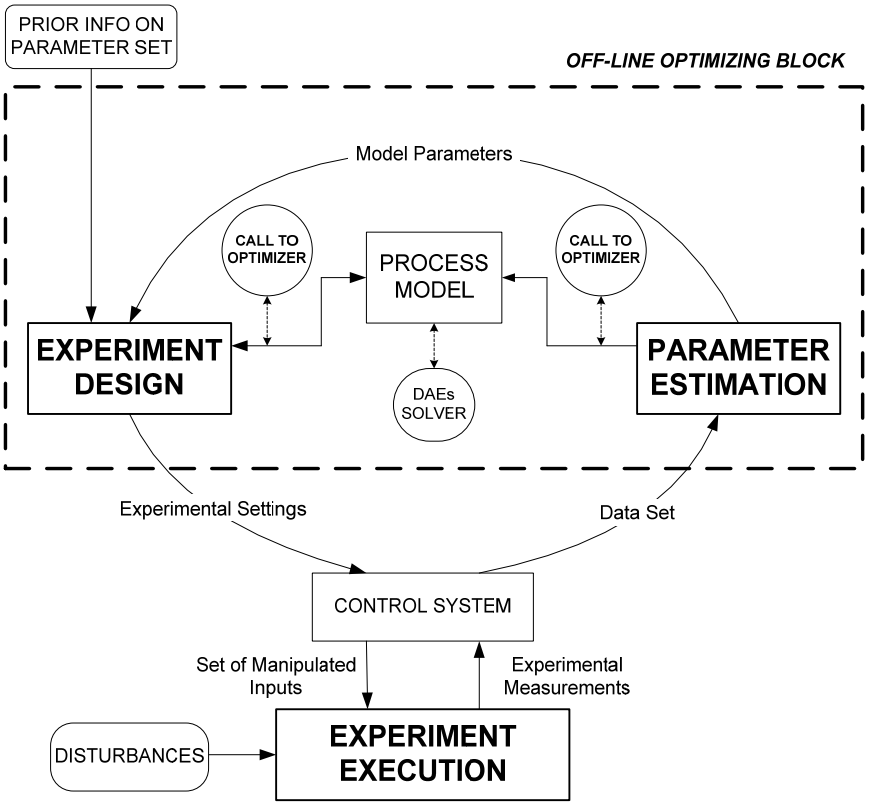


Figure 3.1 *Schematic representation of the tasks involved in a standard session of sequential experiment design for parameter estimation (the key activities are printed in boldface).*

It has been mentioned in the previous Chapter that a key issue in the design of an experiment is the information content of the experiment. The information path involved in a classical experiment design/parameter estimation session is subject to sources and sinks of information, as illustrated in Figure 3.2.

Prior information on the parametric set describes the level of confidence of the experimenter on the initial guess of the model parameters before an experiment is designed, and allows for the definition of the preliminary uncertainty region of model parameters. As the experimental sessions are repeated, prior information will be updated thanks to the contribution of each new experiment. The experiment design step and the following experimental evidence serve as the major sources of information. Designing an experiment provides an expected gain on information, while executing the experiment makes the actual information gain available. The expected information gain is affected by such factors as the optimisation criterion used for

experimental design, the preliminary guess on model parameters and related statistics (defined by the prior information), and the efficiency of the optimiser invoked by the experiment design routine. With reference to the latter issue, it should be remembered that Fisher-based experiment design techniques involve a highly nonlinear optimisation problem, where numerical issues as well as severe computational effort are experienced in complex systems with a large number of design variables.

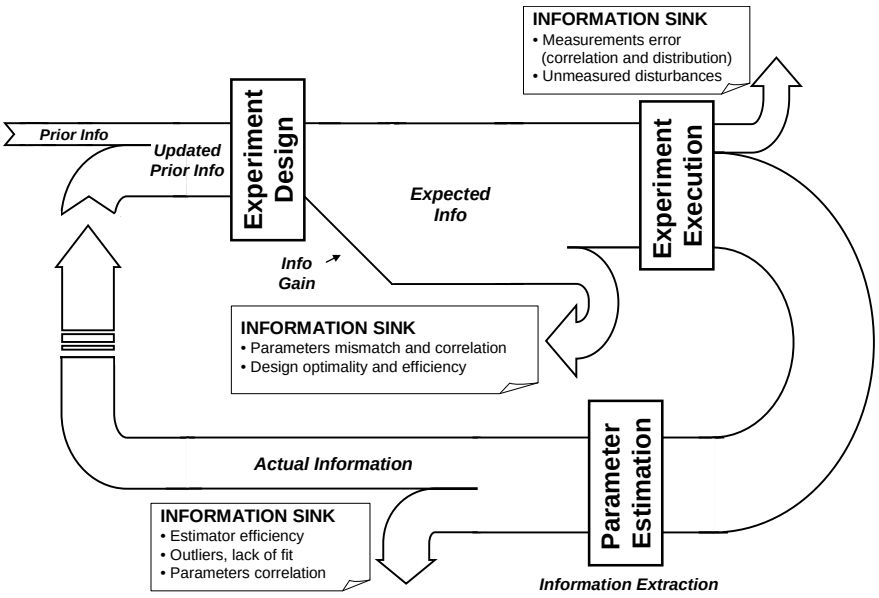


Figure 3.2 *Sankey diagram for the information fluxes in one standard experiment design/parameter estimation cycle.*

Parameter estimation usually results in a highly nonlinear optimisation problem for process engineering systems. The approach here proposed aims at modifying the experiment design and parameter estimation tasks in order to exploit the experimental information more efficiently, i.e. as soon as it becomes available (Stigter *et al.,* 2006). Analysing the information flux of the running experiment as soon as it is generated makes it possible to exploit the benefits of a fast update of the information gain and to impact on the economy of the experimentation itself. In fact, the online analysis of information would allow to carry out intermediate parameter estimation steps, which in turn would permit to re-design the remaining part of the same experiment and to gain further information. An increase in the information collected from a single experiment may significantly reduce the experimental effort in terms of number of trials, consumption of raw materials, number and/or kind of inputs to be manipulated, measurement sampling schedule, and duration of the experimental session. Note that, in principle, this approach is not different from what is done in online parameter estimation through state estimation approaches (e.g., classical extended Kalman filtering), where the state estimates at a given time can be improved using process measurements (i.e., information) available up to that time (Panjarnpornporn and Saroush,

2007; Ray, 1980). A similarity can also be traced with model-predictive control (Camacho and Bordons, 2001), where the scheduled control action is updated at each step following a comparison between the expected output profiles and the actual ones.

The OMBRE approach requires to update the manipulated input profiles and the sampling schedule of the running experiment by performing one or more intermediate experiment design/parameter estimation steps before the end of the experiment. Each experiment redesign is performed on the basis of the current value of the parameter set, which is the value of the estimated model parameters until that moment. The update of the parameter set gives the possibility to decrease the information loss due to parametric mismatch, with great benefit for the global efficiency of design. Furthermore, this methodology can be usefully embedded in a wider definition of optimal experiment design involving the proper choice of experiment structure and design criteria, where the design of experiments, the parameter estimation session and the management of experimental tests are dynamically interlinked.

3.3 Sequential design vs online redesign of dynamic experiments

It is assumed that the process model is described by the generic set of DAEs previously introduced in §2.1:

$$\begin{aligned} &\mathbf{f}\left(\dot{\mathbf{x}}(t),\mathbf{x}(t),\mathbf{u}(t),\mathbf{w},\boldsymbol{\theta},t\right)=0 \\ &\hat{\mathbf{y}}(t)=\mathbf{g}\left(\mathbf{x}(t)\right) \end{aligned} \tag{2.1}$$

with the initial conditions (2.2). If we consider the design of the N-th experiment in a standard sequential approach, matrix $\mathbf{V}_\theta$ is the inverse of the $(N_\theta \times N_\theta)$ information matrix $\mathbf{H}_\theta$ defined as:

$$\mathbf{H}_\theta\left(\boldsymbol{\theta},\boldsymbol{\varphi}\right)=\sum_{k=0}^{N-1}\mathbf{H}^*_{\theta|k}\left(\boldsymbol{\theta},\boldsymbol{\varphi}_k\right)+\mathbf{H}^*_\theta\left(\boldsymbol{\theta},\boldsymbol{\varphi}\right)+\left(\boldsymbol{\Sigma}_\theta\right)^{-1}=\mathbf{H}^*_\theta\left(\boldsymbol{\theta},\boldsymbol{\varphi}\right)+\mathbf{K} \quad , \tag{3.1}$$

where $\mathbf{K}$ is the constant matrix comprising the information obtained from the previous $n_{exp}-1$ experiments and from the $(N_\theta \times N_\theta)$ prior variance-covariance matrix of model parameters $\boldsymbol{\Sigma}_\theta$. $\mathbf{H}^*_{\theta|k}$ is the dynamic information matrix of the k-th experiment ($\mathbf{H}^*_{\theta|0}$ is the zero matrix, and superscript * indicates that the information matrix refers to a single experiment). $\mathbf{H}^*_\theta\left(\boldsymbol{\theta},\boldsymbol{\varphi}\right)$ is defined as:

$$\mathbf{H}^*_\theta\left(\boldsymbol{\theta},\boldsymbol{\varphi}\right)=\sum_{i=1}^{N_y}\sum_{j=1}^{N_y}s_{ij}\mathbf{Q}_i^T\mathbf{Q}_j \quad . \tag{3.2}$$

Therefore, to design an experiment in a standard sequential experiment design/parameter estimation session, the variables that need to be optimised are:

i) the initial conditions $\mathbf{y}_0$ (where $dim(\mathbf{y}_0) \leq N_y$);

ii) the $(n_{sw} - 1)$ times at which each control variable changes in value; these time instants are collected in the $\mathbf{t}_{sw}$ vector of switching times, characteristic of each control variable;

iii) the n_{sw} time invariant values for each of the control variables;

iv) the n_{sp} sampling times for each of the measured outputs;

v) the duration of the experiment.

It can be easily recognised that a large-scale non linear optimisation problem is obtained as the number of switching intervals and sampling times grow. To reduce the computational load, in this study we assume that the control variables are all switched at the same instants, and the outputs are all sampled at the same instants. Furthermore, it is assumed that the length of an experiment is assigned *a priori*: although one typical objective of experiment design is to reduce the experiment duration, the latter assumption allows for an easier comparison of different configurations without any loss of generality.

Equation (3.1) is sufficiently general to be extended for use within a strategy for online re-design of experiments. Through this strategy one seeks to update the information available at a given updating time t^{up} by executing online, at the same time (either assigned or to be optimised), a parameter estimation session followed by a redesign of the remaining part of the experiment. In this way, the original trajectories of the control variables and the sampling schedule are adjusted for this remaining part. One or more updates can be attained in the redesign, each one adding a new component (in the form of (2.8)) to the experiment design vector $\boldsymbol{\varphi}$, so that this vector can be rewritten as

$$\boldsymbol{\varphi} = \left[\boldsymbol{\varphi}_1, \boldsymbol{\varphi}_2, ..., \boldsymbol{\varphi}_j, ..., \boldsymbol{\varphi}_{n_{up}+1}\right]^{\mathrm{T}} \quad , \tag{3.3}$$

where n_{up} is the number of control updates, and $\boldsymbol{\varphi}_j$ is the ED vector before the j-th update. Note that $\boldsymbol{\varphi}_j$ contains the (sub-)lengths of the single updating intervals, whose actual duration may depend on the re-design strategy (this will be discussed later on); however, the overall duration of the experiment is set, and is not affected by the design procedure. In a general fashion, each component $\boldsymbol{\varphi}_j$ of $\boldsymbol{\varphi}$ could have a different dimension in terms of number of discretised control variables and/or sampling points. Furthermore, $\boldsymbol{\varphi}_1$ will be the only component enclosing initial values for the outputs.

The amount of information that need maximising in the j-th re-design can be expressed in terms of the dynamic information matrix:

$$\mathbf{H}^*_{\theta|j}\left(\boldsymbol{\theta}, \boldsymbol{\varphi}_j\right) = \sum_{k=0}^{j-1} \breve{\mathbf{H}}^*_{\theta|k}\left(\boldsymbol{\theta}, \boldsymbol{\varphi}_k\right) + \breve{\mathbf{H}}^*_{\theta}\left(\boldsymbol{\theta}, \boldsymbol{\varphi}_j\right) + \left(\boldsymbol{\Sigma}_\theta\right)^{-1} = \breve{\mathbf{H}}^*_{\theta}\left(\boldsymbol{\theta}, \boldsymbol{\varphi}_j\right) + \mathbf{L}\,, \tag{3.4}$$

where the sum between the prior information on model parameters ($\mathbf{\Sigma}_\theta^{-1}$) and the information acquired before the *j*-th re-design can be expressed as a constant term **L**. The symbol ($\breve{}$) indicates that the information matrix refers to a single updating interval, and $\breve{\mathbf{H}}_{\theta|0}$ is the zero matrix. Note the similarity between information matrices (3.1) and (3.4): the main difference is that in (3.1) the vector to be optimised is $\boldsymbol{\varphi}$, whereas in (3.4) the ED vector is $\boldsymbol{\varphi}_j$.

It should be noted that if an OMBRE strategy is adopted, more degrees of freedom are available to the experiment designer for optimisation. However, as will be clarified later, each of the optimisation problems can be made less complex than the optimisation required in standard sequential ED. Also note that an "extended" design vector can be defined by including in the optimisation scheme also the n_{up}-dimensional vector of updating times $\mathbf{t}^{up}$ (not discussed in this work):

$$\boldsymbol{\varphi} = \left[\boldsymbol{\varphi}_1, \boldsymbol{\varphi}_2, ..., \boldsymbol{\varphi}_i, ..., \boldsymbol{\varphi}_{n_{up}+1}, \mathbf{t}^{up}\right]^{\mathrm{T}} \quad . \tag{3.5}$$

A single experiment can be seen as a sequence of $(n_{up}+1)$ sub-experiments designed independently, each one of length $\tau_i = t_i^{up} - t_{i-1}^{up}$ (with $i = 1,2,\ldots,n_{up}+1$, $t_0^{up} = 0$), where τ_i is the length of the *i*-th "updating interval". The designer can set the level of excitation during each updating interval, i.e. the number of switching times per updating interval (for example, if this number is the same for all the updating intervals, we say that the sub-experiments are homogeneously excited). A further design parameter is the number (and the time placement) of measurement samples taken per updating interval; this is a critical difference with respect to other adaptive methods proposed in the literature (Stigter *et al.*, 2006), where the sampling time is defined *a-priori*.

Note that, hypothetically, after one sample measurement is taken, one could redesign the remaining part of the experiment (with the restriction that the first parameter estimate be obtained after N_θ / N_y samples at least). However, an excessively small number of experimental data could prove counterproductive (particularly in the early parameter estimations), as it could lead to an imprecise estimation and drive the following redesign to sub-optimal solutions.

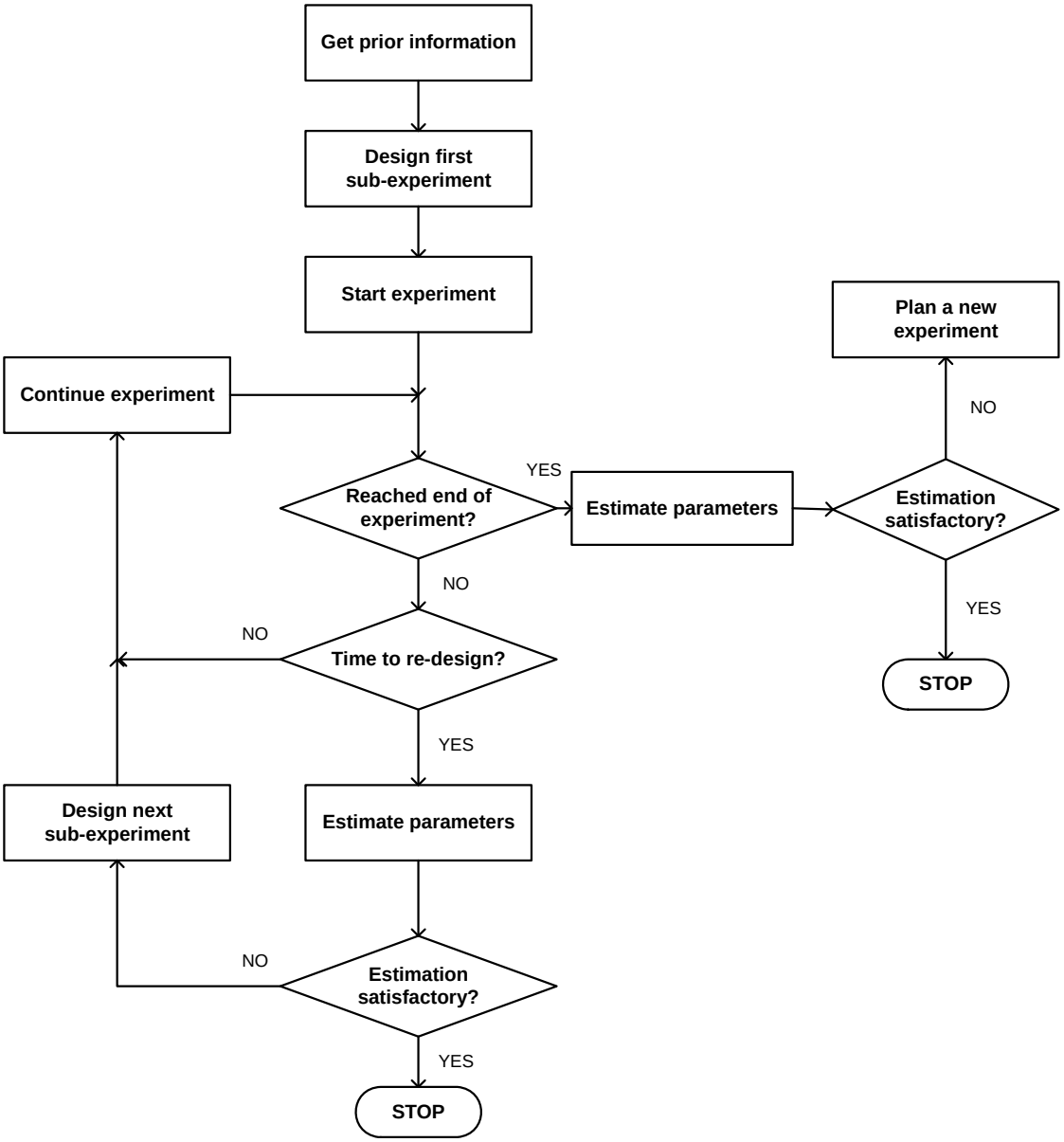


Figure 1.3 *Flow chart illustrating the main steps of the OMBRE approach.*

To conclude, OMBRE is carried out according to the following steps (Figure 3.3):

1. acquire prior knowledge on the parametric set
2. choose an updating rationale (two possible rationales will be discussed later) and design the first sub-experiment
3. start the experiment
4. when a parameter update is scheduled, estimate the model parameters:
    a. if the desired estimation quality is reached, then stop the re-design procedure (and possibly the experiment itself); otherwise
    b. re-design the remaining part of the experiment, implement the design in the running experiment, and go to step 4

5. if the desired estimation quality is not reached at the end of the experiment, design a new experiment.

In this study we assume that the time lengths needed to perform the experiment (or sub-experiment) design, or to update the control variable profile, or to take a measurement, or to perform the estimation of parameters are all negligible. However, delays can be taken into account.

Figure 3.4 illustrates the effect of OMBRE on a generic control variable u for a process with a single response ($N_y = 1$), a single manipulated input ($N_u = 1$), overall duration τ = 45 h (assigned), one update (n_{up} = 1) at $t = t^{up}$, and an overall number of sampling points n_{sp} = 5. Only one parameter θ needs estimating. During the first updating interval there are three switching levels and two sampling points to collect (i.e., $n_{sw,1}$ = 3; $n_{sp,1}$ = 2), while during the second updating interval there are five switching levels and three sampling points ($n_{sw,2}$ = 5; $n_{sp,2}$ = 3).

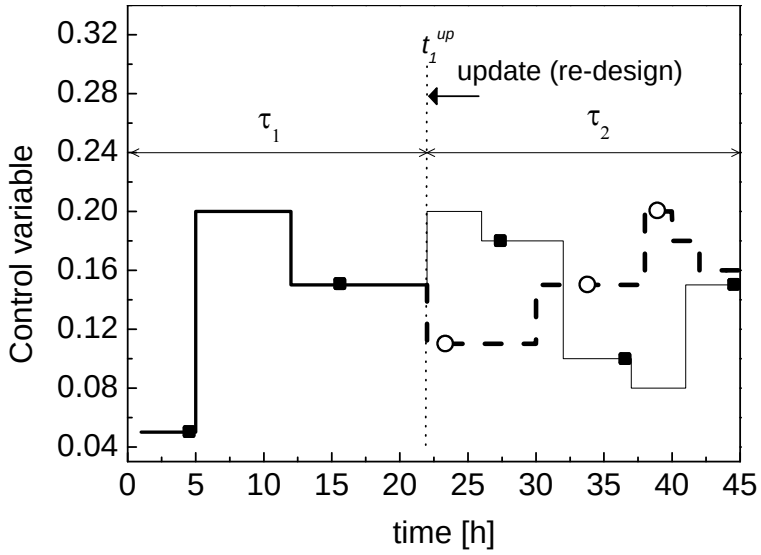


Figure 3.4 *Online experiment redesign: change from the original control trajectory (solid line) to the updated control trajectory (dashed line). At* $t > t_1^{up}$ *the original control variable profile (solid thin line) and the original sampling schedule (black squares) are discarded; a new sampling schedule (hollow circles) is designed for the second sampling interval.*

The original control trajectory is based on the information on the parameter available at time zero, i.e. before the experiment is started ($\hat{\theta} = \hat{\theta}_{t=0}$). At $t = t_1^{up}$ the control trajectory is updated thanks to a new design (based on the new estimated value $\hat{\theta} = \hat{\theta}_{t=t_1^{up}}$), therefore providing the new updated control trajectory.

The experimental budget may have a strong influence on the formulation of the ED problem, and may define lower and upper bounds for the control variables and for the number and/or frequency of the measurement samples. The experimental budget represents the maximum experimental effort that the experimenter can sustain: it depends on the cost of each

experiment (e.g., materials, energy, labour, time), on the characteristics of the control system (e.g., bounds on the number or frequency of samplings and/or control switches), and on organising factors (e.g., equipment availability, operators' shifts). In this paper, the experimental budget is defined in terms of the number of samples (n_{sp}) and control switches (n_{sw}) allowed, and of the overall experiment duration (τ).

3.4 Case study 1: biomass fermentation process

The OMBRE technique presented in the previous sections is applied to a biomass fermentation process for baker's yeast that appeared in some papers on the subject (e.g., Espie and Macchietto, 1989; Asprey and Macchietto, 2000). Assuming Monod-type kinetics for biomass growth and substrate consumption, the system is described by the following set of DAEs:

$$\begin{aligned} &\frac{\mathrm{d}x_1}{\mathrm{d}t} = \left(r - u_1 - \theta_4\right)x_1 \quad , \\ &\frac{\mathrm{d}x_2}{\mathrm{d}t} = -\frac{rx_1}{\theta_3} + u_1\left(u_2 - x_2\right) \quad , \\ &r = \frac{\theta_1 x_2}{\theta_2 + x_2} \\ &\hat{y}_i = x_i \quad , \quad i = 1,2 \end{aligned} \tag{3.6}$$

where x_1 is the biomass concentration (g/L), x_2 is the substrate concentration (g/L), $u_1(t)$ is the dilution factor (h^{-1}), and $u_2(t)$ is the substrate concentration in the feed (g/L). The model was demonstrated to be structurally identifiable with respect to the parametric set $\boldsymbol{\theta} \in \Re^4$ (the vector of parameter units for $\boldsymbol{\theta}$ is [h^{-1}, g/L, –, h^{-1}]^T), and therefore the parameter estimation problem is well posed. The experimental conditions that characterise an experiment are the initial biomass concentration x_1^0 (range 1-10 g/L), the dilution factor u_1 (range 0.05-0.20 h^{-1}), and the substrate concentration in the feed u_2 (range 5-35 g/L). The initial substrate concentration x_2^0 is set to 0 and cannot be manipulated for experiment design purposes. It is assumed that a single experiment only can be carried out to properly estimate the parameter set $\boldsymbol{\theta}$. Additionally, it is assumed that the global experimental budget is represented by a number of n_{sp} = 24 sampling points and n_{sw} = 12 switching levels to be distributed on a maximum experimental horizon of τ^{max} = 72 h. The input profiles are represented as piecewise-constant profiles; the measurement sampling times and the control variable switching times can be different. The time elapsed between any two sampling points is allowed to be between 0.01 h and τ_i, and the duration of each control interval between 0.1 and 40 h. The model parameters are normalised before performing any experiment design step.

The integration of the DAE system was performed adopting the DASOLV routine of the process modelling tool gPROMS® (by Process Systems Enterprise, Ltd.), while the nonlinear programming problem is solved for $\boldsymbol{\varphi}$ by using the Sequential Reduced Quadratic Programming (SRQP) optimisation routine, with lower and upper bounds on control variables. The same routine of gPROMS® was also used in the parameter estimation step, with upper and lower bounds on parameters values.

In all the case studies discussed in the Thesis, a two-step multiple shooting technique (Bock *et al.*, 2003) was used in order to reduce the possibility of incurring into local minima in the design step. However, as will clarified later, for a proper choice of the OMBRE configuration, the re-design strategy may allow to split the large-scale n_φ-dimensional optimisation problem into (n_{up}+1) smaller-scale optimisations, with great benefit for both robustness and efficiency of computation.

Synthetic "experimental" data were obtained by simulation of model (3.6) with $\boldsymbol{\theta} = \begin{bmatrix} 0.3100 & 0.1800 & 0.5500 & 0.0500 \end{bmatrix}^T$ as the "true" parameters set. The measurements were corrupted by normally distributed noise with a mean of zero and

$$\boldsymbol{\Sigma} = \begin{bmatrix} 0.5 & 0. \\ 0. & 0.8 \end{bmatrix} \quad . \tag{3.7}$$

Approximately, this amounts to about 14 % error on the average value of x_1 during a run, and 18 % on the average value of x_2. This matrix describes a measurement system providing large measurement noise. The initial guesses for the parameters are represented by the set $\hat{\boldsymbol{\theta}}^0 = \begin{bmatrix} 0.5270 & 0.0540 & 0.9350 & 0.0150 \end{bmatrix}^T$, corresponding to a starting estimation point that is quite far from the true value (relative error ≈ 70%). Therefore, we are considering a case in which the experimenter has a poor knowledge on the parametric system, and the measurements are imprecise. The initial guess of model parameters strongly affects the performance of the design, but, in general, the designer does not know whether the initial guess is good or not: the initial guess is simply the best available knowledge before setting up the new experiment.

Preliminary information on model parameters depends on the form of the prior distribution. A uniform distribution reflecting on a diagonal form of $\boldsymbol{\Sigma}_\theta$ is assumed; θ_i may vary within the interval [0.001;1.000] with $i = 1, \ldots, N_\theta$.

3.4.1 Analysis of different configurations for online re-design of experiments

Several configurations for re-design were analyzed in order to assess the effectiveness of the OMBRE technique. To allow for an easier illustration of the features of OMBRE, only two such configurations will be reported. Note that an E-optimal design criterion was used in all

cases (both standard experiment design and OMBRE) because it was found to be particularly suitable for the model being analysed (Galvanin *et al.*, 2007). However, the discussion that follows remains to a large extent unchanged if other design criteria are considered.

A standard experiment design (Figure 3.1) performed on all $n_\varphi = 60$ design variables is compared with two re-design configurations. In both OMBRE configurations, the number of updates to be performed during an experiment is assigned *a priori*, and the number of measurement samples is assigned to be the same within each updating interval. Therefore, the two OMBRE configurations differ for how the switches and the measurement samples are distributed within the updating intervals and for the length of each updating interval.

1. OMBRE-A: In this configuration a parameter estimation is performed after the last measurement sample available in the current (i.e., *j*-th, with $0 < j \le n_{up}$) updating interval has been taken, regardless of the time elapsed so far. Then a standard ED follows which, over the remaining length of the experiment, optimises a number of variables equal to $n_\varphi - \sum_{i=0}^{j} n_\varphi^{(i)}$, where $n_\varphi^{(i)}$ is the number of decision variables actually saturated in updating interval *i*. At the beginning of the session, *j* is set equal to 0 and $n_\varphi^{(0)} = 0$. Therefore, in general the updating intervals result to have different lengths, and the number of control switches within each interval is different.
2. OMBRE-B: In this configuration all updating intervals are assigned *a priori* to have the same length and number of control switches (i.e., the sub-experiments are homogeneously excited). Parameter estimation and sub-experiment re-design are accomplished when the scheduled length of the updating interval has expired, regardless of when the last sample measurement in that interval has been taken.

Table 3.1 summarizes the settings of the OMBRE configurations. The last column of this table clarifies that the two OMBRE configurations result in a sequence of design optimisation problems of different complexity. In OMBRE-A, the dimension of the optimisation problem is the same as in standard experiment design at the beginning of the session, and (for a given number of updates) it gradually decreases with the execution of the experiment. On the other hand, in OMBRE-B the complexity of the optimisation problem is smaller than in standard experiment design from the very beginning; the dimension of the problem depends only on the number of updates considered, and does not change with the progress of the experiment.

Table 3.1 *Case Study 1: summary of OMBRE configuration settings for different numbers of updating intervals.*

Configuration	Number of updates n_{up}	Number of samples per updating interval	Number of switching levels in *j*-th updating interval	Number of design variables in *j*-th updating interval
OMBRE-A	1; 2; 3	12; 8; 6	$n_{sw} - \sum_{i=0}^{j} n_{sw}^{(i)}$	$n_{\varphi} - \sum_{i=0}^{j} n_{\varphi}^{(i)}$
OMBRE-B	1; 2; 3	12; 8; 6	6; 4; 3	$\frac{n_{\varphi}}{n_{up}+1}$

3.4.2 Standard experiment design: results

The estimation results related to a standard session of experiment design/parameter estimation are reported in Table 3.2. An estimation result is taken as "good" if the *t*-value for that parameter is larger than a reference *t*-value based on a Student distribution. Note that it is impossible to guarantee a satisfactory estimation of all the model parameters with a single experimental run of 72 hours. The *t*-values of $\hat{\theta}_2$ and $\hat{\theta}_4$ are definitely unsatisfactory, and the 95% confidence intervals (c.i.) of those parameters are excessively large. The estimate is neither precise nor accurate.

Table 3.2 *Case Study 1*: *parameter estimation from a standard session of ED/PE (reference t-value:1.680,* asterisk denotes t-values failing the test).*

Parameters	Estimate	True Values	95 % c.i.	*t*-values
θ_1	0.2573	0.3100	0.0890	2.968
θ_2	0.0797	0.1800	0.2963	0.453*
θ_3	0.4535	0.5500	0.0774	2.020
θ_4	0.0224	0.0500	0.0882	0.412*

3.4.3 OMBRE-A: results

The OMBRE-A configuration is assessed by performing one or two or three updates of control variables (sub-cases 1, 2 and 3, respectively). See Table 3.3 for a summary of the re-design settings. Experiment redesign is shown to be always beneficial (Tables 3.4, 3.5 and 3.6).

Table 3.3 *Case Study 1: a summary of re-design settings in OMBRE-A configuration.*

	OMBRE-A.1		**OMBRE-A.2**			**OMBRE-A.3**			
n_{up}	1		2			3			
τ_i [h]	15.5	56.5	4.3	14	53.7	3.8	7.9	11.3	49
n_{sw}	5	7	2	6	4	2	3	4	3
n_{sp}	12	12	8	8	8	6	6	6	6

Table 3.4 *Case Study 1*: *final parameters estimation from OMBRE-A.1 configuration (reference t-value:1.680, asterisk denotes t-values failing the test).*

Parameters	Estimate	True Values	95 % c.i.	*t*-values
θ_1	0.3142	0.3100	0.0286	11.010
θ_2	0.3301	0.1800	0.2187	1.510*
θ_3	0.5417	0.5500	0.0773	7.012
θ_4	0.0470	0.0500	0.0246	1.911

Table 3.5 *Case Study 1*: *final parameter estimation from OMBRE-A.2 configuration (reference t-value:1.680, asterisk denotes t-values failing the test).*

Parameters	Estimate	True Values	95 % c.i.	*t*-values
θ_1	0.3088	0.3100	0.0165	18.730
θ_2	0.2942	0.1800	0.4380	0.671*
θ_3	0.5175	0.5500	0.0573	9.033
θ_4	0.0472	0.0500	0.0087	5.428

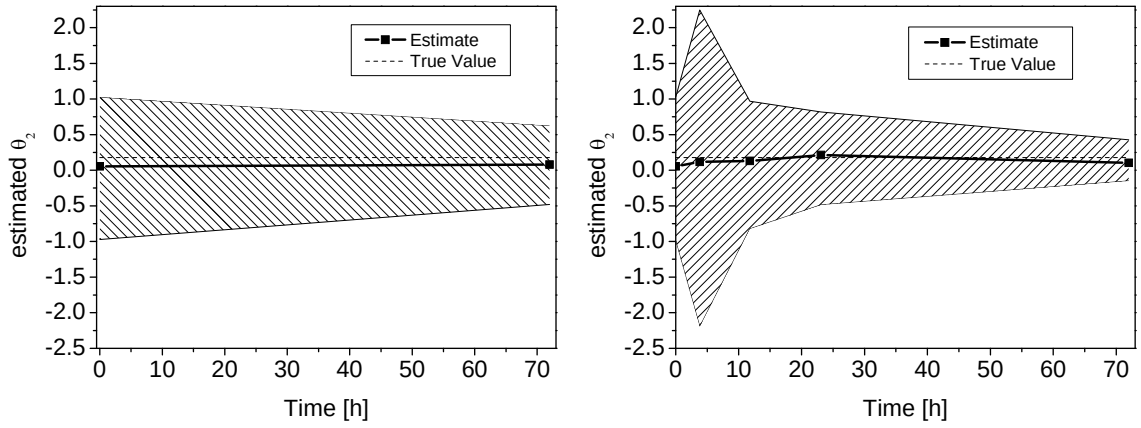
Table 3.6 *Case Study 1*: *final parameter estimation from OMBRE-A.3 configuration (reference t-value:1.680, asterisk denotes t-values failing the test).*

Parameters	Estimate	True Values	95 % c.i.	*t*-values
θ_1	0.3197	0.3100	0.0245	13.030
θ_2	0.1024	0.1800	0.0728	1.408*
θ_3	0.5643	0.5500	0.0500	11.290
θ_4	0.0588	0.0500	0.0158	3.715

A single update of the control profile has a significant impact on the precision of the estimates (*t*-values). However, note that the improvement on the confidence intervals of parameters $\hat{\theta}_2$ and $\hat{\theta}_3$ is not so marked. When two and three updates were considered, it was observed that the reduction of the uncertainty region is not gradual with n_{up}, and the parameters estimates (particularly, parameter $\hat{\theta}_2$) exhibit an oscillatory behaviour during the experiment. That could depend on the design configuration itself. The system is not homogeneously excited (see Table 3.3): for instance, note that in cases A.2 and A.3 only two switches have been performed when the first set of samples is collected. As a limited number of state levels is known, that means that an erroneous/incomplete information can be delivered and used for estimation purposes.

Figure 3.5 helps clarifying these issues and shows that in an OMBRE-A configuration the uncertainty concerning a subset of parameters (e.g., $\hat{\theta}_2$) does not necessarily decrease smoothly. As the level of excitation changes during the experiment, the initial uncertainty may determine an ineffective design in the first updating interval and, as a result, a poor parameter estimation. From Figure 3.5b it can be observed that the uncertainty about parameter $\hat{\theta}_2$ actually increases after the first update.

One possible reason is that the most informative measurements might have been designed to occur at a later time, i.e. they would occur *after* the first updating interval, and therefore when the first update is carried out all that expected information is yet to be exploited. Furthermore, the actual sensitivity of the parameters to variations in the measurements still could be poorly represented when the first re-design is accomplished: sampling points and switches may be misplaced and when more information is gathered the remaining experimental budget is not sufficient for an effective design.



(a) *(b)*

Figure 3.5 *Case Study 1: estimation profiles of* $\hat{\theta}_2$ *for a standard experiment design (a) and for OMBRE-A.3 re-design (b). The shaded uncertainty area is represented by the square root of the 95 % confidence intervals.*

From this perspective, it makes sense to go for a more "conservative" approach and divide the overall experiment duration into intervals of even lengths, as in the OMBRE-B configuration. Although such a configuration may fail to intensify the manipulation of controls where the system is more sensitive, each sub-experiment is indeed designed to obtain the maximum information gain *within that updating interval*. Results will be discussed in the following subsection.

3.4.4 OMBRE-B: results

The OMBRE-B configuration "freezes" the re-design settings, in the sense that both the number of measurement samples and the number of control switches are fixed for each interval (see Table 3.7). As in the previous configuration, a number of one or two or three updates are considered (sub-cases 1, 2 and 3 respectively).

Table 3.7 *Case Study 1: re-design settings in OMBRE-B configuration.*

Sub-Case	**OMBRE-B.1**		**OMBRE-B.2**			**OMBRE-B.3**			
n_{up}	1		2			3			
τ_i [h]	36	36	24	24	24	18	18	18	18
n_{sw}	6	6	4	4	4	3	3	3	3
n_{sp}	12	12	8	8	8	6	6	6	6

Results are quite interesting (Table 3.8-10): by adopting an OMBRE-B re-design, the precision appears to increase with the number of updates, and a single experiment is enough to estimate all the parameters in a satisfactory way (actually, only two updates can be sufficient, see Table 3.9). In OMBRE-B.3 parameters θ_1, θ_3 and θ_4 are particularly well estimated (around 1 % the relative error from the true value); the quality of the θ_2 estimation is also well within the acceptability range.

Table 3.8 *Case Study 1: final parameters estimate from case study OMBRE-B.1 configuration (reference t-value:1.680, asterisk denotes t-values failing the test).*

Parameters	**Estimate**	**True Values**	**95 % c.i.**	***t*-values**
θ_1	0.3104	0.3100	0.0209	14.840
θ_2	0.1130	0.1800	0.1135	0.996*
θ_3	0.5645	0.5500	0.0564	10.010
θ_4	0.0533	0.0500	0.0194	2.742

Table 3.9 *Case Study 1: final parameters estimate from case study OMBRE-B.2 configuration (reference t-value:1.680, asterisk denotes t-values failing the test).*

Parameters	**Estimate**	**True Values**	**95 % c.i.**	***t*-values**
θ_1	0.3124	0.3100	0.0193	16.170
θ_2	0.2445	0.1800	0.0886	2.760
θ_3	0.5431	0.5500	0.0479	11.330
θ_4	0.0475	0.0500	0.0185	2.562

Table 3.10 *Case Study 1: final parameters estimate from case study OMBRE-B.3 configuration (reference t-value:1.680, asterisk denotes t-values failing the test).*

Parameters	**Estimate**	**True Values**	**95 % c.i.**	***t*-values**
θ_1	0.31161	0.3100	0.0130	23.960
θ_2	0.1614	0.1800	0.0875	1.844
θ_3	0.5606	0.5500	0.0290	19.330
θ_4	0.0499	0.0500	0.0095	5.250

It clearly appears that by using the OMBRE-B configuration it is possible to reach a satisfactory parameter estimation with a minimal experimental effort by properly choosing the re-design settings. The experiment itself could even terminate before the maximum allowed length as soon as a target precision of model parameters has been reached. As previously

discussed, OMBRE-B is built in such a way that each updating interval is designed as to obtain the maximum amount of interval contained in that interval: that allows for a more homogeneous excitation so that a significant information content can always be exploited.
The final parameter estimation obtained by the OMBRE-B.3 configuration can even be improved if a different design criterion is exploited within the OMBRE framework. In particular, an OMBRE-SV additional configuration can be considered where the on-line re-design is carried out performing three updates including an SV design criterion (based on the minimisation of the second maximum eigenvalue of $\mathbf{V}_{\theta}$, see §2.2.3) in the second updating interval.

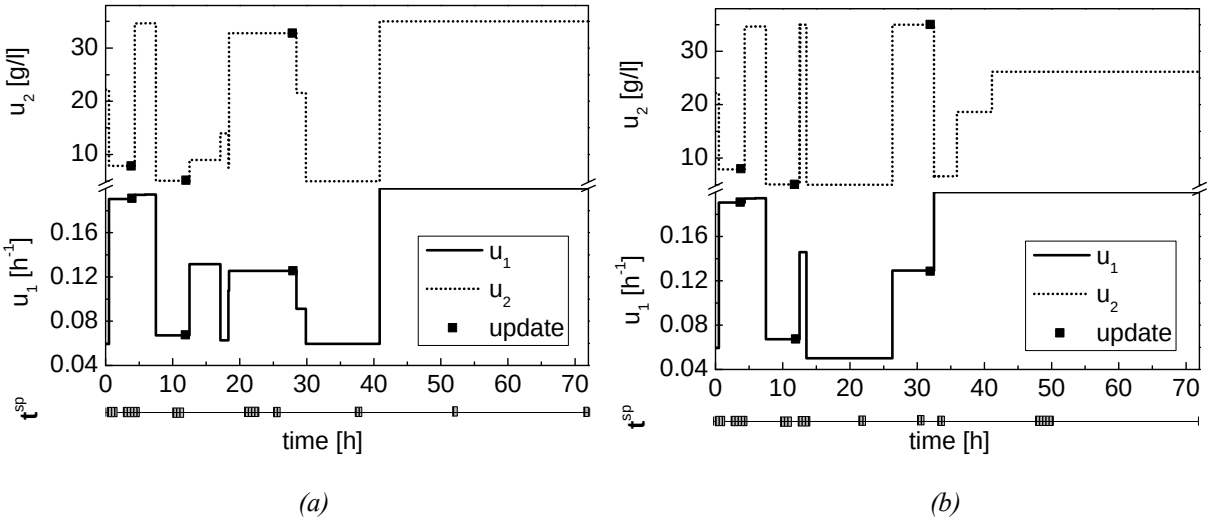


Figure 3.6 *Dilution factor (u_1), substrate concentration in the feed (u_2) and distribution of samples (t^{sp}) as planned by OMBRE-B.3 (a) and OMBRE-SV (b). Black squares show the updating times.*

Table 3.11 *Case Study 1: final parameters estimate from case study OMBRE-SV configuration (reference t-value:1.680, asterisk denotes t-values failing the test).*

Parameters	Estimate	True Values	95 % c.i.	*t*-values
θ_1	0.3102	0.3100	0.0086	36.011
θ_2	0.1105	0.1800	0.0623	1.774
θ_3	0.5598	0.5500	0.0238	23.485
θ_4	0.0545	0.0500	0.0072	7.622

Results are very interesting: the maximisation of a different direction of information provided by the SV criterion provides a change in the excitation policy of the manipulated inputs (Figure 3.6) and in the optimal allocation of sampling points, resulting in a sensible improvement on the final parameter estimation (Table 3.11). The analysis of the 95% confidence intervals shows the benefits from adopting such an approach in terms of reduction of the overall uncertainty region of model parameters.

3.5 Case study 1: additional discussion

In this section, the effect of the OMBRE approach in terms of both accuracy and efficiency of the design will be analyzed. Two heuristic indexes can be introduced to assess the quality of the estimate of different re-design configurations:

- A global accuracy index I_π considering the global contribution of relative errors $\varepsilon_i^{(\theta)}$ of the estimates

$$I_\pi = \sqrt{\sum_{i=1}^{N_\theta}\left(\frac{\hat{\theta}_i - \theta_i}{\theta_i}\right)^2} = \sqrt{\sum_{i=1}^{N_\theta}\left(\varepsilon_i^{(\theta)}\right)^2} \quad ; \tag{3.8}$$

- A global precision index I_α that considers the global relative variability of the parametric system in terms of standard deviation σ_{θ_i} of the estimates

$$I_\alpha = \sqrt{\sum_{i=1}^{N_\theta}\left(\frac{\sigma_{\theta_i}}{\theta_i}\right)^2} \quad . \tag{3.9}$$

The global accuracy and precision indexes are plotted in Figure 3.7, where the best estimates are localised close to the origin. From Figure 3.7 it is possible to observe that the OMBRE-B with three updates gives the finest results in terms of overall precision and accuracy of estimation. The OMBRE-A configuration is definitely more erratic in its performance and demonstrates that the benefits of the re-design depends on the distribution of samples and control switches along the experiment.

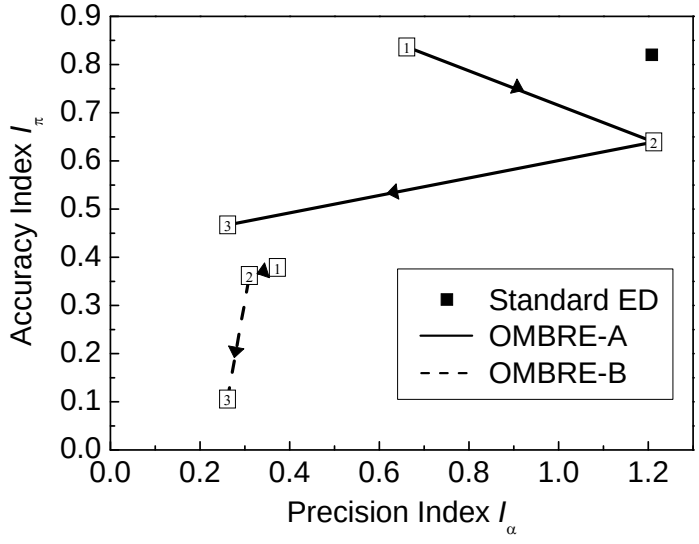


Figure 3.7 *Case Study 1: accuracy Vs. precision plots for all analysed configurations (the numbers inside squares are the numbers of OMBRE updates).*

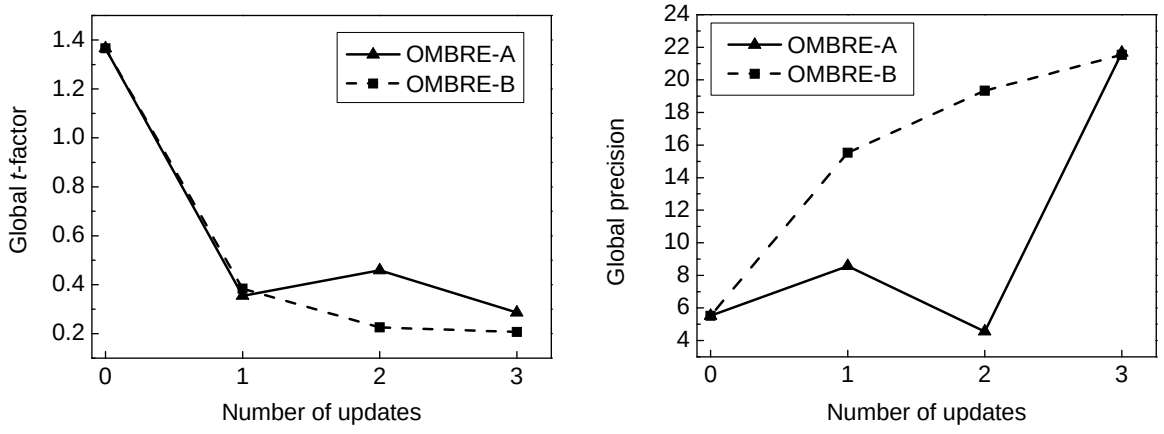
This kind of global analysis cannot be performed in practice, because the true vector of model parameters is obviously not known. Therefore, new heuristic indicators are introduced to provide a measure of precision in a more general fashion. The term

$$\Omega_\theta = \left(\sqrt{\sum_{i=1}^{N_\theta} \sigma_{\theta_i}^2} \right)^{-1} \tag{3.10}$$

is a measure of the parameters precision in a global sense (the variances $\sigma_{\theta_i}^2$ are the diagonal elements of $\mathbf{V}^\theta$, describing a global uncertainty region): the larger Ω_θ, the higher the precision. On the other hand, the statistical *t*-test can be exploited to define a "global *t*-factor" (GTF) precision index:

$$GTF = \frac{1}{N_\theta} \sum_{i=1}^{N_P} t_i^{-1} \quad . \tag{3.11}$$

High *t*-values indicate that parameters are well determined in the model. Therefore, the GTF index emphasizes the effect of the worst parameter estimation in each specific configuration set: the lower GTF, the better the estimate.
The GTF values and the global precision of the estimates for a variable number of updates are shown in Figure 3.8 (connectors between points have been reported only for clarity).



(a) *(b)*

Figure 3.8 *Case Study 1: global t-factor* GTF *(a) and global precision* Ω_θ *(b) for selected configurations of re-design at a variable number of updates.*

The GTF plot shows that, as the number of updates increases, the OMBRE-B configuration gives the best performance in term of parameters' precision. Note from Figure 3.8b that the OMBRE-B re-design exhibits a gradual increment of precision, while OMBRE-A shows an oscillating behaviour. The same plot shows that the level of global precision reached by

OMBRE-A with n_{up} = 3 is comparable with that of OMBRE-B, although the comparison based on the true values (Figure 3.7) has already shown that the two configurations differ significantly in terms of accuracy of the estimates.
One could think that by increasing the number of updates it might be possible to further improve the precision of the estimate. Figure 3.9 shows the GTF and Ω_θ indexes of the estimates for an OMBRE-B configuration when n_{up} is increased from one to five.

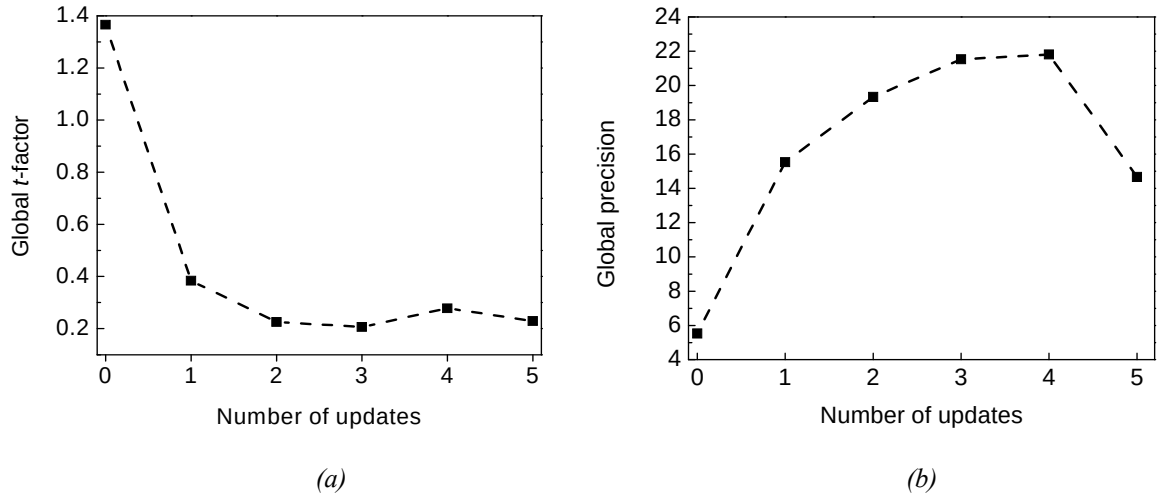


Figure 3.9 *Case Study 1: Global* t*-factor* GTF *(a) and global precision* Ω_θ *(b) for OMBRE-B re-design with* n_{up} *from one to five.*

As shown in Figure 3.9b, the precision slightly increases passing from 3 to 4 updates, and then drastically decreases for n_{up} = 5. The GTF analysis (Figure 3.9a) shows no improvement in global precision passing from 3 to 4 or 5 updates. Although not reported here, we observed that after three updates the estimation of the parameter θ_2 worsens significantly. Results are not so surprising: if the number of updates is increased at a fixed number of design variables, a point is encountered at which the optimiser has no leverage to boost the overall information through the re-design (for instance, note that for OMBRE-B.5, the switches available for design optimization are only two for each updating interval).

3.6 Case study 2: synthesis of urethane

In this section a second more complex model will be taken into account as a second instance to demonstrate the effectiveness of the OMBRE methodology. We will consider the industrial kinetic model proposed by Körkel *et al.* (1999) and Bauer *et al.* (2000) to describe the reaction of urethane in a simultaneous and consecutive reaction with chemical equilibrium:

$$\begin{aligned} A + B &\rightarrow C \\ A + C &\leftrightarrows D \end{aligned} \qquad (3.12)$$

$$3\mathrm{A} \rightarrow \mathrm{E}$$

where A is phenylisocyanate, B is butanol, C is urethane, D is allophanate and E is isocyanurate; dimethylsulfoxide (S) is used as solvent. The experiments for these reactions are carried out in a semi-batch reactor with two feed vessels $v1$ and $v2$, one for phenylisocyanate (and the solvent) and one for butanol (and the solvent). At the beginning, the reactor contains solvent, phenylisocyanate and butanol. It is assumed that the reactor temperature T can be manipulated directly.
The model is represented by the following set of DAEs:

$$\begin{aligned}
&\frac{dn_C}{dt} = V\left(r_1 - r_2 + r_3\right) \ ; \\
&\frac{dn_D}{dt} = V\left(r_2 - r_3\right) \ ; \\
&\frac{dn_E}{dt} = Vr_4 \ ; \\
&n_A + n_C + 2n_D + 3n_E - n_A^0 - f^{v1} n_A^{v1} = 0 \ ; \\
&n_B + n_C + n_D - n_B^0 - f^{v2} n_B^{v2} = 0 \ ; \\
&n_S - n_S^0 - f^{v1} n_S^{v1} - f^{v2} n_S^{v2} = 0 \ ;
\end{aligned} \tag{3.13}$$

with initial conditions for the three differential variables:

$$n_C(0) = n_D(0) = n_E(0) = 0 \ . \tag{3.14}$$

where the molar numbers n_i for species i are the state variables of the nonlinear DAE system. The following correlations need also considering:

$$V = \sum_{i=1}^{6} \frac{n_i M_i}{\rho_i} \ ; \tag{3.15}$$

$$r_1 = k_1 \frac{n_A}{V} \frac{n_B}{V} = k_1 c_A c_B \quad ; \quad r_2 = k_2 c_A c_C \quad ; \quad r_3 = k_3 c_D \quad ; \quad r_4 = k_4 c_A^2 \ . \tag{3.16}$$

$$k_i = k_{refi} \exp\left(-\frac{E_{ai}}{R}\left(\frac{1}{T} - \frac{1}{T_{refi}}\right)\right) \qquad i = 1,2,4 \ ; \qquad k_3 = \frac{k_2}{k_c} \ ; \tag{3.17}$$

$$k_c = k_{c2} \exp\left(-\frac{\Delta h}{R}\left(\frac{1}{T} - \frac{1}{T_{g2}}\right)\right) \ ; \tag{3.18}$$

In this model eight parameters are unknown: the steric factors k_{refi} (i = 1, 2, 4), the activation energies E_{ai} (i = 1, 2, 4), the equilibrium constant k_{c2} and the reaction enthalpy Δh of the reversible reaction. The reaction rates r_i are expressed in [mol/(h·L)]. Molar masses M_i [kg/mol], densities ρ_i [kg/m^3], reference temperatures T_{ref1}, T_{ref2}, T_{ref4}, T_{g2} [K] and the gas constant R [J/(mol·K)] are set as constants.

As in Körkel *et al.* (1999), Bauer *et al.* (2000) two "accumulated" feeds f^{v1} and f^{v2} from the two feed vessels are considered: they can vary from zero up to the initial molar hold-ups of the vessels, described by n_A^{v1}, n_B^{v2}, n_S^{v1} and n_S^{v2}, i.e. the initial molar numbers of phenylisocyanate, butanol and solvent within the two feed vessels. Feeds f^{v1} and f^{v2} and temperature T are the experiment design variables. However, for ease of implementation the actual vector of time dependent design variables is

$$\mathbf{u} = \begin{bmatrix} z_1 & z_2 & T \end{bmatrix}^T \tag{3.19}$$

where z_1 and z_2 are non negative piecewise constant functions defined as:

$$z_1 = \frac{df^{v1}}{dt} \quad ; \quad z_2 = \frac{df^{v2}}{dt} \quad . \tag{3.20}$$

The temperature profile T is discretised as a piecewise linear function within the range [300 K; 473 K]. The vector of time-invariant control variables **w** takes into account the initial molar numbers of the species within the feed vessels and inside the reactor:

$$\mathbf{w} = \begin{bmatrix} n_A^0 & n_B^0 & n_S^0 & n_A^{v1} & n_S^{v1} & n_B^{v2} & n_S^{v2} \end{bmatrix}^T . \tag{3.21}$$

The measured variables are the molar concentrations [mol/L] of urethane (c_C), of allophanate (c_D) and isocyanurate (c_E). It is assumed that the measurement errors are uncorrelated and with $\sigma_{c_C} = \sigma_{c_D} = \sigma_{c_E} = 0.1$ mol/L. During each experiment performed n_{sp} = 18 samples are collected. Thus, the design of a single experiments implies the optimisation of the following variables (n_φ = 69):

1. the optimal sampling scheduling of the 18 samples;
2. eight switching times for T, z_1 and z_2;
3. eighteen switching levels for T, nine for z_1 and nine for z_2;
4. the seven initial conditions collected in **w**.

It is assumed that each experiment lasts 90 hours.

Note that the results cannot be compared to the ones presented in Körkel *et al.* (1999) and Bauer *et al.* (2000), since in the original papers *i)* there are more design variables (90 instead of 69), *ii)* phenylisocyanate, too, can be measured by titration (although less frequently than the other species), and *iii)* more precise measurements are assumed. In any case, the objective

here is not to compare the proposed methodology to the one presented in the cited papers, but to provide a realistic case study to assess the performance of the OMBRE approach with respect to a standard experiment design.
The initial guesses and the "true" values of the parameters set are summarised in Table 3.12. The final estimates obtained in (Körkel *et al.*, 1999) were taken as the true values.

Table 3.12 *Case Study 2: vector of initial guesses and vector of "true" values of model parameters as adopted in the case study.*

	Δh [J/mol]	E_{a1} [J/mol]	E_{a2} [J/mol]	E_{a4} [J/mol]	k_{c2} [L/mol]	k_{ref1} [L/molh]	k_{ref2} [L/mol·h]	k_{ref4} [L/mol·h]
$\hat{\boldsymbol{\theta}}^0$	-17031	35240	85000	35000	0.170	5.00E-4	8.0E-8	1.00E-8
$\boldsymbol{\theta}$	-18300	29440	71014	23020	0.217	1.25E-3	7.29E-6	8.80E-7

Apart from being a more complex system than the one considered in Case study I, the model is quite a good benchmark to assess the OMBRE approach. In fact, the experiments are supposed to last for a long time, i.e. there might be a great benefit in terms of time and labour in increasing the design efficiency by exploiting the collected information while an experiment is running. Furthermore, such a long duration makes the computational time required for online parameters' estimations and experiment re-designs a minor issue.
The D-optimal criterion (Pukelsheim, 1993) was adopted to design the experiments. Although our experience suggests that it is often outperformed by the E-optimal criterion, it is nonetheless the most widely used approach to experiment design.
Two design configurations are compared and discussed:

- an OMBRE with OMBRE-B approach (number of samples and of control switches equally distributed);
- a standard sequential experiment design.

As in Case Study 1, each parameter estimation session adopts a maximum likelihood criterion acting on the overall parametric pool. The results obtained through each experimental session are collected in Tables 3.13 and 3.14 for the OMBRE approach and the standard sequential ED, respectively.
The OMBRE design allows to reach a satisfactory parameter estimation after 210 hours, with two experiments performed and a third experiment that stops after the first estimation of the parameters (i.e. right before starting the first re-design). On the contrary, when a standard experiment is used, it is clearly shown that after three experiments (and a global duration of the experimental time of 270 hours) it is still impossible to estimate all the parameters in a statistically sound way (the final statistics show that parameters k_{c2} and k_{ref1} are still estimated unsatisfactory). Although not reported here, it was verified that one additional experiment (for a total elapsed time of 360 h) is needed in order to have a reliable estimation of all parameters using a standard ED.

Table 3.13 *Case Study 2: parameter estimation obtained through an OMBRE-B approach with n_{up} = 2. Time t_{tot} stands for the total elapsed time. Asterisks denote estimates failing the t-test.*

	Exp1			Exp2			Exp3
t_{tot}	*30 h*	*60 h*	*90 h*	*120 h*	*150 h*	*180 h*	*210 h*
Δh	-16000*	-17996*	-18240*	-18056*	-18999*	-17226	-17214
E_{a1}	28253*	30362*	30928*	30989*	32267	32842	33127
E_{a2}	65903	65120*	64660*	64021	71424	72298	72207
E_{a4}	22000*	22050*	22019*	22306*	23898*	24365	24492
k_{c2}	0.2846*	0.2847*	0.2847*	0.2840*	0.2846*	0.3000*	0.2951
k_{ref1}	8.96E-4*	8.96E-4*	9.53E-4*	1.04E-3*	1.00E-3*	1.10E-3*	1.26E-3
k_{ref2}	5.12E-7*	8.04E-6*	7.71E-6*	8.84E-6*	8.09E-6	8.66E-6	8.95E-6
k_{ref4}	4.09E-7*	4.10E-7*	4.09E-7*	6.41E-7*	5.14E-7*	5.87E-7	6.33E-7
GTF	7.831	5.521	4.430	2.567	2.856	1.663	0.235
Ω_0 **(×10^6)**	6.7	13.2	14.7	22.5	12.4	81.0	109.0

Table 3.14 *Case Study 2: parameter estimations obtained through a sequential experiment design of three experiments. Time t_{tot} stands for the total elapsed time. Asterisks denote estimates failing the t-test.*

	Exp1	Exp2	Exp3
t_{tot}	*90 h*	*180 h*	*270 h*
Δh	-16775*	-17393*	-15986
E_{a1}	28968*	35387*	28828
E_{a2}	66844	69222	74117
E_{a4}	16037*	22561	26710
k_{c2}	0.2847*	0.2311*	0.2082*
k_{ref1}	1.27E-3*	1.58E-3*	1.29E-3*
k_{ref2}	8.92E-6*	8.22E-6	9.40E-6
k_{ref4}	7.57E-7*	7.57E-7*	7.79E-7
GTF	5.960	2.694	0.423
Ω_0 **(×10^6)**	9.3	16.5	109.0

In terms of global indexes, it can be observed that the GTF generally decreases in both the OMBRE and the standard designs. However, note that at the end of each experiment the value is smaller in the case of the OMBRE approach, which therefore demonstrates a higher precision. Similar considerations can be drawn for the second precision index, Ω_θ: after each one of the first two experiments, the OMBRE design always outperforms the standard design. At the end of experiment 3 the precision index is the same, but less time and measurements were needed in the OMBRE design. To conclude, it can be stated that also for Case study 2 the OMBRE technique is a more efficient approach to the design of experiments for parameter estimation: on the one side, the overall experimental time as well as the number of measurement samples can be significantly reduced; on the other side, the optimisation problem is split into three smaller optimisation problems with great benefits for the robustness of computation.

3.7 Final remarks

A novel online model based re-design of experiment (OMBRE) approach for optimal ED was presented and discussed in this Chapter. This procedure demonstrates the possibility and the benefits of adopting a whole online re-design while the experiment is being performed. In a standard sequential design perspective, the experiment design, experiment execution and parameter estimation phases are carried out in a strictly sequential manner, and therefore each experiment is fully planned on the basis of the initial parameter estimate only. The OMBRE technique allows for the progressive update of the experimental settings through intermediate design of experiments, in order to maximise the informative level of the experiment while it is still running. The methodology proved to have more advantages over standard optimal experiment design techniques in terms of computational robustness and efficiency and, most importantly, of experimental efficiency.

Chapter 4

A backoff strategy for MBDoE under parametric uncertainty*

Model-based experiment design techniques are flexible techniques for the estimation of the process model parameters, allowing for the definition, within the optimisation scheme, of a set of active constraints possibly acting on the physical system. However, uncertainty in the model parameters can lead the constrained design procedure to predict experiments that turn out to be, in practice, suboptimal, thus decreasing the effectiveness of the experiment design session. Additionally, in the presence of parametric mismatch, the feasibility constraints may well turn out to be violated when that optimally designed experiment is performed, leading in the best case to less informative data sets or, in the worst case, to an infeasible or unsafe experiment. In this Chapter, a novel and general methodology is proposed to formulate and solve the experiment design problem by explicitly taking into account the presence of parametric uncertainty, so as to ensure both feasibility and optimality of the planned experiment. A prediction of the system responses for the given parameter distribution is used to evaluate and update suitable backoffs from the nominal constraints, which are used in the design session in order to keep the system within a feasible region with specified probability. This approach is particularly useful when designing optimal experiments starting from limited preliminary knowledge of the parameter set, with great improvement in terms of design efficiency and flexibility of the overall iterative model development scheme. The effectiveness of the proposed methodology is demonstrated and discussed by simulation through two illustrative case studies concerning the parameter identification of physiological models related to diabetes and cancer care.

4.1 Introduction

The goal of a constrained MBDoE is to achieve both optimality (maximisation of the expected information) and feasibility (no constraint violations) during the experimental trials. Since the methodology is model-based, both model mismatch (i.e. a model structure inadequate to represent the physical systems) and parametric mismatch (i.e. incorrect values of the parameters) may affect the consistency of the whole design procedure (Ford *et al.*,

* Portions of this Chapter have been published in Galvanin *et al.* (2009c) and Galvanin *et al.* (2010a).

1989). Despite the importance of ensuring optimally informative as well as feasible experiments, there has been relatively little work to develop a model-based experiment design technique capable of overcoming both of the above issues.

In the topic of process systems design the problem of constrained optimisation under uncertainty, seen as a trade-off between feasibility and optimality, has long been recognised as a key issue (Grossmann and Sargent, 1978) because the presence of both variations in the operating conditions and uncertainty in the process model (in terms of process model parameters and mathematical structure) deeply affects the optimality of process and equipment design (Raspanti *et al.*, 2000). Several approaches have been proposed to solve the process design problem in the presence of parametric uncertainty, where uncertain parameters are described by probability distribution functions and the design problem is formulated using probabilistic decision criteria.

Several work have appeared where the issue has been tackled through a robust implementation based on the solution of a max-min optimisation problem (worst case approach; Halemane and Grossmann, 1983; Swaney and Grossmann, 1985). In this way the design solution (formally an "overdesign") represents the best decision based on the actual knowledge on the process. Different methodologies have been proposed to relax the worst case assumption, where an expected value approach is used to increase the design feasibility (Pistikopoulos, 1995; Mohideen *et al.*, 1996; Ierapetritou and Pistikopoulos, 1994; Li *et al.*, 2008). A somehow similar route was considered by Monningmann and Marquardt (2003), who proposed a robust optimisation approach to guarantee feasibility and stability over the expected range of variation introducing conservatism to handle parametric uncertainty.

In fact, as discussed by Chachuat *et al.* (2008), in the presence of model uncertainty feasibility is often of greater importance than optimality. In order to tackle this issue, a more tailored strategy is to enforce feasibility by the presence of backoffs from active constraints. In the backoff approach, which also may be implemented according to a worst-case approach (Bahri *et al.*, 1995) or to an expected value approach (Loeblein *et al.*, 1999), or defining the magnitude of the output variation (Lear *et al.*, 1995), the actual operating point is moved away from the nominal operating point in order to ensure feasibility of the process to compensate for the effect of disturbances.

Other formulations have been proposed to solve specific operational issues like flexibility (i.e. the ability of the process to preserve feasibility in the presence of uncertainties; Grossmann *et al.*, 1984; Bansal *et al.*, 2000), robustness (i.e. the ability to preserve optimality conditions for disturbances in the inputs; Bernardo and Saraiva, 1998), controllability (i.e. the ability of the system to recover from process disturbances or dynamic plant behaviour; Bahri *et al.*, 1996), economic performance (i.e. the choice of the compromise between feasibility and optimality in terms of the economy of the process itself; Loeblein and Perkins, 1998) and the integration of some of the aforementioned issues (Bahri *et al.*, 1997; Bernardo *et al.*, 2000).

From an MBDoE perspective, robust techniques for optimal experimental design have been proposed in literature (Körkel *et al.*, 2004; Asprey and Macchietto, 2002) to preserve the optimality of the design in the presence of parametric uncertainty, either through a worst case approach or performing a dynamic optimisation over all the predicted uncertainty region of model parameters (expected value approach). Rustem and Zakovic (2003) proposed a semi-infinite programming algorithm to solve the global optimisation design and the feasibility problems in parallel, with great benefit in terms of computational time saving; in this case the robust constrained MBDoE problem was solved with constraints on the design variables only. Rojas *et al.* (2007) proposed a min-max approach to solve the robust optimal design problems with simple constraints on the manipulated inputs. Interestingly, the authors also compare different design criteria linking robust control techniques (Hjalmarsson, 2005) and nominal experimental design procedure. Chu and Hahn (2008) proposed a technique to integrate optimal parameters selection with experimental design under parametric uncertainty for nonlinear dynamic systems. The robust design was performed by adopting a hybrid method combining a genetic algorithm and a stochastic approximation technique.
However, a framework for explicitly taking into account the feasibility issue within an MBDoE approach has not been presented so far. In this Chapter, a new methodology is illustrated and discussed to address the problem of the constrained optimal experimental design under parametric uncertainty. Similarly to what was successfully proposed in other fields (and discussed in the above), a backoff policy is adopted that allows guaranteeing the feasibility of the optimally designed experiment in the presence of parametric uncertainty. The technique is particularly suitable for planning experiments in such systems (for example, physiological systems or reactive systems) where the operability is strictly reduced by the presence of active constraints on state variables that are inherently related to the physical system. The proposed technique is illustrated and discussed through two simulated case studies concerning parameter identification in physiological models related to the care of diabetes mellitus and of cancer.

4.2 Problem definition

A general dynamic deterministic model of the form (2.1) can be subject to a set of constraints in the form

$$\mathbf{C} = \mathbf{x}(t) - \mathbf{G}(t) \leq 0 \tag{4.1}$$

where $\mathbf{C}$ is an N_c-dimensional set of constraint functions expressed through the set $\mathbf{G}(t) \in \Re^{N_c}$ of (possibly time-varying) active constraints on the state variables $\mathbf{x}(t)$, reflecting

the (possible) constraints acting on the physical system. The optimal design under constraints problem can be formulated as finding:

$$\boldsymbol{\varphi}_{\mathrm{OPT}} = \arg\min\left\{\psi\left[\mathbf{V}_{\theta}\left(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi}\right)\right]\right\} \tag{2.14}$$

subject to **C**. In addition to (4.1), a n_{φ}-dimensional set of constraints on the design variables may be present, too, usually expressed as

$$\varphi_i^l \le \varphi_i \le \varphi_i^u \qquad i = 1 \ldots n_{\varphi} \tag{4.2}$$

with lower (superscript *l*) and upper (superscript *u*) bounds on the elements of $\boldsymbol{\varphi}$, constraining the design to a hyper-rectangular sub-space of the overall design space $\Re^{n_{\varphi}}$.

The solution to the constrained MBDoE optimisation problem is the optimal design vector $\boldsymbol{\varphi}$ that through model (2.1) simultaneously satisfies the design optimality condition (2.14), the feasibility constraints on the state variables (4.1) and the constraints on the design variables (4.2). Note that both the optimality and the feasibility conditions are evaluated at the current estimated value of model parameters $\hat{\boldsymbol{\theta}}$, which is different from the true (and unknown) value of model parameters $\boldsymbol{\theta}$. The parametric mismatch affects both the optimality condition (2.14) and the feasibility condition (4.1) as well as the constraints in (4.2). Prior knowledge on the physical system (in particular of the sources of uncertainty) and a preliminary analysis of the model around a set of nominal experimental conditions may help to define the boundaries of an "expected" uncertainty region of model parameters. Hyper-rectangular uncertainty regions are frequently used (Mohideen *et al.*, 1996; Bahri *et al.*, 1997) but, as suggested by Rooney and Biegler (2001), the adoption of non linear confidence regions derived from the likelihood ratio test leads to a more accurate representation of the uncertainty.

In order to predict the effect of parametric uncertainty on the optimality and feasibility conditions, a stochastic approach may be adopted, taking into account all the possible realisations of the parameter vector elements over all the (expected) uncertainty. In the stochastic approach the entire set of possible realisations of $\boldsymbol{\theta}$ has to be defined through some probabilistic assumptions, concerning the type of distribution and the deviation metrics from the current estimate of the model parameters, $\hat{\boldsymbol{\theta}}$. In this perspective the set of model parameters can be regarded as a stochastic variable (symbol ~), i.e. a function $\tilde{\boldsymbol{\theta}} : \boldsymbol{T}^{N_{\theta}} \rightarrow \Re^{N_{\theta}}$ considering all the possible realisations from the N_{θ}-dimensional expected uncertainty of model parameters $\boldsymbol{T}$ to the N_{θ}-dimensional field of real numbers.

In the presence of parametric uncertainty, the solution of the constrained MBDoE problem is not deterministic and the solution of the optimal design under constraints problem is a stochastic design vector $\tilde{\boldsymbol{\varphi}}$ (i.e. a set of possible realisations of the optimal design vector) satisfying at the same time the model equations, the design optimality condition and the

feasibility constraints on both state and design variables. The stochastic design vector represents the field of optimal and feasible solutions of the design problem in the presence of parametric uncertainty where the optimal design problem under constraints is solved over $\boldsymbol{T}$. Considering that, unless a large number of identical experimental facilities is available, only one experiment can be performed at a time, the above general formulation needs simplifying so that a unique feasible optimal solution for the experiment design problem is found. The design objective function (2.14) can be evaluated, adopting a conservative approach, considering an expected value or worst case metric for $\mathbf{V}_\theta$ (emphasizing robustness, as is done in Asprey and Macchietto, 2002), or, as is done in this work, at the actual information point (emphasizing optimality). Thus, the following set of equations has to be solved

$$\boldsymbol{\varphi}_{\mathrm{OPT}} = \arg\min\left\{\psi\left[\mathbf{V}_\theta\left(\hat{\boldsymbol{\theta}},\boldsymbol{\varphi}\right)\right]\right\} \tag{2.14}$$

subject to

$$\mathbf{f}\left(\dot{\tilde{\mathbf{x}}}(t),\tilde{\mathbf{x}}(t),\mathbf{u}(t),\mathbf{w},\tilde{\boldsymbol{\theta}},t\right)=0 \tag{4.3}$$

$$\hat{\mathbf{y}}(t)=\mathbf{g}(\tilde{\mathbf{x}}(t)) \tag{4.4}$$

$$\mathbf{C}=\mathbf{x}(t)-\mathbf{G}(t)+\boldsymbol{\beta}\left(\tilde{\mathbf{x}}(t),\tilde{\mathbf{x}}(t),\mathbf{u}(t),\mathbf{w},\tilde{\boldsymbol{\theta}},t\right)\le 0 \tag{4.5}$$

$$\varphi_i^l \le \varphi_i \le \varphi_i^u \qquad i = 1 \ldots n_\varphi \tag{4.2}$$

where $\boldsymbol{\beta}$ is a N_c-dimensional set of time-dependent backoff functions taking into account the effect of parametric uncertainty on the state variables at the designed experimental conditions. Note that $\boldsymbol{\beta}$ is a function of a subset of the design vector $\boldsymbol{\varphi}$ (i.e., of $\mathbf{u}$ and $\mathbf{w}$ only). The adoption of a backoff strategy allows satisfying the stochastic feasibility condition

$$\tilde{\mathbf{C}}=\tilde{\mathbf{x}}(t)-\mathbf{G}(t)\le 0 \tag{4.6}$$

where the effect of parametric uncertainty is taken into account exclusively through the backoff vector $\boldsymbol{\beta}$. Since the backoff vector is a function of stochastic variables, a stochastic simulation approach has been adopted here. The stochastic simulation procedure for backoff vector evaluation consists of three key steps:

1. characterisation of the parametric uncertainty: some assumptions have to be made on the multidimensional uncertainty domain $\boldsymbol{T}$ of model parameters and a reliable sampling of $\boldsymbol{T}$ has to be carried out;

2. mapping the uncertainty region of the state variables: in our approach several simulations are carried out adopting random values for model parameters and a subsequent statistical analysis of the profiles of state variables is used to provide a probabilistic description of the uncertainty region of the state variables;
3. backoff formulation and policy: starting from the description of the uncertainty region of the state variables, the user can build the set of backoff functions in (4.5). Note that the experimenter's decisions may deeply affect the fulfilment of (4.6) since some constraints could be enforced or relaxed through a backoff policy.

The steps involved in the stochastic simulation approach for the backoff building are analysed in detail in the following subsections.

4.2.1 Characterisation of the parameter uncertainty

If a probability function is associated with the expected parameter uncertainty domain, then it is possible to define $\boldsymbol{T}$ as

$$\boldsymbol{T} = \left[\widetilde{\theta}_{ij} \middle| \widetilde{\theta}_{ij} \in p_\theta\left(\hat{\boldsymbol{\theta}}, \xi_\theta\right), \quad i = 1...N_\theta, j = 1...N\right] \tag{4.7}$$

where ξ_θ is a n_{ξ_θ}-dimensional vector of parameters defining the specific probability distribution p_θ, $\widetilde{\theta}_{ij}$ is the realisation of the i-th element of the parameters vector in the j-th event and N is the population abundance. Note that the elements of $\widetilde{\boldsymbol{\theta}}$ could be either independently distributed or correlated random variables, coming either from a joint probability distribution or from a set of univariate probability distributions. A sampling of the expected uncertainty domain $\boldsymbol{T}$ needs to be carried out in order to assess the effect of the possible realisations of the unknown parametric set on the state variables of the model. Different sampling methods can be used at the purpose (Cochran, 1977).

A critical aspect of the sampling procedure is the choice of the number N' of samples of the parameters probability distribution. For one random variable (Bartlett *et al.*, 2001) the following formula can be used, according to the central limit theorem

$$N' = \frac{t' \hat{\sigma}^2}{\varepsilon'^2} \tag{4.8}$$

with t' the t-value for the selected confidence level α (set by the experimenter), ε' the error that the experimenter is willing to expect and $\hat{\sigma}^2$ the expected variance value. No general formulas for N' to define an appropriate sampling in multivariate distributions are available, and a multivariate statistical analysis of the sampled region is highly recommended (Bilodeau and Brenner, 1999). Chao (2007) proposed a principal component analysis (PCA) method for sampling from multivariate distributions to summarize most of the variability using the

principal components with highest variance. Global sensitivity analysis (GSA) methods involving FAST, Sobol (Saltelli *et al.*, 1999) or the more computationally efficient DGSM techniques (Kucherenko *et al.*, 2009) could be useful to detect the most relevant subsets of model parameters, allowing to decrease the sampling size of the analysis. The main drawback is that GSA is usually evaluated at some specified experimental conditions and, because of the computational effort, it is difficult to integrate it in a MBDoE optimisation framework.

4.2.2 Mapping the uncertainty region of the state variables

After sampling the space of uncertain model parameters $\boldsymbol{T}$, a stochastic simulation is carried out where model (2.1) is solved repeatedly for the entire sub-set of possible realisations of the parametric uncertainty. The goal of the stochastic simulation is to evaluate a set of time dependent statistical parameters $\boldsymbol{\xi}_x(t)$ describing $p_{x|\boldsymbol{\varphi}}(\boldsymbol{\xi}_x(t),t)$, i.e. the probability distribution of the state variables in the presence of parametric mismatch at the given experimental settings defined by $\boldsymbol{\varphi}$. Since the state variables are usually correlated, $p_{x|\boldsymbol{\varphi}}(\boldsymbol{\xi}_x(t),t)$ generally defines a time-dependent joint confidence region of the state variables. A set of N' simulations based on the N' sampled values of the model parameters around the nominal point $\hat{\boldsymbol{\theta}}$ at the experimental conditions $\boldsymbol{\varphi}$ is carried out, generating the N'-dimensional set of dynamic responses, which are collected in a $N' \times N_y$ time dependent matrix $\mathbf{X}$. The problem of mapping the uncertainty region of the state variables can be interpreted as finding the n_{ξ_x}-dimensional set of time-dependent parameters $\boldsymbol{\xi}_x(t)$ that are specific for describing the given distribution (e.g., for a normal distribution, n_{ξ_x} = 2 and the distribution parameters are the vector of average values and the variance matrix of model parameters).

It must be pointed out that:

- the number of simulations might be sufficient for a complete description of p_θ, but not of $p_{x|\boldsymbol{\varphi}}(\boldsymbol{\xi}_x(t),t)$ since the model is nonlinear and the two distributions are usually different;
- the evaluation of $\mathbf{X}$ is computationally expensive, involving the repeated numerical integration of a non linear differential system.

We define the N_x-dimensional vector of average responses $\bar{\mathbf{x}}$ as

$$\bar{\mathbf{x}}(t) = \frac{\sum_{i=1}^{N'} \mathbf{X}_i(t)}{N'} \tag{4.9}$$

and the N_x-dimensional variance vector is

$$\boldsymbol{\sigma}_x^2(t) = \frac{\sum_{i=1}^{N'} (\mathbf{X}_i(t) - \bar{\mathbf{x}})^2}{N' - 1}. \tag{4.10}$$

In the hypothesis of *i*) independence and identical distribution of the responses for each x_i trajectory after random sampling on $\boldsymbol{\theta}$ during the whole experimental horizon (i.e., each x_i trajectory belongs to the same kind of distribution at a given experimental time and can be treated as a purely random variable), *ii*) finite variance of the model responses, *iii*) N' being a sufficiently large number of simulations, and *iv*) linear correlation between $\boldsymbol{\theta}$ and x_i, then it is possible to apply the central limit theorem. Under those assumptions any x_i can be considered normally distributed with mean $\bar{x}_i$ and standard deviation $\boldsymbol{\sigma}_{x,i}$. The basic idea idea is to capture the overall uncertainty of state variables through a mean-variance regression model whose responses can be represented by mean profiles and deviations from the mean profiles. This approach resembles the one used in nonlinear optimisation under uncertainty (e.g., Darlington *et al.*, 1999) and robust design through metamodeling (e.g., Apley *et al.*, 2006). For a normal distribution the confidence intervals $\boldsymbol{\kappa}$ for a (1 – α) = 95% and (1 – α) = 99.7% confidence levels can be easily approximated by the following expressions

$$\boldsymbol{\kappa}^{95\%} \simeq 2\boldsymbol{\sigma}_x = 2\sqrt{\frac{\sum_{i=1}^{N'}\left(\mathbf{X}_i - \bar{\mathbf{x}}\right)^2}{N'-1}} \tag{4.11}$$

$$\boldsymbol{\kappa}^{99.7\%} \simeq 3\boldsymbol{\sigma}_x = 3\sqrt{\frac{\sum_{i=1}^{N'}\left(\mathbf{X}_i - \bar{\mathbf{x}}\right)^2}{N'-1}}\,. \tag{4.12}$$

The normal distribution usually provides a starting point for the evaluation of the shape of the actual $p_{x|\boldsymbol{\varphi}}\left(\boldsymbol{\xi}_x(t),t\right)$ distribution that, in practice because of a non-linear correlation between x_i and $\boldsymbol{\theta}$, might present some peculiarities:

1. different dispersion around the vector of mean values;
2. asymmetric dispersion around a critic value (skewed distribution) with consequent inconsistency of the standard normality assumption.

To overcome these issues more complex distributions may be considered (skew normal, Weibull, multivariate normal, Rosin-Rammler, bimodal etc.).

4.2.3 Backoff formulation and policy

Once a predicted uncertainty region of the state variables is defined, the backoff vector $\boldsymbol{\beta}$ of (4.5) can be approximated by

$$\mathbf{C} = \mathbf{x}(t) - \mathbf{G}(t) + \boldsymbol{\beta}\left(p_{x|\varphi}\left(\xi_x(t),t\right),\boldsymbol{\alpha},t\right) \le 0 \tag{4.13}$$

where the N_c-dimensional time-varying backoff vector is a function of the probability distribution of the state variables at the experimental settings $\boldsymbol{\varphi}$, and of a confidence vector $\boldsymbol{\alpha}$. The confidence vector can be set by the experimenter to tune the backoff from the active constraints **G**. Prior information on the system and convenience factors (e.g., the constraints on some state variables might be relaxed or enforced according to their relative importance) can guide the choice of the proper confidence vector. One possible backoff formulation is:

$$\boldsymbol{\beta}\left(p_{x|\boldsymbol{\varphi}}\left(\boldsymbol{\xi}_x(t),t\right),\boldsymbol{\alpha},t\right)=\boldsymbol{\kappa} \tag{4.14}$$

where the backoff takes into account the overall (1 – α)% uncertainty region of state variables at the nominal conditions. In order to increase the flexibility of the backoff strategy it is also possible to adopt the expression

$$\boldsymbol{\beta}\left(p_{x|\boldsymbol{\varphi}}\left(\boldsymbol{\xi}_x(t),t\right),\boldsymbol{\alpha},\Lambda,t\right)=\boldsymbol{\Lambda\kappa} \tag{4.15}$$

where $\boldsymbol{\Lambda}$ is a N_c-dimensional vector of coefficients larger than 1, used to increase conservatism. Through (4.15) the experimenter can always favour one direction of the variability instead of another, thus guiding the backoff policy. It must be pointed out that both backoff formulations (4.14) and (4.15) do not depend on the closeness to the active constraints, but on the predicted uncertainty region of the state variables only. More complex formulations may include the backoff action in the region of possible constraints violation only (i.e. for all the possible realisations of $\hat{\boldsymbol{\theta}} \in \boldsymbol{T}$ at given $\boldsymbol{\varphi}$).

4.3 Integration of the stochastic information: MBDoE with backoff algorithm

The stochastic approach for backoff building described in the previous section needs to be integrated into a constrained MBDoE scheme. The final goal of the whole procedure is to estimate the set of model parameters in the most precise and reliable way by performing a sequence of highly informative experiments within the feasible design region. For a sequence of experiments to be designed, the general scheme is shown in Figure 4.1.

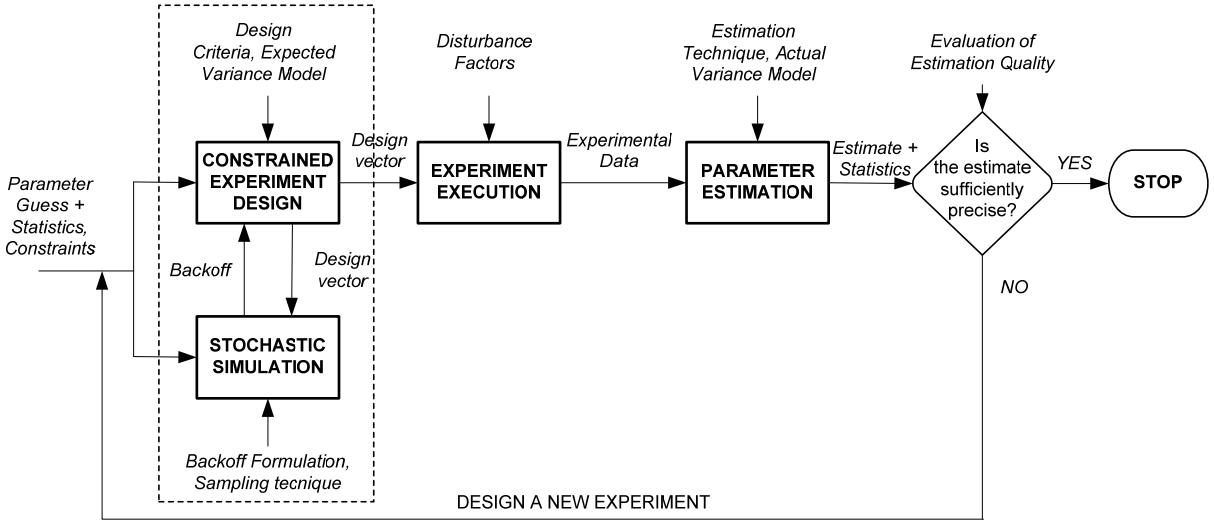


Figure 4.1 *Constrained MBDoE with backoff: iterative scheme. The sequence of operations enclosed in the dashed box is detailed in Figure 4.2.*

The methodology involves an iterative scheme requiring as initial inputs *i)* the definition of the active constraints **C**, *ii)* some knowledge on the parameter system (initial value of the model parameters and related statistics), and *iii)* some information about the backoff policy and sampling technique.

The key activities are as follows:

1. the design with backoff step including the simultaneous execution of the following tasks:
    i) the constrained design of the experiment, with the optimality condition (2.14) and feasibility condition (4.5) adjusted for the backoff from the active constraints;
    ii) the stochastic simulation providing the backoff vector $\boldsymbol{\beta}$, given the nominal value of model parameters;
2. the experiment execution, performed at the designed experimental conditions;
3. the parameter estimation (different estimation techniques can be used: least-squares, maximum likelihood, Bayesian estimation) from the collected experimental data;
4. the assessment of the statistical precision of the parameters.

The sequence of activities can be iterated until a sufficiently precise estimation is achieved. Figure 4.2 shows the flux of information and tasks occurring in the stochastic simulation (step 1.i) defining the back-offs $\boldsymbol{\beta}$ (depending on $\boldsymbol{\varphi}$), and in the MBDoE (step 1.ii) defining the design vector $\boldsymbol{\varphi}$ (depending on $\boldsymbol{\beta}$).

The critical steps are the description of the predicted uncertainty region of model parameters and the mapping of the predicted uncertainty region of the state variables. As for the first issue, the focus is on how to exploit the prior information and available knowledge in order to define the domain $\boldsymbol{T}$ of parametric uncertainty in a reliable way. In particular, it is not trivial to define a probability density function representing the variability of the parametric set. As

for the second issue, the problem of mapping the predicted uncertainty region of state variables is an approximation problem solved through a probabilistic approach driven by the experimenter. In fact, the problem can be seen as choosing an optimal trade-off between the accurate mapping of the uncertainty region of the state variables and the computational effort for the stochastic simulation.

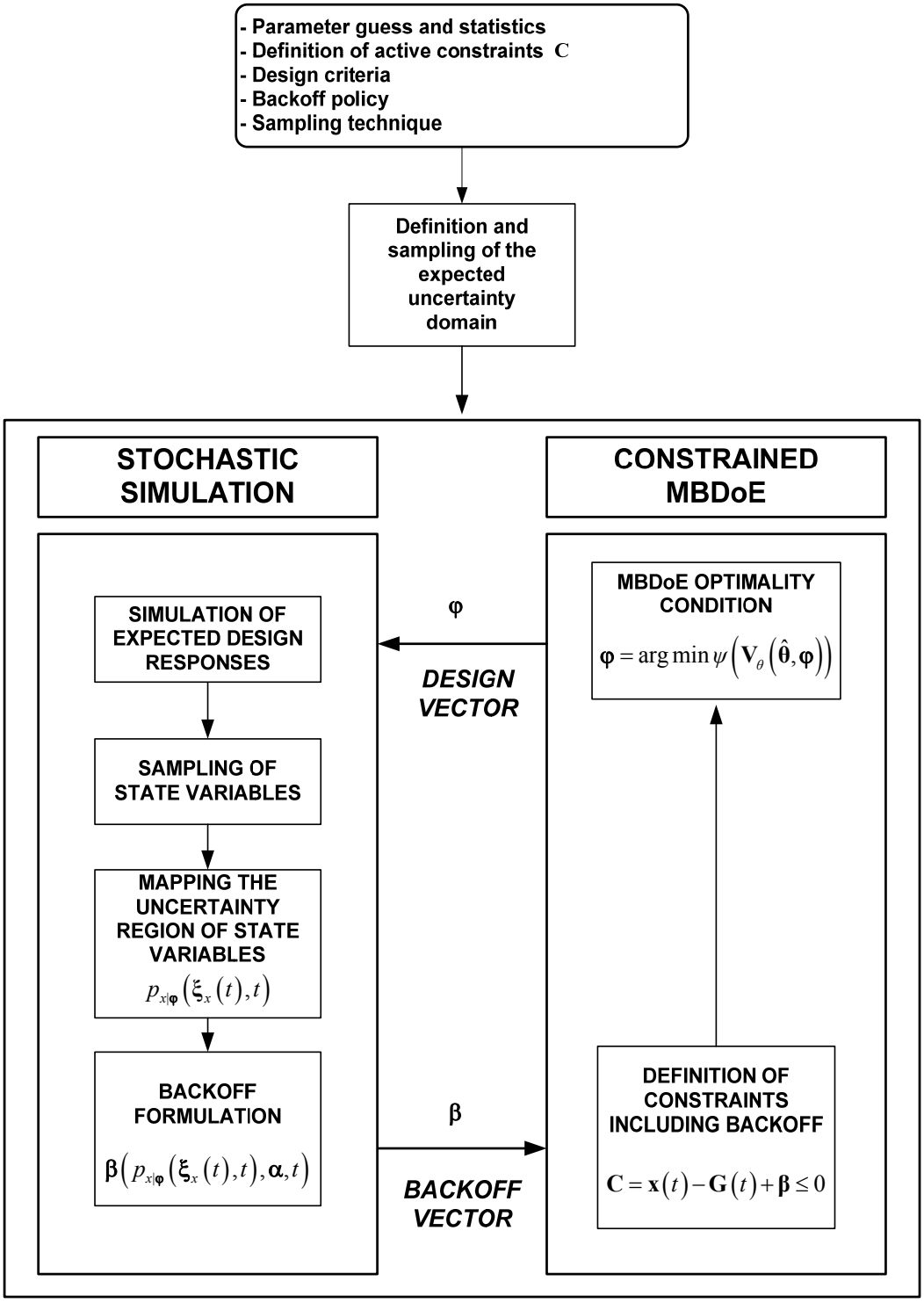


Figure 4.2 *Flux of information in the constrained MBDoE and stochastic simulation coupling.*

Two case studies are examined in this Chapter; they differ in terms of the number of model parameters to be estimated, and of the type of active constraints on the state variables. Both examples consider physiological models; however, the methodology can be applied without any further extension to generic process models.

The gPROMS® modelling environment (PSE Ltd., 2008) is used for modelling, simulation and optimisation purposes, as well as to design the experiments. The SRQPD optimisation solver of gPROMS has been coupled with the SIMLAB® software (Joint Research Centre, 2009) to generate the perturbed set of model parameters for the stochastic simulations. An SQP (sequential quadratic programming) routine was adopted in a two-step multiple shooting technique (Bock *et al.*, 2003) to solve the nonlinear optimisation problem.

4.4 Case study 1: optimal insulin infusion rate in a subject affected by diabetes

Optimal MBDoE techniques can be applied to a detailed model of glucose homeostasis to design a set of clinical tests that allow estimating the model parameters in a statistically sound way for a subject affected by type-1 diabetes mellitus (more details about physiological models for type-1 diabetes mellitus, and related identification issues, will be discussed later on in the Thesis). However, because of the parametric mismatch between the subject and the model (both are represented by the same DAE model, but with different sets of parameters), a design strategy may provide an infeasible solution due to a violation of the existing constraints on the output (blood glucose concentration). Here, the goal is to assess the effectiveness of a backoff-based experiment design strategy aimed at ensuring, in the presence of parametric mismatch, a feasible and optimally informative clinical test for parameter estimation purposes. A simplified model of glucose homeostasis (Lynch and Bequette, 2002) is adopted to describe blood glucose and insulin concentrations dynamics. The model is represented by the following set of differential equations:

$$\frac{\mathrm{d}C_g}{\mathrm{d}t} = -\theta_1 C_g - X\left(C_g + C_{g,b}\right) + D\left(t\right) \tag{4.16}$$

$$\frac{\mathrm{d}X}{\mathrm{d}t} = -\theta_2 X + \theta_3 I \tag{4.17}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = -n\left(I + I_b\right) + \frac{u\left(t\right)}{V_I} \tag{4.18}$$

where C_g is the blood glucose concentration (mg/dL), X the insulin concentration (mU/L) in the non accessible compartment, I the insulin concentration (mU/L) and $u(t)$ the rate of

infusion of exogenous insulin (mU/min). The meal disturbances model adopted in the study is the one proposed by Hovorka *et al.* (2002):

$$D(t) = 2.5At\exp(-0.05t) \tag{4.19}$$

with A the amount of glucose of the meal (g_{CHO}). The basal parameters (considered as constants) are given in Table 4.1.

Table 4.1 *Case study 1: value of model constants and description of basal parameters.*

Basal parameters	Description	Value
$C_{g,b}$	Basal glucose concentration in the blood [mg/dL]	81
I_b	Basal insulin concentration [mU/L]	15
V_I	Insulin distribution volume [L]	12
n	Disappearance rate of insulin [min^{-1}]	5/54
u_b	Basal insulin infusion rate [mU/min]	10.0

The constraints on the system are the upper (G_1 = 150 mg/dL) and lower (G_2 = 60 mg/dL) thresholds on blood glucose concentration, which is the only state variable being constrained (i.e. $y = C_g = x_1$). In reality, the lower bound only is a hard constraint not to be violated. However, for the sake of example, both constraints will be treated as hard ones. Additional equality constraints are set on the final glucose concentration (which must be equal to the basal value of $C_{g,b}$ = 81 mg/dL) and on the final insulin infusion rate (which must be equal to u_b).

The test has to be optimally informative and safe for the subject. Accordingly, a MBDoE with backoff is realised, where the design vector is

$$\boldsymbol{\varphi} = \left[u(t), \mathbf{t}^{sp}\right] \ . \tag{4.20}$$

The design variables are the insulin infusion rate and the vector of sampling times. The experiment design sessions are carried out by approximating the insulin infusion rate $u(t)$ as a piecewise constant function, with n_{sw} = 7 switching times and n_z = 8 switching levels. The optimal scheduling of a preset number n_{sp} = 10 of samples is also to be optimised, considering a minimum time of 10 min between two consecutive glucose concentration measurements. The glucose amount in the meal A is kept constant and equal to 60 g of carbohydrates. The measured variable is the blood glucose concentration C_g, with an expected relative error on the measurements of 3% of the reading. The chosen design criterion is the E-optimal experiment design for all the design configurations. The two constraints equations including backoff in the form (4.13) are:

$$C_1 = y + \beta_1 - G_1 \leq 0 \tag{4.21}$$

$$C_2 = -y + \beta_2 + G_2 \leq 0 \tag{4.22}$$

with $\boldsymbol{\beta} = \begin{bmatrix}\beta_1 & \beta_2\end{bmatrix}^{\mathrm{T}}$ depending on the probability distribution of the system response at the nominal conditions $p_{x_1|\boldsymbol{\varphi}}\left(\boldsymbol{\xi}_{x_1}(t), t\right)$. The nominal values for the model parameters, valid for a healthy subject, are $\hat{\boldsymbol{\theta}} = \begin{bmatrix}0.02873 & 0.02834 & 1.30E-5\end{bmatrix}^{T}$.

As discussed by Furler *et al.* (1985), a subject affected by diabetes should have a lower value of the first parameter. Here it is assumed that:

1. the subject is diabetic and his/her condition is defined by the parameter set $\boldsymbol{\theta} = \begin{bmatrix}0.0250 & 0.0150 & 1.26E-5\end{bmatrix}^{\mathrm{T}}$ (the relative deviations from the healthy subject set are therefore of −13%, −47% and −3% respectively);
2. the experimental design procedure is based on the $\hat{\boldsymbol{\theta}}$ set describing a healthy subject.

To take into account the uncertainty of model parameters in mapping $p_{x_1|\boldsymbol{\varphi}}$ a stochastic approach is followed by running $N' = 500$ simulations; therefore, the expected uncertainty of the model parameters adopted in the study is the following:

$$\boldsymbol{T} = \left[\tilde{\theta}_{ij} \middle| \tilde{\theta}_{ij} \in p_{\theta}\left(\hat{\theta}_i, \xi_{\theta}\right), i = 1...3, j = 1...500\right] \tag{4.23}$$

defining an hypher-rectangular region of uncertainty where

$$\begin{aligned}
\tilde{\theta}_1 &\in R_1\left(\hat{\theta}_1 - \xi_{\theta_1}, \hat{\theta}_1 + \xi_{\theta_1}\right) = p_{\theta}\left(\hat{\theta}_1, \xi_{\theta_1}\right) \\
\tilde{\theta}_2 &\in R_2\left(\hat{\theta}_2 - \xi_{\theta_2}, \hat{\theta}_2 + \xi_{\theta_2}\right) = p_{\theta}\left(\hat{\theta}_2, \xi_{\theta_2}\right) \\
\tilde{\theta}_3 &\in R_3\left(\hat{\theta}_3 - \xi_{\theta_3}, \hat{\theta}_3 + \xi_{\theta_3}\right) = p_{\theta}\left(\hat{\theta}_3, \xi_{\theta_3}\right)
\end{aligned} \tag{4.24}$$

$\mathbf{R} = \begin{bmatrix}R_1 & R_2 & R_3\end{bmatrix}^{\mathrm{T}}$ is a family of independent uniform distributions defined by a set of upper and lower variability bounds set by $\boldsymbol{\xi}_{\theta} = \begin{bmatrix}\xi_{\theta_1} & \xi_{\theta_2} & \xi_{\theta_3}\end{bmatrix}^{\mathrm{T}} = \begin{bmatrix}0.006 & 0.015 & 0.1E-5\end{bmatrix}^{\mathrm{T}}$. These settings for the perturbed values of parameters include a wider uncertainty on the second parameter representing a subject with an altered insulin sensitivity.

Before the MBDoE procedure is started, the two systems (the model and the subject) have very different responses. If the uncertainty region of the state variables is built assuming a normal distribution and a 99.7 % confidence region, it was observed that the distribution of the system responses is skewed. Therefore the hyphothesis of a normal distribution provides a poorly accurate representation of the distribution of the system responses for this case study. As a consequence, in order to increase conservatism, the backoff is defined as the maximum variation from the nominal profile, i.e. the uncertainty region of the state variables is

described through the maximum and minimum blood glucose concentration profiles over the parameter uncertainty domain.

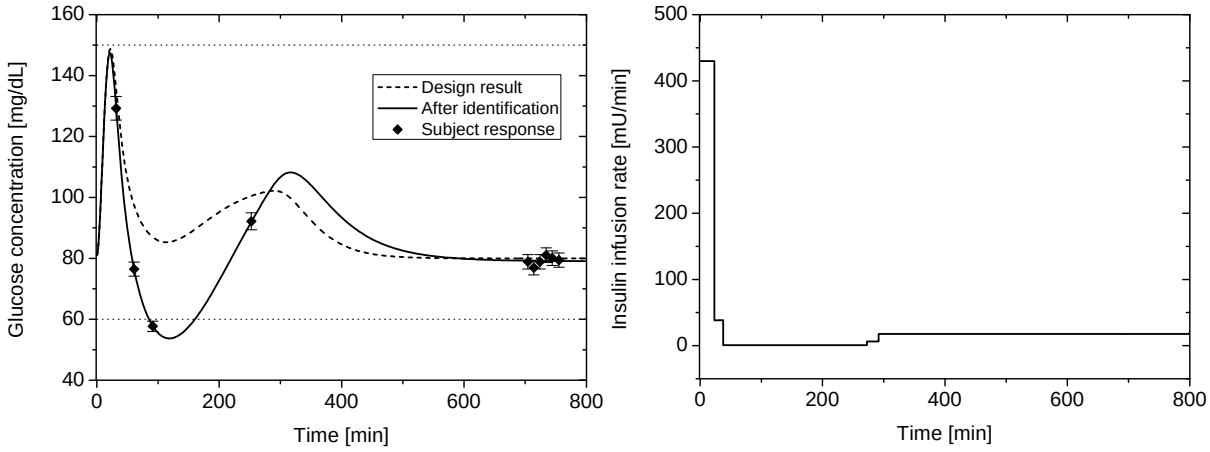
To verify the effectiveness of a backoff-based experimental design, two different configurations were compared:

1. standard MBDoE with simple constraints and no backoff;
2. MBDoE with backoff from constraints.

Results are illustrated in the following lines.

4.4.1 Standard design

The results from the simple design (Figure 4.3) can be seen as a motivating example for the adoption of a backoff-based strategy. The optimal design conditions do not comply with the lower constraint on the glucose concentration when applied to a diabetic subject. The test is unsafe for the subject because hyphoglycaemia is achieved at $t \simeq 90$ min.



(a) *(b)*

Figure 4.3 *Case study 1, standard MBDoE. (a) Glucose concentration profiles predicted by the model during the experiment design (broken line) and after parameter identification (solid line); the subject actual response to the designed experiment is indicated by diamonds with measurement error bars. (b) Profiles of the designed insulin infusion rate.*

Table 4.2 *Case study 1, standard MBDoE. Parameter estimation, initial guess, true values, and statistics as 95% confidence intervals, t-values (reference t value = 1.898) and standard deviations.*

model parameter	final value	initial guess	true value	confidence interval 95%	95% *t* value	standard deviation
θ_1	0.028204	0.028735	0.0250	0.01396	2.021	0.00590
θ_2	0.014063	0.028344	0.0150	0.00241	5.843	0.00102
θ_3	1.241E-5	1.300E-5	1.26E-5	1.189E-6	10.44	5.028E-7

It can be noted that the parameter set is estimated well (Table 4.2) using the data from the test: as expected, the designed experiment, although infeasible, is optimally informative for parameter estimation purposes.

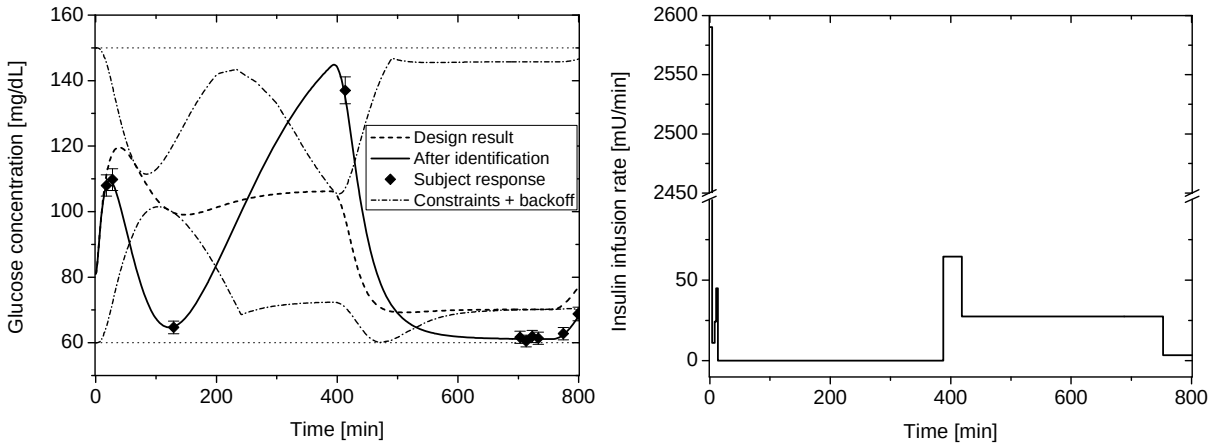
4.4.2 MBDoE with backoff

To avoid constraint violations in the presence of parametric uncertainty, the experiment design procedure is coupled to a stochastic simulation to estimate the necessary backoff solving the optimisation problem given by (2.14) and (4.2-4.5) . In this way

$$\boldsymbol{\beta} = \boldsymbol{\beta}\left(R_{x_1|\boldsymbol{\varphi}}\left(x_1^{MIN}, x_1^{MAX}, t\right), \boldsymbol{\alpha}, t\right) = \boldsymbol{\beta}\left(\hat{u}, p_\theta\left(\hat{\boldsymbol{\theta}}, \boldsymbol{\xi}_\theta\right), \boldsymbol{\alpha}, t\right) \tag{4.25}$$

and the backoff is a function of $R_{x_1|\boldsymbol{\varphi}}\left(x_1^{MIN}, x_1^{MAX}, t\right)$, a uniform distribution defined by the highest value and the lowest value of x_1 at the t time. This distribution is function of the parametric uncertainty distribution (4.24) and the estimated value of the actual manipulated input. The simulation is carried out with N' = 500 and is computationally expensive, although the calculations burden could be reduced if an appropriate initial guess profile of the manipulated input is chosen (e.g., by using by the solution of a standard design or, more efficiently, by evaluating the profile of the manipulated inputs that satisfy the constraints of the problem with backoff through a preliminary dynamic optimisation).

Figure 4.4 shows the resulting profiles for the experimental design with backoff, and Table 4.3 shows the parameter estimation after the designed experiment with backoff. The parameter estimation is again statistically satisfactory (as can be seen from the 95% confidence *t*-test values and from the narrow confidence intervals) and the parameter values close to those of the diabetic subject. It is interesting to note that the design with backoff defines a test that is now both feasible and optimally informative. As can be seen from Figure 4a, the dynamics of glucose concentration are constrained within a narrow range of operability to take into account the stochastic contribution to the response of the parametric uncertainty. Also note that according to Table 4.3, the design with backoff allows obtaining a more precise estimation of the model parameters. This may sound counter-intuitive as the design space is restricted by the effect of the backoffs, it can be verified that the design with backoff optimisation does predict a less informative experiment (the final value for the design objective function is 0.00547 against 0.00310 for the standard design). Thus, the "unexpected" better estimation of the parameter values can be explained by the fact the design (and the design objective function) depends on the current value of the model parameters, whereas the actual design and subsequent estimation of the parameter values are based on the actual (unknown) values of the parameters.



(a) *(b)*

Figure 4.4 *Case study 1, MBDoE with backoff. (a) Glucose concentration profiles predicted by the model during the experiment design (broken line), after parameter identification (solid line), and effect of backoff on active constraints (dash-dot lines); the subject actual response to the designed experiment is indicated by diamonds with measurement error bars. (b) Profiles of the designed insulin infusion rate.*

Table 4.3 *Case study 1, MBDoE with backoff. Parameter estimation, initial guess, true values, and statistics as 95% confidence intervals, t-values (reference t value = 1.898) and standard deviations.*

model parameter	final value	initial guess	true value	confidence interval 95%	95% *t* value	standard deviation
θ_1	0.02517	0.028735	0.0250	0.00336	7.480	0.00142
θ_2	0.01513	0.028344	0.0150	0.00193	7.848	0.00081
θ_3	1.287E-5	1.300E-5	1.26E-5	1.244E-6	10.350	5.260E-7

4.5 Case study 2: optimal chemotherapeutic drug administration

A second case study considers the model originally proposed by Martin (1992) for the optimal chemotherapeutic drugs administration to people affected by cancer. This model was further analysed by Banga *et al.* (2005) in the topic of robust dynamic optimisation, in order to determine the optimal cancer drug scheduling to decrease the size of a malignant tumour as measured at some particular time in the future. Note that more complex models can be found in the literature, e.g. in the optimisation study by Dua *et al.* (2008). Here, the goal is to assess the effectiveness of a backoff-based experiment design strategy on ensuring, in the presence of parametric mismatch, a feasible and optimally informative clinical test for parameter estimation purposes, with the additional constraint of maintaining an effective therapy in terms of a reduction of the number of cancer cells to be observed during the test.

The cell-cycle non specific model comprises the following set of equations:

$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = -\theta_1 x_1 + \theta_2 (x_2 - \theta_3) H \tag{4.26}$$

$$\frac{\mathrm{d}x_2}{\mathrm{d}t} = u_d - \theta_4 x_2 \tag{4.27}$$

$$\frac{\mathrm{d}x_3}{\mathrm{d}t} = x_2 \tag{4.28}$$

where x_1 represents the reduction of tumour cells (dimensionless), x_2 is the drug concentration in the body in drug units (D), x_3 is the cumulative (toxic) effect of the drug (D×days); θ_1, θ_2, θ_3 and θ_4 are the model parameters to be estimated, u_d is the drug administration rate (D/days) and t is the time (days). The tumour mass in terms of the number of cancer cells is given by

$$N_{cells} = 10^{13} \exp(-x_1) \quad . \tag{4.29}$$

The drug concentration must be kept below an assigned level during the treatment period and the cumulative effect of the drug must be kept below the ultimate tolerance level. Function H depends on x_2 and θ_3 as in the following:

$$H = \begin{cases} 1 & , \quad x_2 \geq \theta_3 \\ 0 & , \quad x_2 < \theta_3 \end{cases} \tag{4.30}$$

This takes into account the fact that the drug is effective only if its concentration in the body is above a threshold level.

The dynamic optimisation problem consists of finding the optimal $u_d(t)$ over $t \in \left[0, t_f\right]$ by maximising

$$J = x_1\Big|_{t_f} \tag{4.31}$$

subject to (4.27-4.29) and to the following path constraints

$$x_2(t) \leq G_1 = 50 \ D \tag{4.32}$$

$$x_3(t) \leq G_2 = 2100 \ D\times\text{days}$$

and to the following interior point constraints

$$x_1\big|_{t=21} \geq G_3 = \ln(200) \tag{4.33}$$

$$x_1\big|_{t=42} \geq G_4 = \ln(400)$$

$$x_1\big|_{t=63} \geq G_5 = \ln(800)$$

stating that there must be at least 50% reduction in the size of the tumour every three weeks. In this case study, we see that $N_y = 1$ and $N_c = 5$ (i.e., this is a problem with a single measured response with multiple constraints); in addition, the control is bounded ($0 \leq u_d(t) \leq 100$). The upper threshold for the cancer biomass is N_{cells} = 1.5E+10, which can be seen as a terminal state for the subject. The maximum experiment time acceptable for the optimisation is t_f = 84 days (12 weeks). The measured variable is $y = \exp(-x_1)$, and the measurements are available with a relative error of 3%. The initial state is taken at $\mathbf{x}^0 = [\ln(100) \quad 0 \quad 0]^T$ and the nominal values of model parameters are shown in Table 4, with a short explanation of their physical meaning.

The model is rather sensitive to the parameter values. Figure 4.5 shows the effect of a change in one parameter value on the proliferation of cancer cells (Figure 4.5a) and on the effectiveness of the drug therapy (Figure 4.5b).

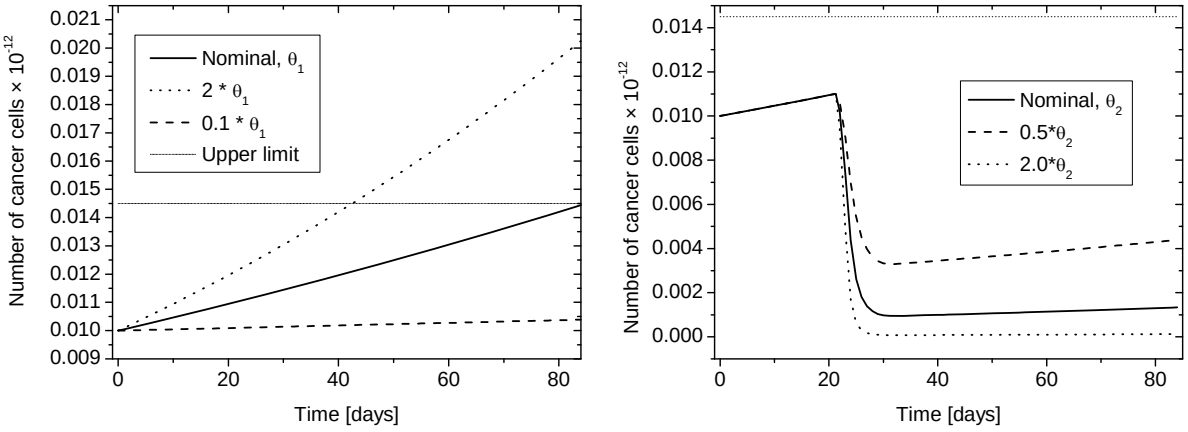


Figure 4.5 *Case study 2: effect of the value of θ_1 and θ_2 on the number of cancer cells over a 12 weeks period. (a) No drug administration. (b) Step administration of drug at the third week.*

A constrained dynamic optimisation adopting (4.31) as the objective function would provide an efficient test, but a low information level for parameter estimation purposes. More importantly, the parametric uncertainty might lead the test to be infeasible and to return sub-optimal solutions. On the other hand, a simple MBDoE procedure based on (2.14) would provide an optimally informative but less effective test protocol, with the same problems of

feasibility and robustness of the solution in the presence of parametric uncertainty. A backoff strategy can guarantee the feasibility of both an optimally informative (i.e. MBDoE-based) and an optimally efficient (i.e. dynamically optimised) test.

To solve the optimisation problems, the model parameters are scaled to unity using the values reported in Table 4.4 (symbol $\hat{\boldsymbol{\Theta}}$ is used for the estimated normalised set). A model with $\boldsymbol{\Theta} = \begin{bmatrix} 1.2 & 0.8 & 1.2 & 0.8 \end{bmatrix}^T$ (i.e. 20% deviation from the nominal) is considered in order to represent a subject with a greater proliferation of cancer cells and a less effective response to drug delivery.

Table 4.4 *Case study 2: nominal values and description of model parameters.*

Parameter	Value	Description
θ_1	9.9E-4	Cancer cells proliferation [days]
θ_2	8.4E-3	Drug action in cancer cells elimination [$days^{-1}D^{-1}$]
θ_3	10	Drug threshold effect [D^{-1}]
θ_4	0.27	Drug elimination from the body [$days^{-1}$]

The manipulated input is approximated with a piecewise constant function with n_{sw} = 10 and n_z = 11. The sampling points (n_{sp}=13) are collected to identify the model parameters with a minimum time between two consecutive measurements of 1 day. An E-optimal criterion is chosen for MBDoE.

The expected uncertainty domain $\boldsymbol{T}$ of model parameters is defined by

$$\boldsymbol{T} = \left[\tilde{\Theta}_{ij} \middle| \tilde{\Theta}_{ij} \in p_{\Theta_i}\left(\hat{\Theta}_i, \xi_{\Theta_i}\right), \quad i = 1...3, j = 1...N' \right] \tag{4.34}$$

where the normalised parameter vector components are assumed to be independent and normally distributed stochastic variables

$$\tilde{\Theta}_i \in p_{\Theta_i}\left(\hat{\Theta}_i, \xi_{\Theta_i}\right) = N_i\left(\mu_i, \sigma_i\right) \qquad i = 1...N_\theta \tag{4.35}$$

with mean $\boldsymbol{\mu} = \hat{\boldsymbol{\Theta}}$ and standard deviation $\boldsymbol{\sigma}$ = 0.15. N' = 100 simulations were carried out to build the (1 – α) = 99.7 % confidence region of system responses. Note that the selected vector of standard deviations define a wide uncertainty region for the model parameters. The choice of the number of simulations is related to the definition of the predicted uncertainty: the wider the uncertain region the smaller the number of simulations required to represent it (i.e., there is a trade-off between calculation/experimental effort and confidence on the parameters value).

Although results are not reported here for the sake of conciseness, both a standard dynamic optimisation (DOPT) as in Banga *et al.* (2005) and a standard MBDoE were carried out. In both cases the fundamental issue is that the interior point constraints on the number of cancer

cells and the upper bound on the cumulative drug concentration in the body were violated. Also a dynamic optimisation with backoff (DOPT-B) was carried out: in this case no violation of the constraint occurred, but yet an evenly spaced (not optimised) sampling policy was not effective for a sound estimation of the model parameters.
To verify the effectiveness of a backoff approach for optimal drug scheduling, and to overcome the limitations of standard optimisation and experiment design optimisation, a constrained design of experiment with backoff (MBDoE-B) is used to determine the optimal drug administration rate. The results in terms of statistics on parameter estimation, feasibility and effectiveness of the care are analysed in the following section.

4.5.1 MBDoE with backoff

In order to formulate the necessary backoff from the active constraints, the distribution of the entire set of state variables (y, x_2, x_3) was approximated by a set of independent normal distributions. The backoff vector in the (4.14) form can be evaluated from the (1 – α)% confidence intervals for the state variables

$$\boldsymbol{\beta}\left(\mathbf{N}\left(\boldsymbol{\xi}_x(t),t\right),\boldsymbol{\alpha},t\right)=\boldsymbol{\kappa} \tag{4.36}$$

where the set of independent normal distributions **N** is defined by $\boldsymbol{\xi}_x(t)$ parameters, defining a vector of average profiles and standard deviations from the average profiles.
The vector $\mathbf{C} = [C_1\ C_2\ C_3\ C_4\ C_5]$ of active constraints on state variables including backoff can be expressed for the state variables x_2 and x_3 as

$$C_1 = x_2(t)+\beta_1(t)-G_1 \le 0 \tag{4.37}$$

$$C_2 = x_3(t)+\beta_2(t)-G_2 \le 0 \tag{4.38}$$

concerning the path constraints, and

$$C_3 = y\big|_{t=21}-\beta_3\big|_{t=21}-G_3 \ge 0 \tag{4.39}$$

$$C_4 = y\big|_{t=42}-\beta_4\big|_{t=42}-G_4 \ge 0 \tag{4.40}$$

$$C_5 = y\big|_{t=63}-\beta_5\big|_{t=63}-G_5 \ge 0 \tag{4.41}$$

for the interior point constraints. The N_c-dimensional vector of backoff functions coming from the normality assumption is

$$\boldsymbol{\beta} = \begin{bmatrix} 2\sigma_y\big|_{t=21} \\ 2\sigma_y\big|_{t=42} \\ 2\sigma_y\big|_{t=63} \\ 2\sigma_{x_2}(t) \\ 2\sigma_{x_3}(t) \end{bmatrix} \tag{4.42}$$

for a confidence level of $(1 - \alpha) = 95\%$. In this case the assumption of indipendence and identically distribution for the states allows describing the uncertainty region of system responses in a satisfactory and adequate way.

A further constraint is added to ensure the effectiveness of the therapy in the worst case (minimum reduction of the size of the tumour over the considered uncertainty domain of model parameters $\boldsymbol{T}$), stating that

$$J\big|_{\boldsymbol{T}} \geq 13.8 - \iota \tag{4.43}$$

where ι is a small non-zero number taking into account the deviation of MBDoE-B objective function from the optimal conditions derived from DOPT-B. The idea underneath this approach is to perform an optimal experiment design ensuring (at least) the effectiveness of a dynamic optimisation with backoff. The MBDoE-B optimisation problem consists on finding the optimal $u_d(t)$ profile satisfying through the model (4.26-4.30) the design optimality condition and the feasibility constraints (4.37-4.41) and (4.43).

Results are shown in Figure 4.6. The backoff strategy guarantees the feasibility of the designed experiment with the specified level of uncertainty. We verified that the final reduction of the mass of the tumour is indeed very similar to the one obtained through a DOPT-B. The optimal settings provided by the optimisation lead the x_2 and x_3 profiles close to the upper path constraints, without crossing them.

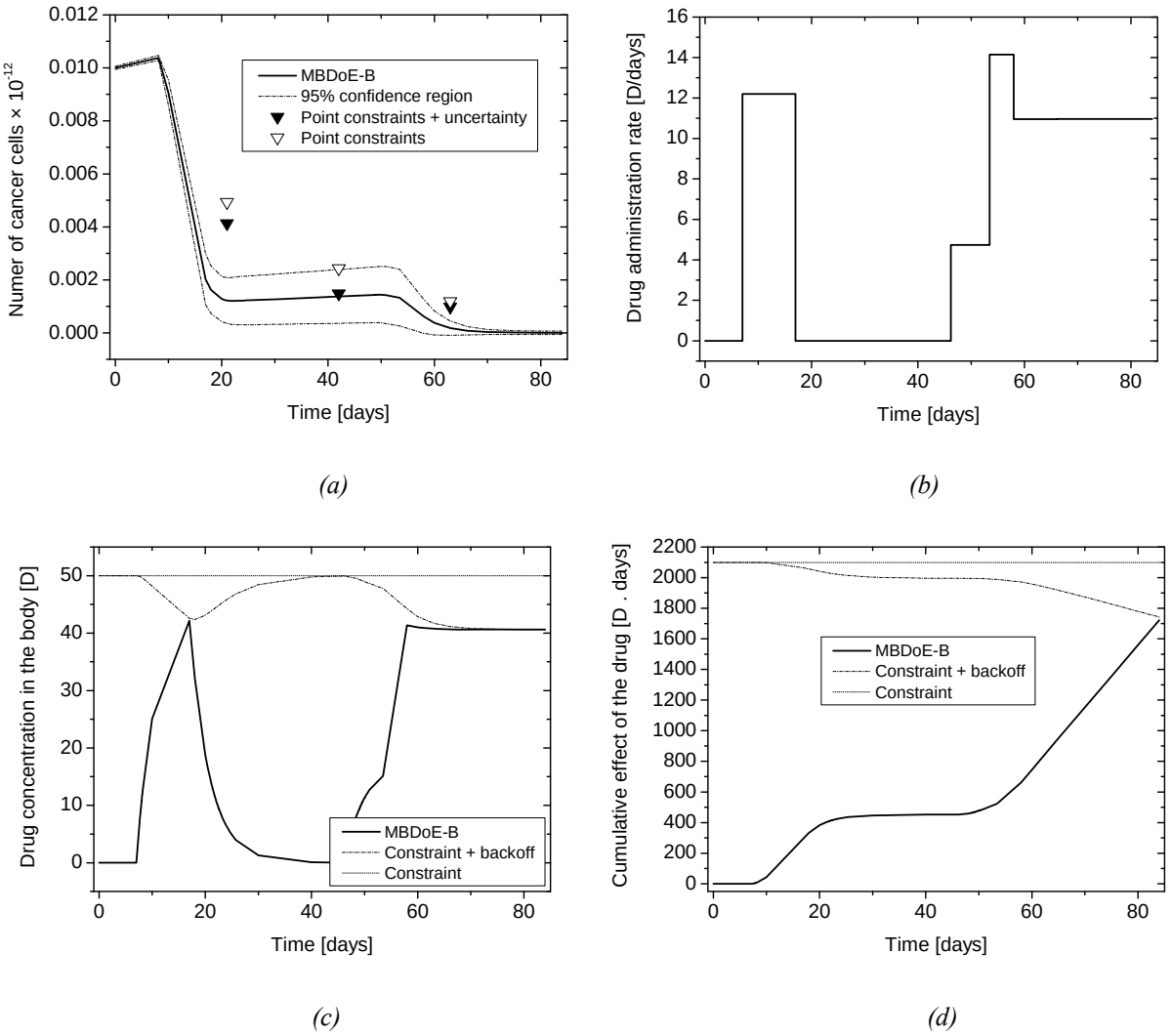


Figure 4.6 *Case study 2, MBDoE-B. (a) Profile of the number of cancer cells N_{cells} (solid line) with 95% confidence region (short dash-dotted lines), point constraints (open triangles) and effect of the backoff on point constraints (closed triangles). (b) Optimal profile for drug administration rate. (c) Drug concentration in the body. (d) Cumulative effect of the drug profiles; path constraints (dot lines) and effect of the backoff on constraints (dash-dotted lines) during the optimisation.*

The measurements from the designed experiment (MBDoE-B) and the estimated profile are shown in Figure 4.7 (also showing how the interior point constraints on the measured variable *y* are largely fulfilled). Note that the design optimisation chooses a very uneven sampling profile (i.e., sample are taken where the information content is higher). The parameter estimation is statistically satisfactory (even if the informative content of the test is lower than the one obtained in the standard MBDoE) as summarised in Table 4.5. Table 4.6 summarises all the simulation results considered in Case study 2 in terms of proposed technique, feasibility and design optimality.

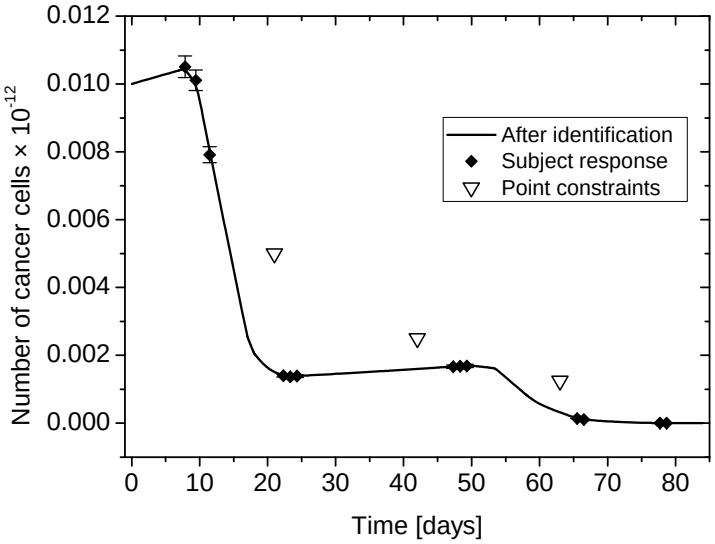


Figure 4.7 *Case study 2, MBDoE-B. Profile of the number of cancer cells N_{cells} predicted by the model after parameter identification (solid line), sample measurements (diamonds) and interior point constraints (open triangles) .*

Table 4.5 *Case study 2, MBDoE-B. Parameter estimation, initial guess, true values and statistics as 95% confidence intervals, t-values (reference t value = 1.833) and standard deviations.*

model parameter	final value	initial guess	true value	confidence interval 95%	95% *t* value	standard deviation
Θ_1	1.2389	1.0	1.2	0.3693	3.355	0.1633
Θ_2	0.7773	1.0	0.8	0.1211	6.417	0.0535
Θ_3	1.1844	1.0	1.2	0.1473	8.038	0.0651
Θ_4	0.7841	1.0	0.8	0.0996	7.871	0.0440

Table 4.6 *Case study 2. Summary of the results achieved with different proposed techniques.*

Experiment	Technique	Feasibility	Design optimality
DOPT	Dynamic optimisation	NO	NO
DOPT-B	Dynamic optimisation with backoff	YES	NO
MBDoE	Constrained experiment design	NO	YES
MBDoE-B	Constrained experiment design with backoff	YES	YES

One drawback of the proposed methodology is the high computational effort for the stochastic simulation required to build the necessary backoff. As mentioned before, parallel computing and SA-based sampling methods can drastically reduce the computational burden. In any case, the computational burden is not a critical issue in this case study as the calculation time (< 5 hours in a Pentium D 3Ghz CPU) is small when compared to the duration of the therapy and is to be done before the therapy has commenced.

4.6 Final remarks

In this Chapter a novel methodology for the constrained MBDoE in the presence of parametric uncertainty was proposed and discussed. The optimal design of an experiment for improving parameter estimation is a particular form of dynamic optimisation problem that can be very effective where both optimality and feasibility of the designed experiment are important issues to consider. Since parameter uncertainty affects both design optimality and experiment feasibility, a modified methodology exploiting stochastic information about the parametric system was adopted in order to design the necessary backoffs from the active constraints. The backoff strategy allows moving the optimal point in order to keep the experiment in the feasible region of the state variables. Two simulated case studies have been proposed to assess the effectiveness of the new technique.

In the first case study the methodology was applied to a model of the glucose homeostasis to detect the best insulin infusion rate profile to infuse in order to estimate the parameters of a subject with type-1 diabetes mellitus when no preliminary information about the subject is available. The backoff strategy allows estimating the parametric set describing the diabetic subject in a safe manner, while a standard design (even if optimal) leads the subject to hypoglicaemia.

In the second case study, dealing with the optimal delivery of chemotherapeutic agents in cancer treatment, the problem of estimating the model parameters was faced by considering the effectiveness of the care (i.e. its capability of decreasing the tumour size in a given amount of time) as well as the optimality and feasibility of the optimised test. Since a standard model-based experiment design leads to an infeasible test when parametric uncertainty is present, an MBDoE with backoff was analysed and discussed. This methodology proved to ensure both optimality and feasibility of the planned experiment, overcoming the limitations of the other two.

Chapter 5

Optimal design of clinical tests for the identification of physiological models of type 1 diabetes mellitus*

Type 1 diabetes mellitus is a disease affecting millions of people worldwide and causing the expenditure of millions of euros every year for health care. One of the most promising therapies derives from the use of an artificial pancreas, based on a control system able to maintain the subject's normoglycaemia. A dynamic simulation model of the glucose-insulin system can be useful in several circumstance for diabetes care, including testing of glucose sensors, insulin infusion algorithms and decision support systems for diabetes.
This Chapter considers the problem of the identification of single individual parameters in detailed dynamic models of glucose homeostasis. Optimal model-based design of experiments techniques are used to design a set of clinical tests that allow estimating the model parameters in a statistically sound way, fulfilling the constraints of safeness for the subject and easiness of conduction. The model with the estimated set of parameters represents a specific subject and can thus be used for customised diabetes care solutions. Simulated results demonstrate how such an approach can improve the effectiveness of clinical tests and serve as a tool to devise safer and more efficient clinical protocols, thus providing a contribution to the development of an artificial pancreas.

5.1 Introduction

Diabetes mellitus is a metabolic disease characterised by insufficient production of insulin by the pancreas and elevated concentrations of blood glucose for prolonged periods of time (i.e., hyperglycaemia). Chronic, untreated hyperglycaemia can lead to serious complications that include cardiovascular diseases, blindness, kidney failure, and stroke. Furthermore, very low values of blood glucose (hypoglycaemia) for even a few hours can result in loss of consciousness and coma. According to the World Health Organization (2006), there were 171 million people in the world suffering diabetes in the year 2000, and this number is projected

* Portions of this Chapter have been published in Galvanin *et al.* (2009b), Galvanin *et al.* (2009d) and Galvanin *et al.* (2010b).

to increase to 366 million by 2030. The national costs of diabetes in the USA for 2002 were $US 132 billion, and are projected to increase to $US 192 billion in 2020.

Type 1 diabetes mellitus (T1DM, also called insulin-dependent diabetes) usually begins before the age of 40, and is characterised by a progressive destruction of the pancreatic islets and by an absolute deficiency of secreted insulin in the body. This determines the incapability to maintain the blood glucose concentration within a narrow range (normoglycaemic levels). People with T1DM must therefore rely on exogenous insulin for survival. The most widespread treatment of T1DM is based on multiple daily self-injections (boluses) of insulin. However, the individual requirement of insulin can be affected by many factors, such as the carbohydrate content (CHO) of a meal, illness, degree of stress, and exercise. Thus, people affected by T1DM have to be instructed on how to regularly check their glycaemia (usually several times a day, using fingersticks) and how frequently (and to which extent) perform insulin self-administration.

A much more convenient approach would be to deliver insulin continuously by inserting a closed-loop controller in the glucose/insulin system (e.g., an artificial pancreas). An artificial pancreas is a portable (or implantable) insulin delivery system that consists of three components: a glucose sensor which provides frequent measurements, an insulin infusion pump, and a control algorithm that calculates the appropriate insulin dosage for the current conditions. A critical assessment of the challenges related to the development of an artificial pancreas has been provided by Bequette (2005).

For the development of an artificial pancreas, the importance of physiological models of the glucose homeostasis cannot be overestimated. A model is an essential requirement for controller design and tuning, particularly if model-based control (e.g., model predictive control) is employed. Furthermore, the model itself can be used as a "virtual subject" to mimic the response to a certain insulin treatment or, more generally, to a decision support system for diabetes care. A wide variety of physiological models have been developed in the last four decades to describe the dynamics of glucose/insulin system. The literature on this topic has been reviewed in recent survey articles (Makroglou *et al.*, 2006; Parker *et al.*, 2001; Bequette, 2005), and therefore we will not present a detailed review here. Probably, the most widely known and used model is the so-called "minimal model" by Bergman *et al.* (1981), where the plasma glucose dynamics and plasma insulin dynamics are described using only three differential equations and few parameters. Despite its simplicity, and despite the fact that (strictly speaking) it was not derived to optimise insulin treatment in individuals with T1DM, this model is able to account for most of the physiological insulin-glucose relationships revealed by clinical evidence both in type 1 and in type 2 diabetes mellitus (Bergman, 2007). Several modifications to the original minimal model have been reported (Sorensen, 2007; Fisher, 1991; Parker *et al.*, 2000) to overcome its main limitations, i.e. that it does not include the dynamics of subcutaneous insulin infusion, and that it does not provide a

description of the rate of glucose appearance following a meal. Recently, very detailed physiological models have been proposed (Hovorka *et al.*, 2002, Dalla Man *et al.*, 2007) that are able to represent the overall glucoregulatory system, including the absorption of subcutaneously-administered short-acting insulin (Wilinska *et al.*, 2005), and glucose ingestion and absorption (Fabietti *et al.*, 2006).

One critical issue for the use of a physiological model is the identification of individual subject parameters. Basically, the identification of the minimal model has been achieved with frequently sampled intravenous glucose tolerance tests (IVGTTs), where a bolus of glucose is intravenously injected, and several samples of the glucose and insulin plasma concentrations are taken following the glucose injection. This kind of test does not upset the subject excessively, but it is not guaranteed that the excitation pattern is the most appropriate to estimate the model parameters with good precision. In fact, the identifiability of a parametric model is strictly related to the structure of the model and to the level of excitation that the experimenter can realise during the experiments (Söderström and Stoica, 1989). Interestingly, as early as 1981, Bergman and coworkers recognised that, in order to estimate the metabolic parameters, the optimal input perturbation might well be different from that of an IVGTT, and different temporal patterns of glucose and/or insulin administration could lead to easier and more accurate parameter identification. In fact, several modifications of the standard IVGTT have been proposed to improve parameter identification. For example, it has been shown that the infusion of insulin some time after the glucose injection in an IVGTT considerably improves parameter estimation (Yang *et al.*, 1987; Boston *et al.*, 2003). Some studies were also performed in order to define the best input profile for the minimum model relying on the computation of a measure of Fisher information matrix for a single test (Cobelli and Thomaseth, 1986).

The availability of a model tailored for a single individual can provide substantial benefits both to the clinician, who would be able to devise a customised diabetes care solution for the subject, and to the engineer, who would have the possibility to design and test conventional and advanced glucose control techniques. However, parameter and measured response cross-correlation, as well as uncertainty in measurements, can make the parameter estimation procedure challenging, and reduce (if not annul) the level of significance of a test performed on a single subject. This is particularly true for detailed physiological models, which particularly suffer from the difficulty of identifying the parameters for a specific subject. Therefore, while clinicians are interested in knowing the parameter values for individual subjects, researchers are likely to analyse response data from multiple subjects altogether: a 'nominal' subject model is thus developed, based on mean values of the literature data (Parker and Doyle, 2001). A further complication on designing *ad hoc* a clinical test for individual parameter identification is that the test must be safe for the subject (i.e., the glycaemic and insulinemic levels must be within the physiological bounds at all times), sufficiently short,

and easy to carry out. In fact, as a result of ethical and practical restrictions imposed on medical measurements, the optimal design, sample scheduling and planning of biomedical experiments has become an important issue for the development of novel experimental protocols (Kalicka and Bochen, 2006). On a process systems engineering perspective, these requirements are typical of an MBDoE problem for parameter identification in a dynamic system where constraints are present both in the inputs and in the outputs. An optimal MBDoE approach is suitable for parameter identification of detailed physiological models. Optimum temporal patterns for the glucose and/or insulin administration, and optimal sampling schedules for the glucose concentration measurements, are determined to identify the model parameters for an individual subject, with the constraint that the designed clinical test (i.e., the "experiment") must be safe for the subject.

5.2 Glucose concentration control issues

In the few last decades, much research activity in the field of T1DM management has been dedicated to understanding how the pancreas β-cells respond to control the glucose concentration in a healthy subject, and to subsequently use this information to determine how an artificial closed-loop algorithm for insulin delivery should behave (Doyle *et al.*, 2007). The first attempts to develop a control algorithm to mimic the pancreatic activity came from the studies by Albisser *et al.* (1974), and the improved proportional plus derivative (PD) algorithm by Clemens (1979) adopted in the Biostator, the first automated insulin delivery system. Nomura and coworkers (1984) proposed a PD-based secretion model to reproduce the pancreatic islets activity. These first developed algorithms were subject-specific and they needed to be reprogrammed as the metabolic conditions of the subject changed in time.

More recently, hyperglycemic clamp tests have shown that the beta-cells respond with a bi-phasic insulin pattern to glucose challenges, while in the fasting state the response is characterized by a basal (steady) insulin level (Bellazzi *et al.*, 2001). This response closely resembles the response of a standard proportional-integral-derivative (PID) controller, which is ubiquitously used in the chemical process industry (e.g. see Seborg *et al.* (2004)), and therefore the PID control approach to glucose control received some attention in the literature (e.g. see Steil and Saad (2006)). It has been recently argued by Bequette (2005) that a bi-phasic beta-cell response does not necessarily mean that the pancreas itself uses a PID algorithm to deliver the insulin in a healthy subject, and that the integral term in PID controllers can cause the overadministration of insulin, resulting in postprandial hypoglycaemia. PD control is therefore also employed for glucose concentration control (Doran *et al.*, 2005).

The major limitation of most of the published studies on PID control of diabetes is that simplified models are often used to represent the insulin/glucose system, and that in most

cases neither noise, uncertainty in insulin sensitivity, unmeasured disturbances are not taken into account. As discussed by Farmer *et al.* (2009) these issues may have a dramatic impact on the control performance and the results available so far in the field of standard PID control of glycemia may be questionable.

Recently, a PID switching control algorithm was successfully applied by Marchetti *et al.* (2008) according to the idea that a time-varying glucose concentration setpoint is a more appropriate reference profile to be tracked. They also showed that a very mild integral action is useful to compensate for individual's changes in insulin sensitivity without leading to postprandial hypoglycaemia. In a similar fashion, Percival *et al.* (2009) proposed a practical approach to design and implementation of a PID control algorithm focusing on controller robustness when changes on insulin sensitivity, meal times and meal sizes occur.

Advanced control strategies have also been recently proposed in literature where the model itself is embedded in the control algorithm, as in model predictive control (MPC) (Hovorka *et al.*, 2004; Parker *et al.*, 1999), adaptive control, optimal control (Fisher, 1991; Ollerton, 1989), neural networks and H-infinity control (Parker *et al.*, 2000). As recognised by Parker and Doyle (2001) the key issue is that the performance of model-based control systems is directly linked to model accuracy.

Some advanced control algorithm tested *in silico* have been also applied *in vivo*. El-Khatib and coworkers have performed real-life trials in pigs using adaptive control with dual insulin and glucagon infusion (El-Khatib *et al.*, 2007), while Hovorka *et al.* (2004) performed trials on subjects affected by T1DM adopting model predictive control strategies (Schaller *et al.*, 2006).

5.3 Standard clinical tests

Standard clinical tests are used both to help diagnose diabetes and to identify simple models of glucose homeostasis. Basically, an input pattern is used to excite the subject's glucoregulatory system in such a way as to subsequently extract some kind of information from the measured time-profiles of the plasma glucose and insulin concentrations. In most cases, the input excitation pattern reduces to the infusion or intake of glucose only, although the infusion of insulin is also possible. To provide a general overview of how these tests are carried out, the most widespread tests (2006) are shortly recalled in the following.

1. *Oral glucose tolerance test (OGTT)*: this is the diagnostic test recommended by the World Health Organization (2006). The test is carried in the morning after about three days of unrestricted diet (greater than 150 g of CHO daily) with the usual physical activity of the subject. A meal of 30-50 g of carbohydrates should be consumed the evening preceding the test. After collection the fasting blood sample, the subject drinks a solution of 75 g of glucose in water over the course of 5 min. Blood is drawn at intervals for measurements

of glucose, and sometimes insulin levels. The sampling frequency can vary according to the purpose of the test. For simple screening, one can take the samples at 0 and 2 h (only two samples collected), but in a research activity the sampling can be very frequent (for example a sample every 2 min).

2. *Intravenous glucose tolerance test (IVGTT)*: it is useful to evaluate the pancreatic activity *in vivo*, but it is mainly used in research activities, because it is much more invasive than the OGTT. Usually it consists in injecting 300 mg/kg of glucose over 60 s in an antecubital vein, and then measuring the plasma insulin and glucose concentrations. The sampling schedule of the standard IVGTT consists of taking three pre-test samples and 23 additional 2-mL samples (the sampling frequency at the beginning of the test is of one sample every 2 min, and one sample every 20 min at the end of the experiment, lasting at least 3 h). In modified IVGTTs, insulin (30 mU/kg) is infused 20 min after the glucose ingestion (Boston *et al.*, 2003).
3. *Postprandial glucose test*: it is useful to screen for diabetes and to evaluate the effectiveness of treatment or dietary therapy for diabetic subjects. It is performed after the subject has eaten a balanced meal containing 100 g (or more) of glucose and then is fasted for 2 h before beginning the test (the sample policy can be variable).
4. *Euglycemic hyperinsulinemic clamp*: it is important to quantify the insulin resistance of a subject by measuring the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycaemia. Through a peripheral vein, insulin is infused at 10-120 mU/(m^2×min) (De Fronzo *et al.*, 1979). At the same time, glucose is infused to maintain blood sugar levels between 91 and 100 mg/dL. The blood sugar levels are controlled every 5-10 min to adjust the rate of glucose infusion. Different insulin doses can be managed to discriminate between the different responses of peripheral tissues and the liver ones. The test takes about 2 h, and the rate of glucose infusion during the last 30 min of the test determines insulin sensitivity.

Tests 1 and 3 are oral tests, and have the advantage of being physiological, i.e. not invasive for the subject. In general, given for granted that the test should be safe (i.e., it should not drive the subject to either hyperglycaemia or hypoglycaemia), an "ideal" test should be the best compromise between the level of stress for the subject, the clinical effort, and the amount of information obtainable.

"Normal" glucose levels are not easy to define (World Health Organisation, 2006) and not universally agreed upon. In this study, unless, otherwise specified, the upper and lower glucose concentration thresholds are set to 170 and 60 mg/dL, respectively. When an identification experiment is being carried out, temporary conditions of high glucose concentration can be easily tolerated by a subject (they are indeed obtained in clinical practice during an IVGTT or OGTT). On the other hand, hypoglycaemic conditions represent a hard

constraint that must never be violated, not even for a short time period. However, in the following study, both the limits on glucose concentration are considered as hard constraints.

5.4 The glucose homeostasis model

As was mentioned in §5.1, recently some detailed models have been proposed that are able to represent the complex dynamic behaviour of the glucose/insulin system, and allow for the simulation of the dynamics of subcutaneous insulin infusion of the rate of glucose appearance following a meal (Hovorka *et al.*, 2002; Wilinska *et al.*, 2005, Fabietti *et al.*, 2006, Dalla Man *et al.*, 2007).

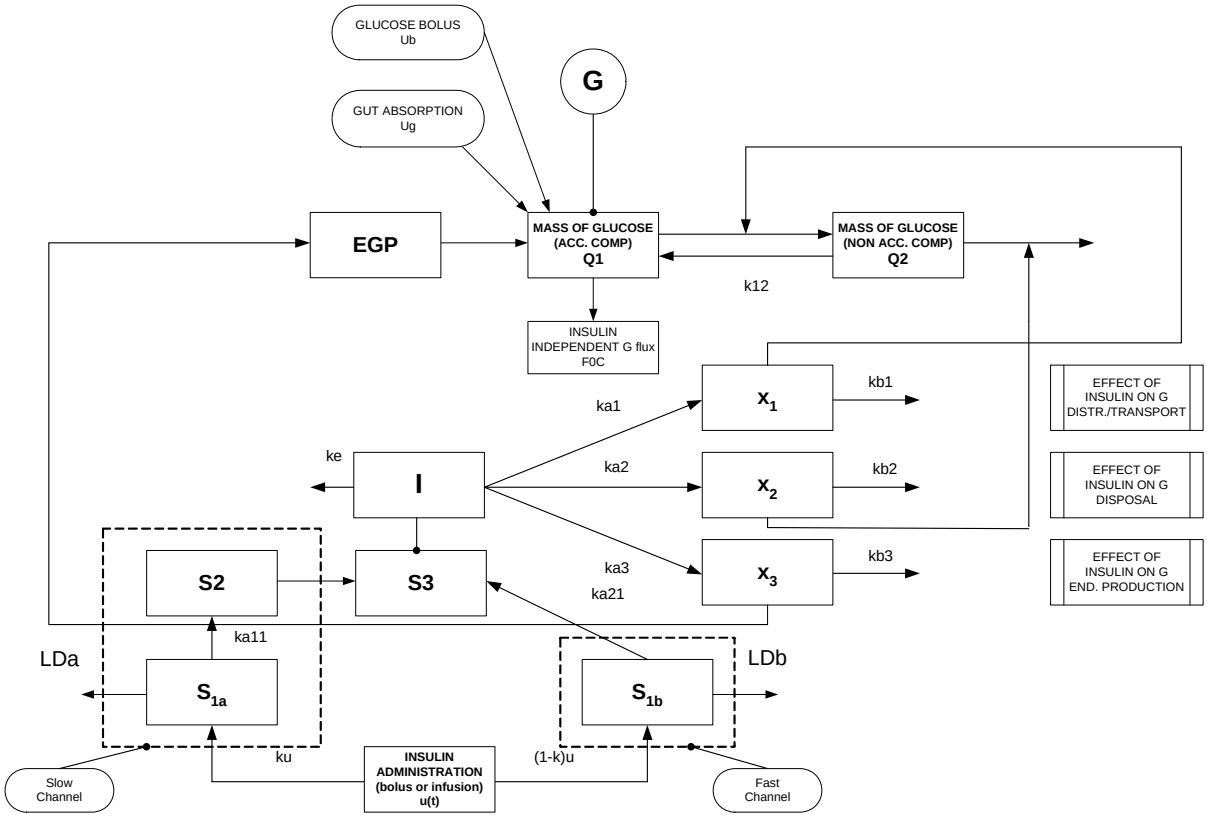


Figure 5.1 *Schematic representation of the Hovorka-Wilinska model (HWM). S1a, S2 and S1b compartments represent the insulin absorption subsystem. The insulin compartment (I) affects the accessible (Q1) and non accessible (Q2) compartments of glucose mass through a three-compartmental subsystem controlling glucose distribution/transport, disposal (glucose hold-up) and endogenous glucose production (EGP). Glucose can also be consumed through an insulin independent stand-alone channel. The system inputs are the bolus/infusion of insulin (insulin administration), and the measured variable is the blood glucose concentration (G). Please refer to Appendix A for more detailed comments on the model and for the explanations of the symbols used in the figure.*

In this first study we refer to the model developed by Hovorka *et al.* (2004), with the modifications of Wilinska *et al.* (2005); this model will be denoted as the Hovorka-Wilinska

model (HWM). We are not claiming that this model is the best one available. In effect, it predicts an excessively slow response to some values of basal insulin infusion rates, producing an excessively prolonged postprandial phase, and also meaningless negative glucose concentration values in some conditions (Finan *et al.*, 2006). Nevertheless, as testified by recent closed-loop control studies (Marchetti *et al.*, 2008; Hovorka, 2005; Hovorka *et al.*, 2004; Percival *et al.*, 2009), this model is sufficiently detailed to provide a sound representation of the glucose homeostasis. Furthermore, it is highly flexible for the management of manipulated inputs like insulin subcutaneous infusion, insulin bolus administration, and glucose oral intake, and can be used to manipulate IVGTT-like inputs.
The system of differential and algebraic equations defining the HWM is reported and commented on in Appendix A. Figure 5.1 shows a schematic representation of the model.
Simulated data only are considered in this research. Therefore, not only the "virtual subject", but also the "real subject" are represented by a detailed physiological model. Additionally, only parametric mismatch was considered, i.e. the real subject model and the virtual subject model have the same structure (HWM), but they differ exclusively by the value of the parameters. For the sake of conciseness, in the following the real subject model will be addressed to as the "subject", while the virtual subject model will be addressed to as the "model". Therefore, the objective is to design a set of experiments (i.e., clinical tests on the subject) where the glucose (and possibly insulin) administration profiles (inputs), as long as the blood sampling schedule, are optimised in order to identify the model parameters in a statistically sound way, fulfilling all the constraints related to subject safety and to easiness of conduction of the experiment.

5.5 Design of experiments under constraints for physiological models

The HWM, and a large number of physiological models, belong to the class of nonlinear dynamic models described by a system of differential and algebraic equations in the (2.1) form. For the model of glucose homeostasis, the time-dependent manipulated inputs $\mathbf{u}(t)$ may comprise the insulin infusion and the insulin bolus administration, whereas the glucose intake can be represented as a time-invariant control variable w. Usually there is only one measurable output $y(t)$ and is constituted by the blood glucose concentration[1] G. For such physiological models the formulation of the design vector (2.8) usually comprises, together with the manipulated inputs $\mathbf{u}(t)$ (approximated with a discrete function, i.e. piecewise constant, piecewise linear or polynomial) and the time-invariant inputs $\mathbf{w}$, the test duration and the set $\mathbf{t}^{sp}$ of time instants at which the output variables are sampled (blood sampling

[1] Interstitial insulin or plasma insulin can be measured, but glucose clamp studies (see Sjöstrand *et al.* (1999)) highlighted a significant variability in the measurements.

schedule). Even if the glucose concentration at $t = 0$ could be approximately managed and stabilised by acting on the insulin infusion during a preliminary phase before the test is carried out, the initial concentration of glucose is not considered as design variable in the following study: when the test begins, the subject it is supposed to be at his own "basal" level of glucose concentration, which is specific for each subject. As a result the design vector becomes:

$$\boldsymbol{\varphi} = \left\{ \mathbf{u}(t), \mathbf{w}, \mathbf{t}^{sp}, \boldsymbol{\tau} \right\}. \tag{5.1}$$

Discrete sampling and off-line analysis allow for the most precise analytical laboratory technique to be used, albeit with a time delay. Recent sampling techniques such as CGM (continuous glucose monitoring) could enrich the information content of the glucose test, allowing for the continuous recording of glucose level over a 24-h period. On the other hand, clinical issues that must still be addressed when a CGM system is used are some accuracy issues mainly related to the lag time between blood glucose and interstitial glucose readings, the need of a calibration with traditional blood measurements, and the fact that, at least in the U.S.A., continuous sensors have been approved for adjunctive use only (Hirsh *et al.*, 2008). In view of the above, although CGM represents a very promising technology, a traditional discrete sampling approach was adopted in this work.

The experiment design needs to take into account the existence of a N_c-dimensional set of equality and inequality constraints $\mathbf{C}$ in the form (4.1). In physiological systems, the set of active constraints is entirely related to the maintenance of the complex dynamics involved in the metabolic functions. For the system under investigation there are physical/physiological constraints that are strictly related to the physiology of the glucoregulatory system and cannot be manipulated for design purposes.

The design under constraints problem concerns the identification of the optimal experimental conditions of the design vector (2.14) subject to constraints (4.1) that here simplify to

$$C_1 = y\left(\boldsymbol{\theta}, \boldsymbol{\varphi}, t\right) - y_{\max} \leq 0 \tag{5.3}$$

and

$$C_2 = y_{\min} - y\left(\boldsymbol{\theta}, \boldsymbol{\varphi}, t\right) \leq 0 \tag{5.4}$$

where $y_{\max}$ and $y_{\min}$ are the time-invariant upper (hyperglycaemia) and lower (hypoglycaemia) bounds on y. Additional constraints in the form (4.1) concerning the glucose and insulin dynamics (e.g. related to the attainment of basal or reference values at the end of the test) can be introduced.

5.5.1 The experiment design procedure

As usual, the model-based design of the clinical test involves a sequential interaction between three key entities:

1. the design of experiment;
2. the execution of the *in silico* test;
3. the parameter estimation.

In this work the selected design criterion is the *D*-optimal one (minimising the determinant of the variance-covariance matrix of model parameters). The experiment is carried out on the subject (nominal values of the HWM parameters), assuming that the disturbance factors are stochastic and ergodic (i.e., they do not change their probability distribution in time). It is assumed that they can be represented as normally distributed noise with zero mean and a constant relative variance of 0.033 (Clarke *et al.*, 2005).

The choice of the proper parameter estimation technique is crucial for MBDoE. Bayesian estimation techniques have been proved to be very efficient for physiological model identification (Pillonetto *et al.*, 2003), but the severe computational effort required and the lack of reliable *a priori* statistics often make them too challenging an approach. Thus, a maximum likelihood estimator is chosen in this work, where the evaluation of the quality of the final estimates is evaluated according to the following factors (with the assumption of Gaussian distribution of measurement errors):

1. *a posteriori* statistics of the estimates (in terms of *t*-test and confidence intervals);
2. goodness of fit (in terms of whiteness test and χ^2 test).

The gPROMS® modelling environment (Process Systems Enterprise Ltd., 2006) is used for modelling, simulation and optimisation purposes, as well as to design the experiments.

5.6 Preliminary dynamic analysis

Some simulations without constraints were carried out to evaluate the response of the glucose/insulin system on the subject and on the model. The model parameters were affected by 30 % error with respect to the subject ones. The sets of subject ($\boldsymbol{\theta}$) and model ($\boldsymbol{\theta}^0$) parameters are collected in Table 5.1. Set $\boldsymbol{\theta}^0$ summarises the information about the subject glucoregulatory system that is available before the MBDoE procedure is started. Experiments are therefore designed in order to "move" from $\boldsymbol{\theta}^0$ to as close as possible to $\boldsymbol{\theta}$ (which in practice is unknown).The input $u(t)$ (mU/min) is an insulin infusion rate and can be written as the sum of three terms:

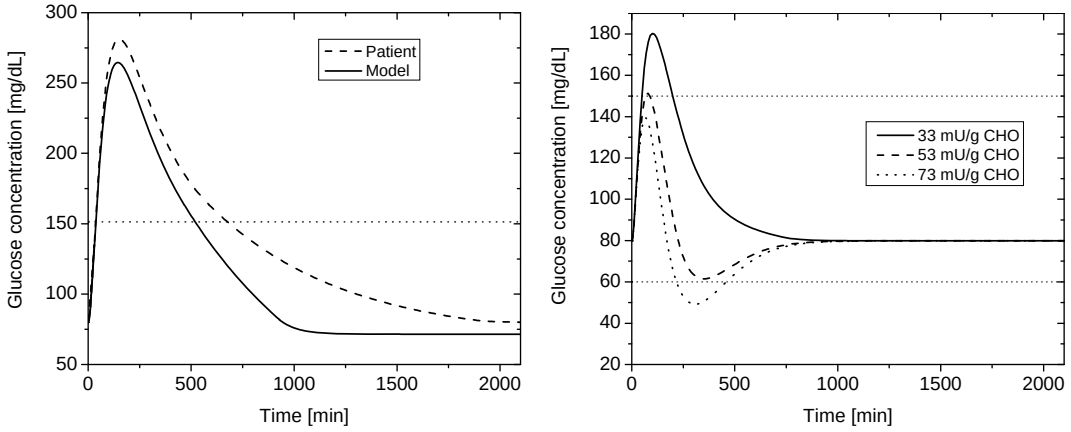
$$u(t) = u_{bas} + u_s(t) + \delta(t)u_{bol} \quad , \tag{5.5}$$

where u_{bas} is the time-invariant basal insulin infusion rate, $u_s(t)$ is a time-dependent insulin infusion rate, and the last term represents the insulin bolus u_{bol} (mU) expressed as a Dirac impulse $\delta(t)$. The last two terms on the right-hand side characterise the exogenous insulin management.

Table 5.1 *Parameters values for the HWM nominal (**θ**) and perturbed (**θ**^{0}) sets.*

Parameter	θ (subject)	θ^0 (model)
S_{IT}^f	51.2E-4	66.6E-4 (+30%)
S_{ID}^f	8.2E-4	5.7E-4 (-30%)
S_{IE}^f	520.0E-4	676.0 E-4 (+30%)
EGP_0 mmol/(kg min)	0.0161	0.0209 (+30%)
F_{01} mmol/(kg min)	0.0097	0.0126 (+30%)

Simulations were carried out to analyse the glucose concentration (G) profiles after a meal of 60 g_{CHO}, with u_{bas} = 9.94 mU/min. Figure 5.2a shows the G profiles for the subject and for the model to be identified when no hexogen insulin is administered (i.e. $u_s(t) = 0$, $u_{bol} = 0$).



(a) *(b)*

Figure 5.2 *Glucose concentration profiles with u_{bas} = 9.94 mU/min, after a meal of 60 g_{CHO}, for: (a) the subject and the model, without exogenous insulin administration; (b) the subject, with an insulin bolus administration, according to different values of the insulin/CHO ratio.*

The glucose concentration dynamics shows some important features:

- for both the subject and the model, a long time interval is needed to restore the basal values (in fact, as previously stated, this is a structural limitation of the HWM); the length of this interval is significantly affected by the parameters values. Note that, due to this structural limitation of the HWM, it is expected that the designed experiments will appear to last longer than they would probably be in practice;

- at steady state, the subject and the model show different values of *G*;
- after about 1 h, and without insulin intake (either bolus or infusion), the subject and the model overshoot the hyperglycaemic threshold, and the condition persists for a long time (~10 h); the parameter values weakly affect the initial dynamics (i.e. the time needed to reach the peak value of *G*), but they affect the duration of the hyperglycaemic condition.

Figure 5.2b shows the effect on the subject of a bolus intake immediately after the meal ingestion. The bolus amount is adjusted according to three different insulin/CHO ratios.It is clearly appears that the use of exogenous insulin strongly reduces the time needed to restore the basal value of *G*. Therefore, it is expected that, to shorten the length of a designed experiment without sacrificing the information it can provide, exogenous insulin should be administered to the subject. Note however that care must be taken in insulin administration, because the hyperglycaemic and hypoglycaemic thresholds can be easily hit if the exogenous insulin administration is too low or too high, respectively.

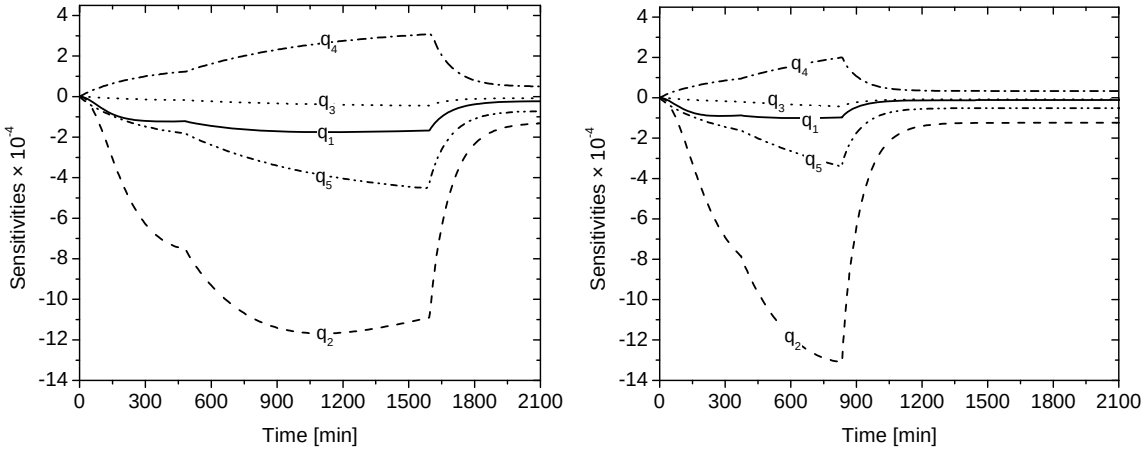
5.6.1 Sensitivity and information analysis

To assess the effect of the HWM parameters on the glucose concentration response for the subject and for the model, a sensitivity analysis was carried out considering the dynamic sensitivities in the form:

$$q_i = \frac{\partial \Gamma}{\partial \theta_i} \qquad i = 1,\ 2,\ \ldots N_\theta \quad , \tag{5.6}$$

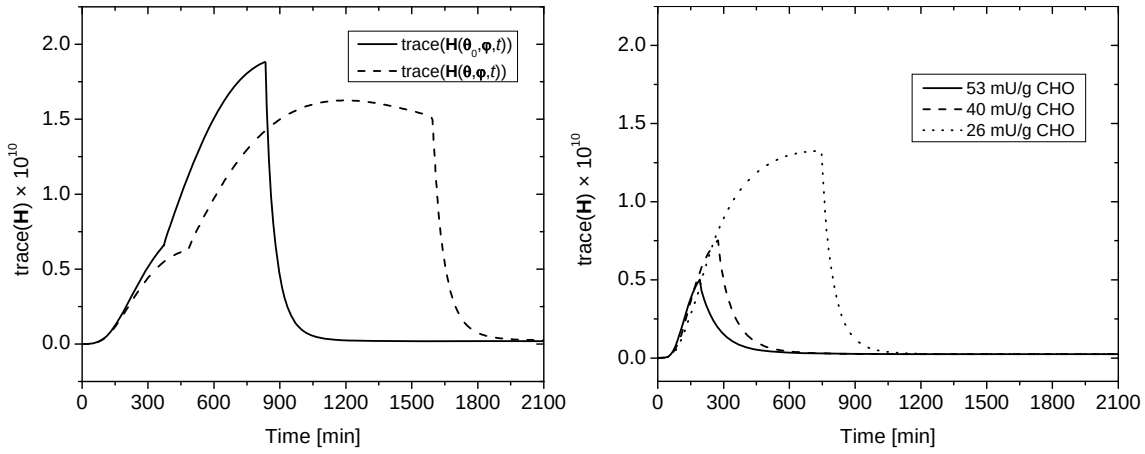
where $\Gamma = G(\boldsymbol{\varphi}, \boldsymbol{\theta})$ or $\Gamma = \hat{G}(\boldsymbol{\varphi}, \boldsymbol{\theta})$ are the glucose concentration response of the subject and of the model respectively. Figure 5.3 shows that the glucose concentration response is highly affected by the parametric set; which reflects the intrinsic variability of the parametric systems in terms of Fisher information (equation (2.6)). Therefore, the MBDoE results can be strongly affected by the mismatch between the actual information content (provided by the subject) and the initial information content (provided by the model). To further clarify this issue, two post-prandial simulations following a meal either with or without insulin infusion policy are run. A dynamic measure of the Fisher information matrix allows quantifying the variance of the overall sensitivities system, and is useful to anticipate the expected information content of an experiment. Thus, the matrix trace was computed at $\boldsymbol{\theta}$ and at $\boldsymbol{\theta}^0$ values for a meal with D_g = 60 g_{CHO}; results are illustrated in Figure 5.4. Figure 5.4a clearly shows that a 30% parametric mismatch implies a large misevaluation of the information content expected from an experiment. In particular, at $\hat{\boldsymbol{\theta}} = \boldsymbol{\theta}^0$ it is expected that the maximum information content can be gained during the 600 – 750 min time period, while the actual information content for this test has a maximum in the time period 900 – 1700 min. As was

suggested by Figure 5.3, too, a parametric mismatch may cause a scarcely effective scheduling of the blood sampling times.



(a) *(b)*

Figure 5.3 *Dynamic sensitivities calculated with u_{bas} = 9.94 mU/min and without insulin infusion policy for (a) the subject and (b) the model.*



(a) *(b)*

Figure 5.4 *Dynamic measure of the Fisher information matrix after a postprandial test (meal of 60 g_{CHO}) with u_{bas} = 9.94 mU/min: (a) without exogenous insulin administration policy, for both θ and $\boldsymbol{\theta}^0$ sets; (b) with different insulin boluses for the $\boldsymbol{\theta}$ set.*

Also note (Figure 5.4a) that a standard post-prandial test of about 8 h gives a very limited amount of information in terms of Fisher information matrix; however, the infusion of insulin in the form of a bolus (Figure 5.4b) allows increasing the information content and reducing the experiment length maintaining a maximum in the information level. Thus, as was anticipated by the analysis of Figure 5.2b, administrating an insulin bolus gives the possibility to shorten the optimal duration of the experiment without upsetting the subject excessively. This is consistent with the modified IVGTT procedures adopted in the clinical practice, where

insulin is infused after the glucose injection to improve parameter estimation (Boston *et al.*, 2003). It may be noted that, as the trace of the Fisher information matrix quickly decreases after the maximum peak, for MBDoE purposes it is very important to exploit the initial glucose dynamics.

If an unbiased estimator (for example the maximum likelihood estimator) is adopted, the parameter estimate tends to the nominal set when the number of samples tends to infinite, i.e.:

$$\lim_{n_{sp}\to\infty} \hat{\boldsymbol{\theta}} = \boldsymbol{\theta} \tag{5.7}$$

and therefore, for a given set of experimental input settings **φ,** it is possible to write:

$$\lim_{n_{sp}\to\infty} \hat{\mathbf{H}}\left(\hat{\boldsymbol{\theta}}, \boldsymbol{\varphi}\right) = \mathbf{H}\left(\boldsymbol{\theta}, \boldsymbol{\varphi}\right) \quad . \tag{5.8}$$

The right member of (5.8) is the true information content of the experiment.

5.6.2 Correlation analysis

The sensitivity analysis can also serve as a rather simple tool to assess the correlation between different parameters. For instance, Figure 5.3 suggests that the dynamics of the glucose sensitivities to $\theta_4 = EGP_0$ and $\theta_5 = F_{01}$) are very similar. In fact, the two curves exhibit the same symmetrical behaviour, independently of the parameter values. This usually indicates a structural unidentifiability (at least within constraints and assumptions considered in this work). We indeed verified that a conventional experiment design approach produce unsatisfactory results when facing the identification of the HWM, even if several experiments are repeated in sequence. In particular, EGP_0 and F_{01} are indeed resilient to the identification procedure, and this occurs because of their large correlation (see equation (A.1)). To quantify the correlation between θ_4 and θ_5 one can analyse the correlation matrix $\mathbf{C}_\theta$, whose elements (correlation coefficients) have the form

$$c_{ij} = \frac{v_{ij}}{\sqrt{v_{ii}}\sqrt{v_{jj}}} \quad . \tag{2.17}$$

Table 2 shows the correlation coefficients after a number (three) of sequential experiments: the quality of the information that can be derived from the designed set of experiments is not sufficient to "separate" the two parameters (θ_4 an θ_5) that are structurally correlated. Thus, a new parameterisation has been introduced and used in this study: instead of EGP_0 and F_{01}, a new parameter θ'_4 is considered and is defined as the ratio between the two original parameters. Therefore it results: $\theta'_4 = EGP_0 / F_{01} = 51.2\text{E}-4$ and $\theta'^0_4 = EGP_0 / F_{01} = 2.1577$.

With a small notation abuse, the set of model parameters initially available, after reparameterisation, will be still indicated with θ^0 in the remainder of the paper.

Table 2. *Elements of the correlation matrix after three sequential designed experiments.*

	1	**2**	**3**	**4**	**5**
1	1.0				
2	0.572	1.0			
3	0.135	-0.113	1.0		
4	-0.596	-0.457	-0.806	1.0	
5	-0.532	-0.377	-0.861	0.995	1.0

5.7 Definition of a reference test

When an MBDoE effort is undertaken, the first design is based on an initial guess of the model parameters. This initial guess might be just a rough approximation for them. From the point of view of the effectiveness of design, the sensitivity analysis has shown that a large parametric mismatch can result in misevaluation of the information content expected from an experiment, which can render the experiment itself uninformative. On a different perspective, the mismatch may lead to an erroneous evaluation of the insulin to be administered to the subject during the designed experiment, which might drive her/him to hypoglycaemic conditions. Therefore, unless reliable experimental data are already available, it may be convenient to carry out a preliminary "reference" test, aimed at obtaining a reasonable estimation of the actual parameter values to be subsequently used to design the first experiment (Forcolin, 2007).

An ideal reference test should be: *i*) safe for the subject, independently of her/his pre-test condition; and *ii*) informative as well as quick and easy to perform. From this perspective, the OGTT and the postprandial tests seem the most suitable reference tests. In view of above, a reference test was set up as follows[2]:

1. glucose administration of 15 g_{CHO} (a snack);
2. no insulin infusion or bolus;
3. duration: $\tau = 12$ h;
4. number of blood samples: $n_{sp} = 10$ (evenly spaced).

It must be pointed out that this reference test has not been optimized and, here, the only objective is to have a subject's tailored initial guess for the model parameters, so as to reduce

[2] We would like to point out that this reference test has not been optimised and we admit that some assumptions may appear questionable (e.g., a rather long test duration after just a snack intake); however, here the "message" is simply that a safe preliminary test should be carried out in order to have a subject's tailored initial guess for the model parameters so as to reduce the risk of an ineffective (and unsafe) design.

the risk of an ineffective (and unsafe) design. The availability of some preliminary clinical information could alternatively be exploited and used to find sensible initial values for the set of parameters.

The parameter estimates and statistics after the reference test are presented in Table 5.3: for numerical reasons, all parameters have been normalised by dividing them by their true values; from now on, we will always refer to the parameters normalised values (indicated by symbol **Θ**); therefore, note that the true value for each normalised parameter is 1. For the same reasons, the insulin subcutaneous administration is normalised, too: in the case of an insulin bolus the manipulated amount is divided by 4000 mU; in the case of an insulin infusion the manipulated variable is divided by 20 mU/min.

Table 5.3 *Parameter estimation after the reference test (the reference t-value is equal to 1.708; asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	1.5924	1.3	4.324	0.368*	1.767
Θ_2	0.8187	0.7	10.52	0.078*	4.298
Θ_3	1.3755	1.3	20.72	0.066*	8.466
Θ'_4	1.2677	1.3	16.86	0.075*	6.891

Table 5.3 shows that the estimation is not statistically satisfactory, because, as discussed before, the reference test is poorly informative; however, it allows for a first "raw" parameter estimation with related statistics (parameter variance-covariance of model parameters, prior uncertainty region, correlation coefficients).

5.8 Design of experimental protocols for parameter estimation

The design of an experimental protocol after a reference test is based on the following requirements:

1. exclusion of non-physiological tests (IVGTT, glucose clamp or similar);
2. possibility to manage a day test;
3. possibility to manage a multiple meal intakes and multiple insulin bolus administrations, or to modify the glucose intake policy of a standard OGTT;
4. constraints on the glycaemic curve: interior constraints to assure normoglycaemia (60-170 mg/dL); end point constraint on the glucose concentration (80 mg/dL); end point constraint on the derivative of the glucose concentration (steady glycaemia at the end of the test). It is important to note that the test formally ends with the last sampling point (which defines the duration of the experiment); however the end point constraints are imposed to guarantee safe conditions for the subject after the clinical test; the end point constraints must be fulfilled within a specified time interval;

5. constraints on the insulin infusion rate: $u(t) = u_{bas}$ at the end of the test.

It must be also guaranteed that the subject returns to the basal settings after performing the day test.

The goal of the suggested protocol is to obtain sufficiently informative data so as to enable the estimation of the set of model parameters in a satisfactory manner with only one designed experiment after the reference test. Two distinct protocols meeting the above requirements are proposed and assessed: a modified postprandial glucose test and a modified OGTT.

5.8.1 Protocol A: modified postprandial glucose test (MPGT)

The purpose is to identify the model set of parameters with a D-optimal designed experiment after two meals (breakfast and lunch, scheduled at 8:00 AM and 1:00 PM). The variables to be optimised are:

- the glucose content of the meals, $D_{g,1}$ and $D_{g,2}$ (bounds on breakfast: 5 – 40 g_{CHO}, bounds on lunch: 30 – 70 g_{CHO});
- the glucose-dependent insulin infusion rate $u_s(t)$ (parameterised as a piecewise constant function, with $n_z = 12$ levels and $n_{sw} = 11$ switching times to optimise), and the amount of insulin of the boluses $u_{bol,1}$ and $u_{bol,2}$;
- the sampling times (however, the total number of samples n_{sp} is assigned *a priori* and the elapsed time between two consecutive samples cannot be shorter than 5 minutes); the last sampling point can be taken not later than 600 min (10 h) from the beginning of the experiment (6:00 PM).

The time distance between consecutive meals is not optimised, and the insulin bolus amount is not constrained to an insulin/CHO ratio. It is imposed that the end point constraint on the glucose concentration and on the derivative of the glucose concentration must be fulfilled within 600 min.

5.8.2 Protocol B: modified OGTT (MOGTT)

The identification is carried out through a D-optimal designed experiment with multiple ingestions of a glucose solution, and insulin bolus intakes. The optimisation variables are:

- the glucose content of the meals (glucose solution drink);
- the time interval between consecutive meals (allowed to vary between 15 and 800 min);
- the amount of each insulin bolus;
- the sampling times (the number of samples n_{sp} is assigned *a priori* and the elapsed time between two consecutive samples cannot be shorter than 5 minutes); the last sampling point can be taken not later than 840 min (14 h) from the beginning of the experiment (10:00 PM).

A rather long maximum duration of the experiment was selected because, as was mentioned in §5.4, the HWM is known to show slower glucose concentration dynamics than in reality.

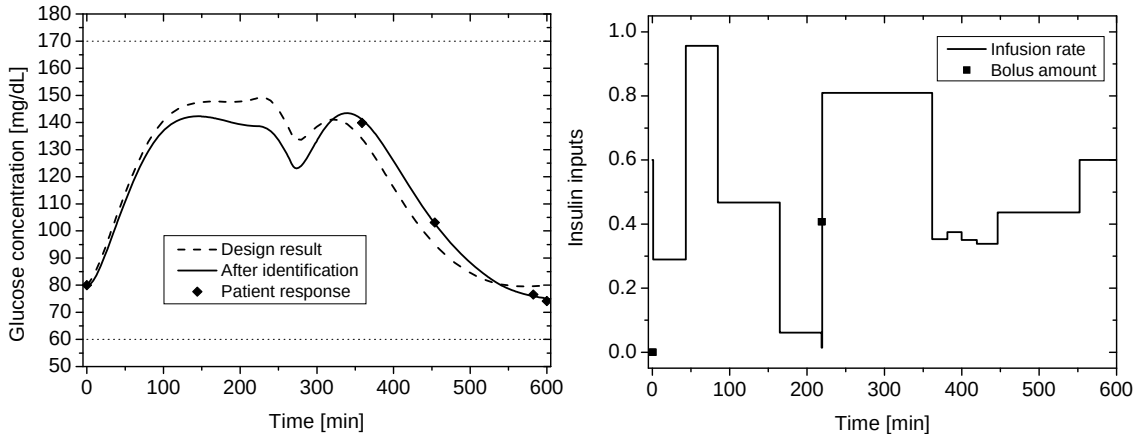
The timing of insulin infusion was not optimised. The amount of bolus per meal was modelled according to the following empirical relationship:

$$u(t) = u_{bas} + \alpha \sum_{i=1}^{N_{meals}} \delta_i(t) k_i D_{g,i} \tag{5.9}$$

where $\alpha' = 52.63$ mU/g_{CHO} represents the optimal insulin/CHO ratio. Since parameter uncertainty could lead the design to constraint violation even if the optimal value of the insulin/CHO ratio is used, the "relaxing factors" k_i have been introduced to evaluate the possible discrepancy between the actual bolus release and the optimal ratio during a standard postprandial glucose test. The relaxing factors are optimised in the design, too (i.e., $\mathbf{k} \in \varphi$).
An additional constraint was superimposed on the total amount of ingested glucose (acceptable range: 75 – 156 g_{CHO}). This range is equivalent to the total amount of glucose ingested through standard breakfast (18 – 36 g_{CHO}), lunch (27 – 60 g_{CHO}) and dinner (30 – 60 g_{CHO}). It is also imposed that the end point constraint on the glucose concentration and on the derivative of the glucose concentration must be fulfilled within 720 min (12 h) from the last meal.
A longer duration must be allowed for when designing an MOGTT test as it was verified that for the experiment to be informative the three meals should be spaced over a sufficiently long period of time. Furthermore, as the designed ingestion of the last meal may occur toward the end of the experiment, a sufficiently long period should elapse before the interior point constraints can be fulfilled.

5.9 MPGT: results and discussion

The first modified postprandial test (MPGT1) optimises the bolus amount, the glucose-dependent insulin infusion $u_s(t)$ and the glucose amount of the meal. The glucose concentration profiles predicted by the model before and after parameter estimation are shown as curves in Figure 5.5a, while the G values for the subject are not known continuously, but only through few sampled data shown as diamonds in the same figure. The actual profiles of the manipulated inputs, as dictated by the MBDoE procedure, are shown in Figure 5.5b.
In MPGT1 only 5 blood samples are allowed (n_{sp} = 5). The values of the other optimised variables (and constraints) are summarised in Table 5.4. The test lasts slightly less than 10 hours (from 8:00 AM to 6:00 PM), i.e. nearly all the possible experiment duration is exploited. Note how the design moves the glucose profile upwards, adopting relatively low values for the exogenous insulin inputs, particularly in the first four hours from the beginning of the test.



(a) *(b)*

Figure 5.5 *Experiment MPGT1. (a) Glucose concentration profiles predicted by the model during the experiment design (broken line) and after the parameter identification (solid line); the subject actual response to the designed experiment is indicated by diamonds. (b) Profiles of the insulin infusion rate (solid line) and of the bolus amount (boxes). In the time scale, 0 represents 8 AM.*

Table 5.4 *Experiment MPGT1: optimal sample scheduling, bolus amount and glucose content of the meal and constraint settings.*

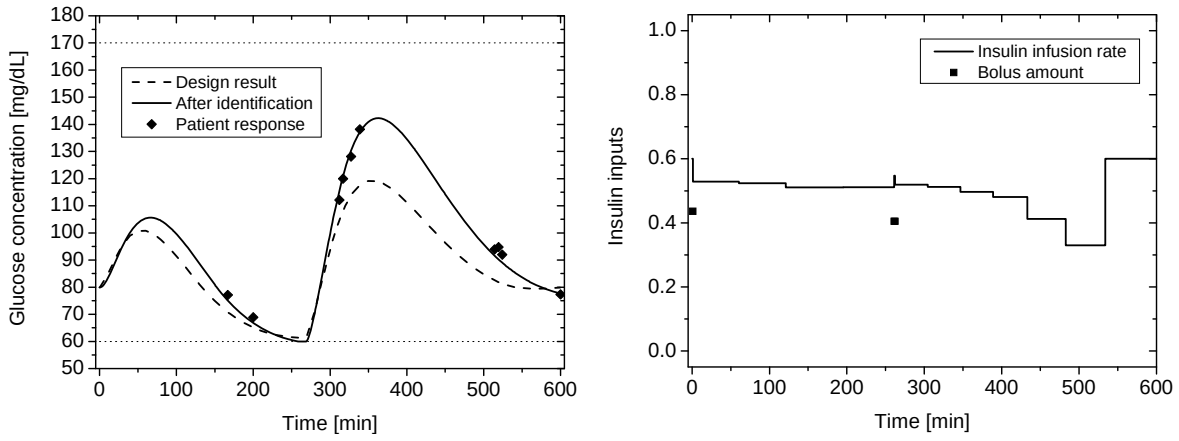
Optimised Design Variable	**Values**
$\mathbf{t}^{sp}$ [min]	[0, 359, 454, 582, 600]
$\mathbf{u}_{bol}$ [mU]	[0.04, 1600]
$\mathbf{D}_{g,i}$ [g_{CHO}]	[18, 30]

Table 5.5 shows that the parameter estimation is not statistically satisfactory for Θ_2 and Θ_3 (the insulin sensitivities of disposal and endogenous glucose production S_{ID}^f and S_{IE}^f).

Table 5.5 *Parameter estimation after experiment MPGT1 (the reference t-value is equal to 1.795; asterisks denote t-values failing the t-test).*

Model Parameter	**Final Value**	**Initial Guess**	**Confidence Interval 95%**	**95% t-value**	**Standard Deviation**
Θ_1	1.0099	1.5924	0.3021	3.343	0.1372
Θ_2	0.7444	0.8187	2.6110	0.285*	1.186
Θ_3	1.2118	1.3755	2.6300	0.461*	1.195
Θ_4	1.0397	1.2677	0.5720	1.818	0.2599

An effective strategy for improving the estimation is to augment the experiment information content, e.g. by increasing the number of blood samples. Experiment MPGT2 is designed assuming n_{sp} = 10. The glucose concentration and exogenous insulin profiles are shown in Figure 5.6, and the optimised variables and constraints are summarised in Table 5.6. Table 5.7 collects the results of the parameter estimation.



(a) *(b)*

Figure 5.6 *Experiment MPGT2. (a) Glucose concentration profiles predicted by the model during the experiment design (broken line) and after the parameter identification (solid line); the subject actual response to the designed experiment is indicated by diamonds. (b) Profiles of the insulin infusion rate (solid line) and of the bolus amount (boxes).*

Table 5.6 *Experiment MPGT2: optimal sample scheduling, bolus amount and glucose content of the meal and constraint settings.*

Optimised Design Variable	Values
$\mathbf{t}^{sp}$ [min]	[167, 200, 312, 317, 327, 338, 514, 519, 524, 600]
$\mathbf{u}_{bol}$ [mU]	[1746, 1619]
$\mathbf{D}_{g,i}$ [g_{CHO}]	[22, 53]

Table 5.7 *Parameter estimation after experiment MPGT2 (the reference t-value is equal to 1.746; asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.9271	1.5924	0.2317	4.001	0.1093
Θ_2	1.1742	0.8187	0.2384	4.925	0.1125
Θ_3	0.9805	1.3755	0.2798	3.505	0.1320
Θ_4	0.9999	1.2677	0.0599	16.700	0.0282

It may be observed that increasing the number of sampling points significantly affects the shape and results of the overall design. The glucose concentration profile presents two peaks following MPGT2: that is, more frequent sampling allows for the repetition of two informative events during the same experiment. On the contrary, in MPGT1 the limited number of available measurements forces the design to concentrate the information content in the final descending branch of the *G* curve, where most samples are taken.

In both cases the test is safe for the subject, but only MPGT2 is sufficiently informative to make it possible to estimate the wholeset of the HWM model parameters in a statistically sound manner. A possible drawback of MPGT2 (and an opportunity for further refinement) is that the two exogenous insulin contributions (i.e., the insulin boluses and the glucose

dependent infusion rate) need optimizing. In particular, the latter may require particular care and be somewhat uncomfortable for the subject as the glucose concentration is pushed toward the lower bound. From this perspective, MOGTT is simpler to carry out, and the only exogenous input of insulin is obtained through a bolus intake.

5.10 MOGTT: results and discussion

In the MOGTT design it is assumed that no exogenous infusion of insulin is optimised, and that the insulin bolus amount is adjusted according to an insulin/CHO ratio. A first experiment (MOGTT1) is designed assuming an optimised insulin/CHO ratio. Four CHO ingestions (meals) are assumed. As in the MPGT2 configuration, we found that five sampling points are insufficient for a sound estimation of the model parameters. Therefore, only the results for $n_{sp} = 10$ will be discussed here.

The glucose concentration profiles are illustrated in Figure 5.7. The four meals are taken in the first half of the test. The initial parameter mismatch leads the glucose concentration profile in the designed experiment to be above the upper threshold during the actual execution of the test. However, as discussed before, this can be tolerated for diagnostic or identification purpose.

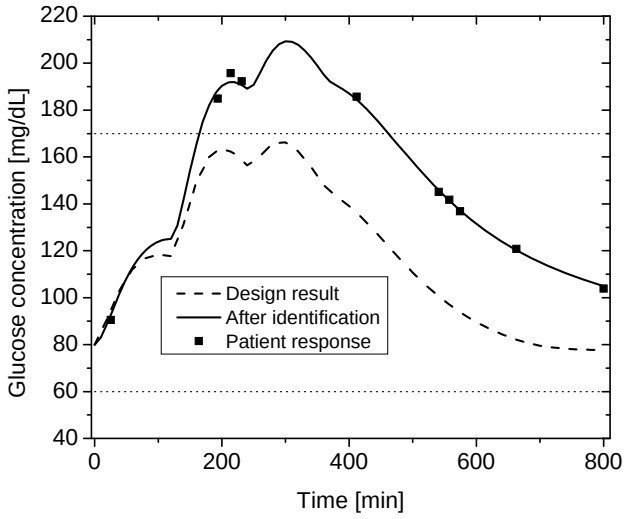


Figure 5.7 *Experiment MOGTT1: glucose concentration profiles predicted by the model during the experiment design (broken line) and after the parameter identification (solid line); the subject actual response to the designed experiment is indicated by diamonds.*

The optimal design settings are shown in Table 5.8. The test returns a satisfactory parameter estimation in statistical terms (Table 5.9).

Table 5.8 *Experiment MOGTT1: optimal settings.*

Optimised Design Variables	Values
$\mathbf{t}^{sp}$ [min]	[25, 193, 214, 231, 412, 541, 557, 574, 663, 800
$\mathbf{t}^{meals}$ [min]	[0, 120, 240, 360]
$\mathbf{D}_g$ [g]	[18.0, 36.0, 26.8, 10.0]
k	[0.45, 0.4, 0.5, 0.5]

Table 5.9 *Parameter estimation after experiment MOGTT1 (the reference t-value is equal to 1.746; asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.98241	1.5924	0.1726	5.692	0.08141
Θ_2	0.82972	0.81871	0.315	2.634	0.1486
Θ_3	1.2115	1.3755	0.3655	3.315	0.1724
Θ_4	1.0689	1.2677	0.1386	7.715	0.06535

The subject's glycaemic stress can be reduced by increasing the number of meals. Experiment MOGTT2 allows for 6 meals, so that the total CHO amount can be taken more gradually. However, we verified that in this case a higher number of sampling points is required to obtain a statistically sound estimation of the model parameters (n_{sp} = 15). Figure 5.8 shows the glucose concentration profiles. Table 5.10 shows the optimal settings, whereas Table 5.11 summarises the (satisfactory) estimation results.

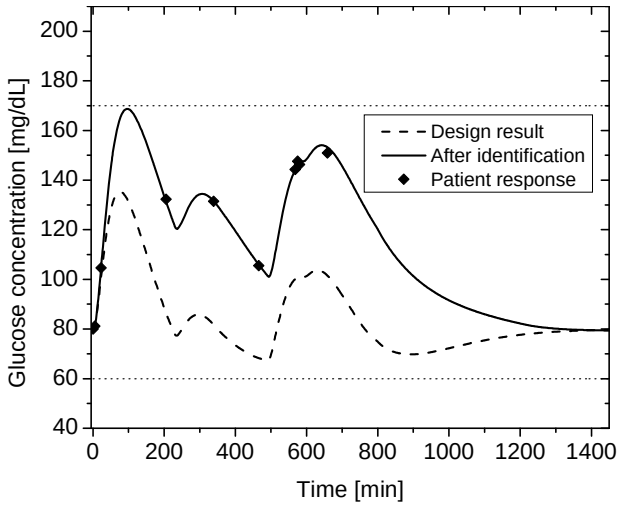


Figure 5.8 *Experiment MOGTT2: glucose concentration profiles predicted by the model during the experiment design (broken line) and after the parameter identification (solid line); the subject actual response to the designed experiment is indicated by diamonds.*

Table 5.10 *Experiment MOGTT2: optimal settings.*

Optimised Design Variables	Values
$\mathbf{t}^{sp}$ [min]	[75, 80, 219, 226, 231, 337, 374, 429, 501, 556, 561, 566, 571, 793, 798]
$\mathbf{t}^{meals}$ [min]	[1, 120, 238, 350, 486, 598]
$\mathbf{D}_g$ [g]	[45.0, 1.0 ,20.0, 1.0, 27.0, 9.0]
k	[0.7, 0.6, 0.5, 0.64, 0.5, 0.65]

Table 5.11 *Parameter estimation after experiment MOGTT2 (the reference t-value is equal to 1.721; asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	1.0047	1.5924	0.3042	3.303	0.1463
Θ_2	0.85	0.81871	0.4423	1.922	0.2127
Θ_3	1.1288	1.3755	0.602	1.875	0.2895
Θ_4	1.0372	1.2677	0.2043	5.078	0.09822

The new designed test provides a sound estimation of the entire parameter set and it is definitely safe for the subject (and also, it is very easy to carry out). The drawback is that it results in a rather long experiment duration (798 min). We verified that it is possible to reduce the duration of the test (to about 600 min) by assigning a set of values for the relaxing factors **k**. However, in such a case the subject/model mismatch may cause the actual glucose concentration level to enter the unsafe zone below 60 mg/dL, notwithstanding the design constraints on the model being met. Note that this problem could be tackled by implementing an active control on the glucose concentration as soon as it gets close to the lower threshold (e.g., by incorporating a feedback controller), through an on-line redesign of the experiment as soon as new measurements becomes available (see Chapter 3) or exploiting a backoff-based MBDoE (see Chapter 4) where the uncertainty on model parameters (and even the structural model mismatch, as will be presented in Chapter 6) is taken into account within the formulation of the design problem itself.

5.11 Summary of results and final remarks

Table 5.12 summarises the results obtained in the current study through the design of different clinical tests for the identification of the Hovorka-Wilinska model.

Table 5.12 *Summary of the results obtained by different protocols for HWM identification.*

Test	Name	Information level	Risk for the subject	Performing easiness	Length [h]
Modified postprandial	**MPGT1**	**Low**	**Absent**	**Moderate**	**10.0**
	MPGT2	**High**	**Absent**	**Moderate**	**10.0**
Modified OGTT	**MOGTT1**	**High**	**Moderate**	**High**	**13.3**
	MOGTT2	**High**	**Absent**	**High**	**11.0**

The best compromises between opponent factors can be identified in the modified postprandial protocol MPGT2 if subcutaneous insulin infusion is possible, or in the modified oral glucose tolerance test MOGTT2. MPGT provides a better parameter estimation and it takes a shorter time to perform than MOGTT; however, it is more complex to be carried out. The results also suggest that insulin administration is greatly helpful for the estimation of the model parameters. This is a particularly useful feature because the set of parameters should represent a "metabolic portrait" of the subject affected by diabetes. The identification problem is a trade-off between acquisition of a large information content (capability to reduce the uncertainty region of model parameters), compliance to a number of constraints (most importantly, safety for the subject) and practical applicability of the test. The results show that is possible to reach a statistically satisfactory parameter estimation for an individual subject using a single modified oral test by managing a proper meal intake and the insulin bolus administration.

Chapter 6

Optimal design of clinical tests for the identification of physiological models of type 1 diabetes mellitus in the presence of model mismatch*

Conventional MBDoE techniques are affected by some limitations. A structural mismatch between the plant's response and the model to be identified, combined to the initial uncertainty in the actual parameter values may lead to plan sub-optimal or even hazardous experiments. This issue is particularly important when the identification of physiological models is considered. In fact, if MBDoE is used to identify a physiological model of diabetes as proposed in Chapter 5, an unsafe test may be carried out, potentially leading the subject to hypoglycaemic or hyperglycaemic conditions. This Chapter deals with the identification of physiological models of diabetes and shows how the above limitations of conventional MBDoE can be tackled through the integrated use of two advanced MBDoE techniques. First, an online model-based redesign technique is utilised to exploit the information embedded in the experimental data as soon they become available and to adjust the experiment while it is still running. Then, a backoff-based MBDoE strategy is implemented to take care of the effect of uncertainty and to define by design an optimally informative and safe clinical test. The effectiveness and features of the proposed approaches are assessed and critically commented on via a simulated case study based on state-of-the art models of glucose homeostasis.

6.1 Introduction

As previously seen in Chapter 5, MBDoE techniques can be successfully applied to the design of clinical tests for the identification of complex models of type 1 diabetes mellitus in the presence of parametric mismatch (i.e. incorrect values of the parameters), demonstrating the possibility to tune up a detailed model to the specific physiological behaviour of a subject. However, although constraints can be handled in the standard design formulation, the presence of a model mismatch (i.e., the subject's physiological behaviour is structurally different from the model representation) may severely affect the quality of the experiment. In

* Portions of this charter have been published in Galvanin *et al.* (2010b) and Galvanin *et al.* (2010c).

general, as discussed by Ford *et al.* (1989), since the design methodology is model-based, both model mismatch and parametric mismatch may affect the consistency of the whole design procedure. The result could be a sub-optimal design (scarcely informative) or, in the worst case, a dangerous or unfeasible test burdening on the subject's health (e.g., the actual subject's response may lead towards hyperglycaemia or, even worse, hypoglycaemia).

Recently, some approaches have been proposed to improve the effectiveness and applicability of MBDoE techniques. Adaptive optimal input design (Stigter *et al.*, 2006) and online model-based redesign of experiments (OMBRE, see Chapter 3) allow exploiting the information acquired during a trial thanks to intermediate parameter estimation sessions, performing an update of the optimally designed experimental conditions while an experiment is still running. This is a highly desirable feature, in view of the fact that modern sampling techniques such as CGM (continuous glucose monitoring systems) allow increasing the available information through a frequent measure of glycaemia (Hirsh *et al.*, 2008). Most importantly, the possibility to exploit the available information content during the experiment may help increasing the safety and feasibility of the clinical test since an online tuning of the model to the actual subject's response is made possible.

On a different perspective, as discussed in Chapter 4, backoff-based MBDoE techniques proved to be very efficient on ensuring feasible and optimally informative tests under parametric uncertainty and were successfully applied to a simple model of glucose homeostasis. The possibility to incorporate a backoff strategy ensuring feasibility in the presence of uncertainty is particularly important when, as usually is the case, the model is not a perfect representation of the real system. According to this approach, model mismatch and parametric uncertainty can be tackled by design in order to guarantee a safe and optimal clinical test.

The goal of the current simulation study is to design a clinical test adopting advanced MBDoE techniques with the purpose of identifying the individual set of parameters of a complex model of glucose homeostasis in the most precise and accurate way, without affecting the subject's safety in terms of hyper- or hypoglicaemia. A model mismatch is introduced considering two distinct state-of-the-art models of glucose homeostasis: a detailed model (Dalla Man *et al.*, 2006) for simulating the real subject (which will be referred to as the "subject") and a different detailed model (proposed by Hovorka *et al.*, 2002, which will be referred to as the "model") for MBDoE identification. First, the identification test will be designed on the "model" by means of MBDoE techniques, and then the design test will be carried out on the "subject" to obtain the "experimental" data to be used for parameter identification. The designed test must be safe (i.e. meeting the assigned constraints on glycaemia), fast, and optimally informative for parameter estimation purposes.

6.2 Glucose homeostasis models

As discussed in Chapter 5, a generic model of glucose homeostasis can be seen as a multiple-input single-output system usually described by a system of differential and algebraic equations (DAEs) where the measured output variable is the plasma glucose concentration G and the manipulative input variables are the amount of carbohydrates of the meal(s) and the subcutaneous insulin infusion rate.

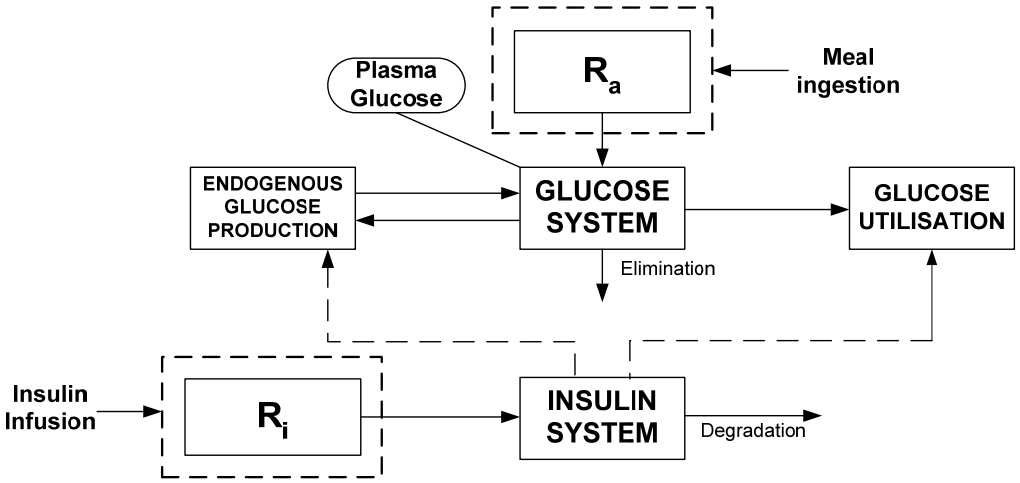


Figure 6.1 *Relationships between functional blocks for a generic model of glucose homeostasis. The insulin infusion submodel and the glucose absorption submodel are evidenced with dashed boxes.*

The meal ingestion and the insulin infusion are modelled by a glucose absorption submodel (providing the rate of appearance of glucose in plasma, R_a) and an insulin infusion submodel (providing the rate of appearance of insulin in plasma, R_i). The connections between functional blocks for a generic model of glucose homeostasis are shown in Figure 6.1. The relationships between the glucose/insulin systems, the endogenous glucose production (EGP), the glucose utilisation and elimination define the metabolic portrait of the individual and are inherently related to the mathematical structure of a specific model and the set of parameters. Several submodels have been proposed in literature to define the rate of appearance of glucose in plasma (e.g., Dalla Man *et al.*, 2006) and the kinetics of subcutaneous insulin absorption (e.g., Nucci and Cobelli, 2000).

In order to mimic a subject affected by type 1 diabetes mellitus the model developed by Cobelli and coworkers and here denoted as Cobelli model (CM) is adopted as the subject, where the secretion model is substituted by a variation of the insulin infusion submodel described in Nucci and Cobelli (2000) as presented in a recent simulation study (Dalla Man *et al.*, 2007). The model developed by Hovorka *et al.* (2002), here denoted as Hovorka model

(HM[1]), with the same insulin infusion submodel, is used as the model during the MBDoE identification procedure.
It has been shown in Chapter 5 that HM identifiable when a proper reparameterisation is realised. Accordingly, it is has been chosen as a suitable candidate to assess the performance of MBDoE techniques. The models of glucose homeostasis and their parameters, together with the details on the insulin infusion model, are presented in Appendix A. The glucose response of the subject (simulated with CM) refers to a 56 years male subject affected by type 1 diabetes with a body weight of 78 kg. The goal of the study is to identify in a statistically sound way the parameters defining the virtual subject (described by HM), by planning an identification test on the real subject (described by CM) through advanced MBDoE techniques.

6.3 MBDoE techniques for the identification of physiological models

Standard and advanced MBDoE techniques are here adopted to estimate the set of parameters of HM. Among the advanced MBDoE techniques an online redesign of the clinical test (see Chapter 3) and an optimal design including backoff (see Chapter 4) are attempted.

6.3.1 Online model-based redesign of the clinical test

Standard MBDoE techniques aim at solving the optimisation problem described by (2.14), (2.1-2.2) and (4.1) starting from a prior estimate of model parameters. Nevertheless, the prior parameter estimate might be considerably different from the parameter set describing the metabolic specificity of the subject. As a consequence a clinical test may turn up to be dangerous for the patient (either the hyperglycaemic or the hypoglycaemic thresholds might be crossed) and scarcely effective. The risk is further increased if there is a structural discrepancy between the model and the subject's physiological behaviour.
However, if an OMBRE approach is adopted (see §3.3), the information gradually acquired from the test by collecting samples can be used thanks to intermediate parameter estimations so that it is possible to redesign the clinical test while it is still running. In this case, assuming that a reliable (albeit not perfect) model is available, the acquired information can be used to tune the model on the subject's behaviour, and to re-design the experiment to increase safety and optimality, accordingly.
As discussed in Chapter 3, different OMBRE configurations can be exploited depending on the updating policy, but in this work we chose the following updating rationale: the test is divided into a number of equally lasting sub-experiments and within each sub-experiment the

[1] In this Chapter, the Hovorka model is used with the Nucci and Cobelli (2000) infusion model, which is different from the infusion model adopted in Chapter 5 (the infusion model proposed by Wilinska *et al*. (2005)). For this reason, in the following the Hovorka model will be referred to as 'HM' rather than 'HWM'.

manipulated input is discretised with the same number of switching times and levels. An update of the design variables is scheduled at the end of each sub-experiment, where a parameter estimation session and a sub-experiment re-design are carried out in sequence. Each sub-experiment re-design is carried out solving the optimisation problem given by (2.14), (2.1-2.2) and (4.1). One additional advantage is that the complexity of the design optimisation problem is greatly reduced (the predicted information is maximised within the single sub-experiment, which is a fraction of the complete test) with great benefit on the computational burden.

6.3.2 MBDoE with backoff

An OMBRE approach may reduce the risk for unsafe or unfeasible clinical tests by adjusting the test as soon as experimental evidence becomes available. However, the model and/or parametric uncertainty is not explicitly dealt with. Thus, to avoid unfeasible solutions "by design", a backoff from active constraints is introduced within the MBDoE framework, taking into account the parametric uncertainty in the design feasibility condition given by (4.1):

$$\mathbf{C} = \mathbf{x}(t) - \mathbf{G}(t) + \boldsymbol{\beta}\left(\tilde{\mathbf{x}}(t), \tilde{\mathbf{x}}(t), \mathbf{u}(t), \mathbf{w}, \tilde{\boldsymbol{\theta}}, t\right) \leq 0 \,. \tag{4.5}$$

In this specific problem, the only variable being constrained is the glucose concentration, and the MBDoE optimisation problem with backoff is the solution of (2.14) and (2.1-2.2) with the feasibility conditions

$$C_1 = y(\boldsymbol{\theta}, \varphi, t) + \beta(t) - y_{\max} \leq 0 \quad \text{and} \quad C_2 = y_{\min} - y(\boldsymbol{\theta}, \varphi, t) + \beta(t) \leq 0 \,. \tag{6.1}$$

Thus, the backoff strategy allows the designer to enforce or relax the active constraints to meet the safety requirements when the test is performed on the subject.
The backoff strategy will be applied within an OMBRE framework. Accordingly, after each sub-experiment is performed, a parameter estimation and a redesign are carried out in sequence, updating both the uncertainty domain of model parameters (necessary to describe a new backoff) and the optimal experimental conditions to maximise the information content within the new sub-experiment.

6.3.4 Some comments on the effect of model mismatch on design

Model mismatch has a marked impact on the information predicted by design and on the feasibility conditions as predicted by the identification model. Let us assume the subject's (CM) measured response on a designed experiment and the model (HM) response be described by the following equations:

$$\textit{Subject}: \quad y^{CM}(t) = \hat{y}^{CM}\left(\hat{\boldsymbol{\theta}}^{CM}, \boldsymbol{\varphi}, t\right) + \varepsilon_y(t) \tag{6.2}$$

$$\textit{Model}: \quad y^{HM}(t) = \hat{y}^{HM}\left(\hat{\boldsymbol{\theta}}^{HM}, \boldsymbol{\varphi}, t\right) + \varepsilon_y(t) \tag{6.3}$$

where $\varepsilon_y(t)$ is the measurement error (same for both subject and model), $\hat{y}^{CM}\left(\hat{\boldsymbol{\theta}}^{CM}, \boldsymbol{\varphi}, t\right)$ is the response predicted by CM with the (formally unknown) set of parameters $\hat{\boldsymbol{\theta}}^{CM}$ and $\hat{y}^{HM}\left(\hat{\boldsymbol{\theta}}^{HM}, \boldsymbol{\varphi}, t\right)$ is the response predicted by HM with the (known but approximately estimated) set of parameters $\hat{\boldsymbol{\theta}}^{HM}$. The subject measured response at the experimental conditions defined by $\boldsymbol{\varphi}$ can thus be described by

$$y^{CM}\left(\hat{\boldsymbol{\theta}}^{CM}, \boldsymbol{\varphi}, t\right) = \hat{y}^{HM}\left(\hat{\boldsymbol{\theta}}^{HM}, \boldsymbol{\varphi}, t\right) + \varepsilon^{MM}(t) + \varepsilon_y(t) \tag{6.4}$$

with $\varepsilon^{MM}(t) = \hat{y}^{CM}(t) - \hat{y}^{HM}(t)$ representing the effect of model mismatch (formally a time-varying "bias") on predicted responses. ε^{MM} is a function of $\hat{\boldsymbol{\theta}}^{CM}$, $\hat{\boldsymbol{\theta}}^{HM}$ and the structural model mismatch. Model and parametric uncertainty may affect both the design optimality and the design feasibility.

When a model mismatch is present, to preserve feasibility during the planned test the conditions given by (5.3) and (5.4) on constrained variables should be modified including the bias term ε^{MM}

$$C_1 = \hat{y}^{HM}\left(\hat{\boldsymbol{\theta}}^{HM}, \varphi, t\right) + \varepsilon^{MM}(t) - y_{\max} \le 0 \quad \text{and} \quad C_2 = y_{\min} - \hat{y}^{HM}\left(\hat{\boldsymbol{\theta}}^{HM}, \varphi, t\right) - \varepsilon^{MM}(t) \le 0 \tag{6.5}$$

Unfortunately, $\varepsilon^{MM}(t)$ cannot be explicitly evaluated (the subject model is obviously unknown). However, it can be enclosed within a backoff formulation of active constraints:

$$C_1 = \hat{y}^{HM}\left(\hat{\boldsymbol{\theta}}^{HM}, \varphi, t\right) + \beta'(t) - y_{\max} \le 0 \quad \text{and} \quad C_2 = y_{\min} - \hat{y}^{HM}\left(\hat{\boldsymbol{\theta}}^{HM}, \varphi, t\right) + \beta'(t) \le 0 \tag{6.6}$$

where $\beta'(t) = \beta(t) + \varepsilon^{MM}(t)$ is a generalised backoff term taking into account both model mismatch (through ε^{MM}) and parameter mismatch (through β). The bias term ε^{MM} can be evaluated following deterministic assumptions (i.e., by assigning a relative or absolute expected deviation from the model predicted response), while β is a function of the expected uncertainty domain of model parameters.

The representation of the bias term ε^{MM} may turn up as a difficult task. In principle, the subject behaviour is unknown and the knowledge available to the experimenter has already been embedded in the model and the present value of its parameters. A conservative approach (adopted in this work) is to assume a fixed value for ε^{MM}, representing the maximum expected

difference between the model and the subject's responses due to a structural mismatch. In case prior knowledge and/or preliminary data are available about a subject's behaviour, then a more sophisticated approach can be used by adopting methods proposed in the scientific control literature (Stanfelj *et al.*, 1993). However, note that the backoffs may still be defined according to a more complex (time-variant) formulation, reflecting the actual knowledge on the subject's response (see Chapter 4).

6.4 Design of the clinical test in the presence of model mismatch

Three different MBDoE strategies have been compared to design a clinical test in order to estimate the set of individual parameters of a subject affected by type 1 diabetes mellitus: a standard MBDoE and two tests based on the OMBRE strategy (with or without a backoff policy). The design of the identification test is based on the following requirements:

1. possibility to manage the amount of carbohydrates ingested during breakfast, lunch and dinner;
2. possibility to manage a day-long test;
3. possibility to manage the multiple insulin boluses and insulin infusion;
4. interior constraints on the glycaemic curve (upper and lower bounds are $y_{\max}$ = 180 mg/dL and $y_{\min}$ = 60 mg/dL and);
5. end point constraints on the glycaemic curve – i.e., at the end of the test the glucose concentration has to be within a narrower range (100 – 140 mg/dL);
6. insulin infusion rate $u(t)$ (mU/min) expressed as

$$u(t) = u_{\text{bas}} + u_S(t) + \delta(t) u_{\text{bol}} \tag{5.5}$$

   where u_{bas} is the basal insulin infusion rate (u_{bas} = 12.9 mU/min), $u_S(t)$ is the time-dependent rate of subcutaneous infusion of insulin (approximated with a piecewise constant discrete function), while the last term is the subcutaneous bolus administration with the time-invariant bolus amount u_{bol} [mU] released at meal time and modelled through a Dirac impulse $\delta(t)$;
7. blood glucose concentration measurements available with a constant relative variance of 0.03 from the reading and a minimum time distance between two consecutive samples of 2 min.

The amount of each subcutaneous bolus is adjusted basing on the following empirical rule:

$$u_{bol} = \alpha k D_g \tag{6.7}$$

where $\alpha = 52.63$ mU/g_{CHO} is an approximated value for the optimal insulin/CHO ratio and D_g is the amount of carbohydrates of a meal [g_{CHO}]. The amount of the bolus is optimised by optimising the relaxing factor k during the MBDoE procedure (see §5.8.2).
The goal of the designed test is to to enable a satisfactory (i.e., statistically sound) estimate of the model parameters when a single daily test is performed on the subject. A type 1 diabetic subject should have a higher (vs. normal) basal glucose concentrations. As a consequence, at the beginning of the test the glucose concentration in the blood of the subject is close to the upper hyperglycaemic threshold (G = 175 mg/dL) and an immediate insulin infusion treatment is required to keep the subject in the feasible glycaemic range.
The daily test is articulated into three phases: *i*) a first phase during the night in which the glycaemia is normalised at around 140 mg/dL at 8 AM (during this phase a sample is collected every hour); *ii*) a second phase lasting 10 hours and comprising two meals at 8:00 AM (breakfast) and 1:00 PM (lunch); *iii*) a third phase lasting 6 hours with one meal at 6:00 PM (dinner). A parameter estimation session is carried out at the end of each phase in every design configuration. During the first phase of the test the insulin infusion rate is kept constant, and after 8 hours a parameter estimation is carried out to achieve a first (approximated) estimation of model parameters. In the second and in the third phase of the experiment the profile of the insulin infusion rate is optimised by design. The details are summarised in Table 6.1.

Table 6.1 *Clinical test scheduling and design variables distribution for parameter identification.*

Design phase	Time interval	Duration	Number of samples	Number of switching levels for u	Description
First	0:00 – 8:00	8 h	8	1	Overnight fast
Second	8:00 – 13:00	10 h	25	16	Breakfast at 8:00 AM
	13:00 – 18:00				Lunch at 1:00 PM
Third	18:00 – 0:00	6 h	15	8	Dinner at 6:00 PM

The MBDoE optimisation is carried out with simple bounds on design variables using the gPROMS® (Process Systems Enterprise, 2004) modelling environment and an SRQPD optimisation solver to solve the nonlinear optimisation problem, adopting a two-step multiple shooting technique to mitigate the risk of incurring into local minima. In every design strategy the selected design criterion is the D-optimal one.

6.4.1 Estimation procedure and quality of the estimates

Both the design step and the estimation step are deeply influenced by the choice of the model parameterisation. The Hovorka model is identifiable when a specific parameterisation is adopted (Table 6.2) to ensure a positive definite information matrix in the design space (note that for numerical robustness, a normalisation procedure is always carried out dividing the estimated values by the normalising factors given by the literature values). This can be

achieved by estimating the ratio between the highly correlated fourth and the fifth parameters of the model (see §5.6.2) and thus considering during the design procedure the $\boldsymbol{\Theta}_{1-4}^{T} = [\Theta_1 \quad \Theta_2 \quad \Theta_3 \quad \Theta_4/\Theta_5]$ parametric subset instead of $\boldsymbol{\Theta}^{T} = [\Theta_1 \quad \Theta_2 \quad \Theta_3 \quad \Theta_4 \quad \Theta_5]$. In this work, in order to increase the HM flexibility and to explicitly include the effect of the renal clearance (related to Θ_5) on the glucose response, a slightly different approach is carried out adopting a two-step maximum likelihood parameter estimation procedure. First, a maximum likelihood estimation is performed on the parametric set $\boldsymbol{\Theta}_{1-4}^{T}$, while Θ_5 is kept fixed. Then, only Θ_5 is estimated keeping $\boldsymbol{\Theta}_{1\text{-}4}$ fixed. The procedure is iterated until the maximum likelihood condition is satisfied.

Table 6.2 *Parameterisation of HM, initial guess of model parameters and normalising factors.*

Parameter	***Expression***	***Initial guess***	***Normalising factors***
Θ_1	$S_{IT}^{f} / S_{IT}^{\prime f}$	0.38	$S_{IT}^{\prime f}$ = 51.2E-4
Θ_2	$S_{ID}^{f} / S_{ID}^{\prime f}$	0.83	$S_{ID}^{\prime f}$ = 8.2E-4
Θ_3	$S_{IE}^{f} / S_{IE}^{f\prime}$	0.88	$S_{IE}^{f\prime}$ = 520.0E-4
Θ_4	$(EGP_0 / F_{01})/(EGP_0^{\prime} / F_{01}^{\prime})$	0.95	$(EGP_0^{\prime} / F_{01}^{\prime})$ = 1.6598
Θ_5	$F_{01} / F_{01}^{\prime}$	1.00	$F_{01}^{\prime}$ = 0.0097 mmol/kg min

Given the assumptions on the distribution of measurements error (assumed to be Gaussian), the maximum likelihood approach provides a set of *a-posteriori* statistics, calculated from the variance-covariance matrix of model parameters ($\mathbf{V}_\theta$), which may be used to evaluate the quality of the estimates. Thus, the effectiveness of a MBDoE strategy can be assessed in terms of

1. confidence intervals analysis and *t*-test: the *t*-values can be calculated from the formula

$$t_i = \frac{\Theta_i}{\kappa_i} \qquad i = 1 \ldots N_\theta \tag{6.8}$$

   where the κ_i are the 95% confidence intervals and compared with a tabulated reference *t*-value from the Student's *t* distribution with n_{sp}-N_θ degrees of freedom;
2. goodness of fit: the sum of squared weighted residuals (*SSWR*) can be evaluated from

$$SSWR = \sum_{i=1}^{n_{sp}} \left(\frac{y_i^{CM} - \hat{y}_i^{HM}}{\sigma_y} \right)^2 = \sum_{i=1}^{n_{sp}} \left(\frac{r_i}{\sigma_y} \right)^2 \tag{6.9}$$

   where y_i^{CM} is the *i*-th sample collected from the test on the subject, $\hat{y}_i^{HM}$ is the model predicted response of the *i*-th sample collected, r_i is the *i*-th residual (the difference

between the predicted and the measured response) and σ_y is the expected standard deviation of the measurements.

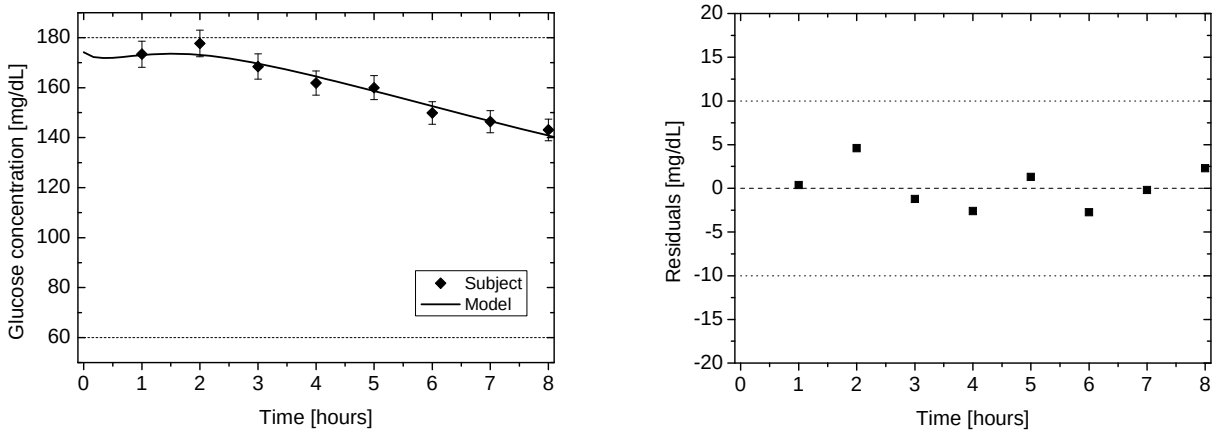
The χ^2-test is here used to assess the model adequacy and the randomness of the residuals, and the *SSWR* index allows quantifying the goodness of fit when coupled with the analysis of the distribution of the residuals along the test horizon. However, it must be pointed out that a standard χ^2-test (see §2.4.1) is much more effective if the bias $\varepsilon^{MM}(t)$ becomes negligible and the measurement errors can be considered random and normally distributed. As a consequence, if there is a relevant model mismatch, the *SSWR* index cannot be compared to a reference χ^2 unless an exact functional approximation of ε^{MM} is available.

6.4.2 Preliminary estimation after an overnight fast

During an overnight fast the subject is kept under a continuous insulin infusion of 6.4 mU/min to normalise the glycaemia. Glycaemic levels are checked every hour and a parameter estimation is performed in order to reach a preliminary parameter estimation (Table 6.3).

Table 6.3 *Parameter estimation after the overnight fast (the reference t-value is equal to 2.354; asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.3769	0.38	168.5	0.002*	52.93
Θ_2	0.8554	0.83	296.1	0.003*	93.03
Θ_3	0.8282	0.88	69.9	0.012*	21.98
Θ_4	0.9636	0.95	73.1	0.013*	22.97
Θ_5	0.8549	1.00	358.6	0.002*	112.70



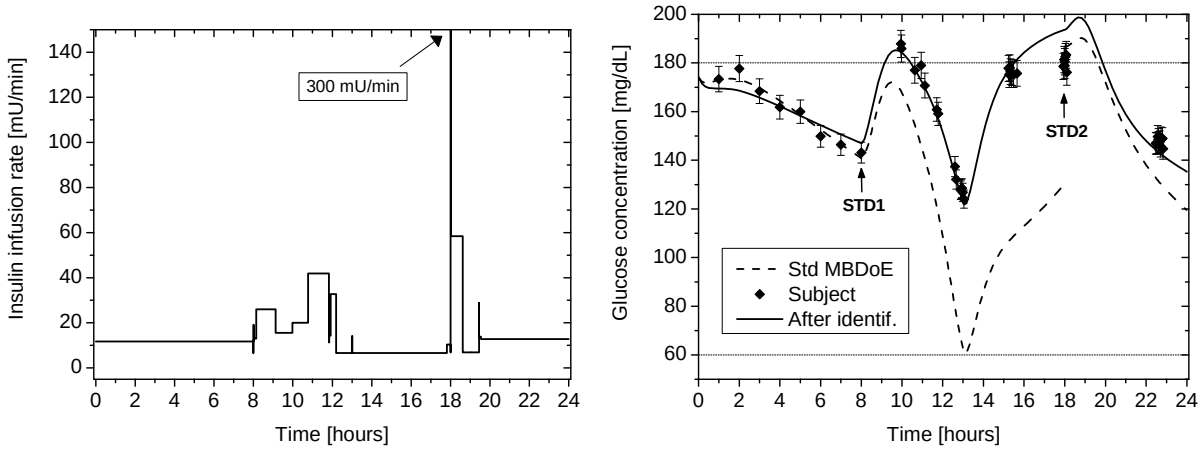
(a) *(b)*

Figure 6.2 *Dynamics of the blood glucose concentration during an overnight fast. (a) Glucose response of the subject (diamonds) and as predicted by the model after preliminary identification (solid line). The bars on the collected samples represent the maximum error on the blood glucose measurements. (b) Distribution of the residuals where the ±10 mg/dL range is identified by dotted lines.*

After the first phase of the identification test only a rough parameter estimation is achieved, as can be noticed from the *a-posteriori* statistics. However, it can be observed from Figure 6.2a that the fitting of the data coming from the subject response is very accurate, the residuals are randomly distributed (Figure 6.2b), and the χ^2-test is satisfied ($SSWR = 1.83 < \chi^2_{ref} = 7.81$).

6.5 Standard MBDoE

The remaining phases of the identification test are planned through a sequence of two standard designed experiments (STD1 and STD2 respectively). The optimised glucose content of the three meals is $\mathbf{D}_g^T = [17.9 \quad 30.5 \quad 5.0]$ [g_{CHO}] and the bolus amount is defined by the vector $\mathbf{u}_{bol}^T = [10.4 \quad 11.3 \quad 359.5]$ [mU]. The profile of insulin infusion rate and the glucose profiles as dictated by a standard MBDoE and as predicted by the model at the end of the test are shown in Figure 6.3. The great uncertainty on preliminary parameter estimation pushes the designed test above the upper threshold of hyperglycaemia during the post prandial periods. Note that the upper constraint on glycaemia is here treated as a hard constraint but, in reality, only hypoglycaemic conditions represent a hard constraint that must never be violated, not even for a short time period. Also note that the proposed design would make *G* hit the lower threshold: although the actual experiment remains well clear of the lower threshold, the discrepancy between the model response and the actual subject's response makes one wonder whether it would be sensible to drive the subject's glycaemic level towards hypoglycaemia region in an actual test. Furthermore, after STD1 the parameter estimation is not statistically satisfactory (Table 6.4) and a supplementary experiment (STD2) is required to improve the information content of the overall test.



(a) *(b)*

Figure 6.3 *Standard MBDoE. (a) Optimised profile of insulin infusion rate. (b) Profiles predicted by a standard design (broken line) and after identification (solid line); the subject actual response is indicated by diamonds. The bars on the collected samples represent the maximum error on the blood glucose measurements.*

Table 6.4 *Parameter estimation after the standard designed experiment STD1 (the reference t-value is equal to 1.701; asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.3275	0.3769	0.167	1.965	0.081
Θ_2	0.7585	0.8554	0.520	**1.458** *	0.254
Θ_3	0.7233	0.8282	2.022	**0.358** *	0.987
Θ_4	0.9713	0.9636	1.819	**0.534** *	0.888
Θ_5	0.2552	0.8549	1.336	**0.191** *	0.652

The remaining part of the identification test (STD2) starts after 18 hours since the beginning of the test and it is designed with the subject in hyperglycaemic conditions. Now the model is able to reproduce the behaviour of the subject with good approximation, but fails on predicting the dynamics during the dinner (as clearly shown by the distribution of residuals of Figure 6.4), where the hyperglycaemic condition pulls the optimiser to release a higher bolus amount. Note that, when the insulin infusion profile is managed, the absolute residuals are neither independent (i.e. they are highly correlated) nor randomly distributed (they are following a deterministic behaviour driven by ε^{MM}) because of model mismatch. In particular when a bolus is released after 18 hours the glycaemic response of the subject is ~10% overestimated by the model.

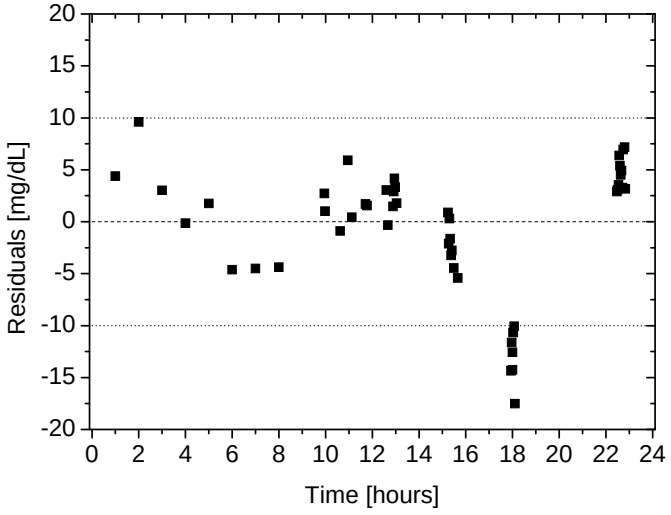


Figure 6.4 *Standard MBDoE: distribution of residuals (black squares) along the experimental horizon.*

The final part of the test allows for a better estimation of the parameters (Table 6.5); however, two parameters are still poorly estimated. A normalisation procedure was attempted because of the great difference between parameters values, to avoid preferential pathways during estimation and design procedures.

Table 6.5 *Parameter estimation after the standard designed experiment STD2 (the reference t-value is equal to 1.691; asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.6472	0.3275	0.133	4.857	0.081
Θ_2	0.4944	0.7585	0.160	3.099	0.254
Θ_3	0.001	0.7233	1.412	**0.001 ***	0.987
Θ_4	0.9703	0.9713	0.022	44.610	0.011
Θ_5	0.1561	0.2552	0.107	**1.461***	0.652

6.6 On-line model-based redesign of the clinical test (OMBRE)

An OMBRE approach can be exploited to extract the information of the test by updating the optimally designed conditions as the test is running and performing seven intermediate parameter estimations between the second and the third phase of the test. Therefore, the second and the third phases of the daily test can be seen as a sequence of eight separately planned sub-experiments lasting 2 hours each. During each sub-experiment five samples are taken and the insulin infusion profile, approximated by a piecewise constant function, is optimised by acting on two switching times and three switching levels. Two different on line redesign strategies are considered for planning the identification test:

1. OMBRE-based design of the clinical test (OMBRE);
2. OMBRE-based design of the clinical test including backoff (OMBRE-B).

The time scheduling for the design updates in both redesign strategies is shown in Figure 6.5.

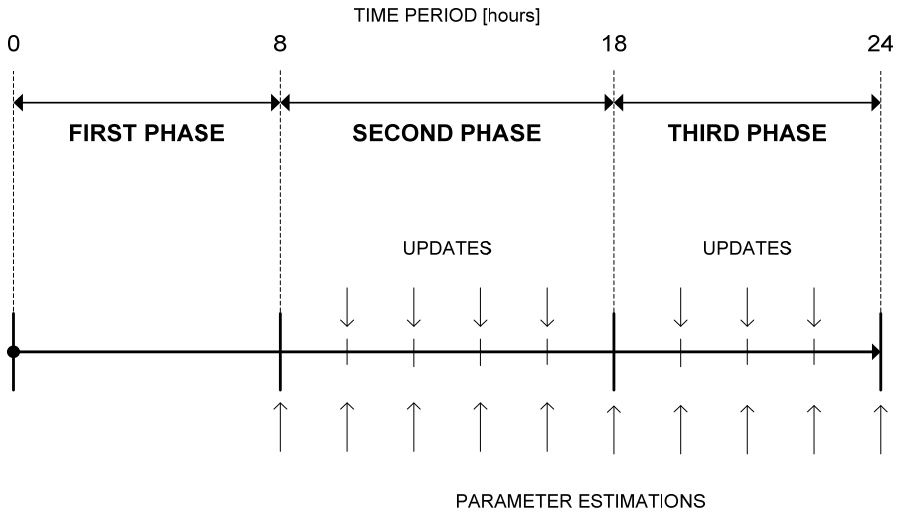


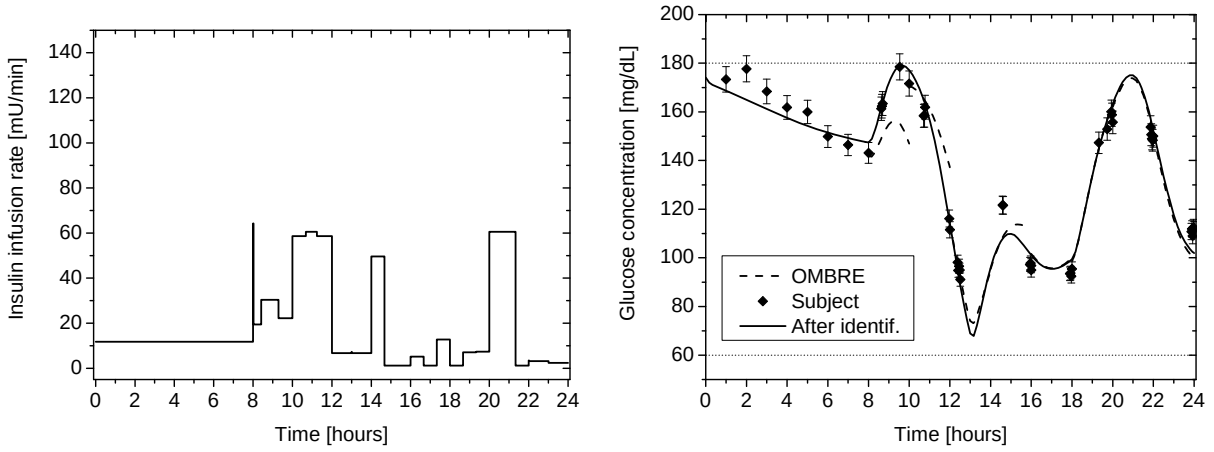
Figure 6.5 *Time scheduling for design updates and parameter estimations in the redesign strategies.*

Both tests consider four redesign updates during the second phase and three additional updates during the third phase. The results are compared and discussed in terms of quality of parameter estimation and distribution of residuals.

6.6.1 OMBRE-based design of the clinical test

The profile of insulin infusion rate and the glucose profiles as dictated by OMBRE and as predicted by the model at the end of the test are shown in Figure 6.6. As can be noticed, the fitting of test samples is greatly improved (even if the model is not capable of predicting precisely the second postprandial glucose peak). Also note that the experiment is definitely safer than in standard MBDoE. In fact, the possibility to update the parameters value and to adjust the experimental plan allows for an online tuning of the model according to the actual subject's response. As a result, the profile predicted by the design gets closer to the experimental data as the test approaches the end. Also note that the insulin infusion profile is managed in a very different way from the one obtained in the standard MBDoE. Here, the optimised glucose content of the three meals is given by $\mathbf{D}_g^T = \begin{bmatrix} 12.6 & 30.5 & 12.3 \end{bmatrix}$ [g_{CHO}] and the amount of the boluses is given by $\mathbf{u}_b^T = \begin{bmatrix} 66.3 & 1.4 & 0.2 \end{bmatrix}$ [mU]. The design strategy handles a lower bolus amount and a higher glucose content for the dinner.

The parameter estimations after 18 hours and at the end of the test are shown in Table 6.6 and 6.7 respectively. The parameter estimation is fully satisfactory for three parameters after the first phase of the test. The addition of a six-hour period allows handling three extra sub-experiments and the result is an improvement on Θ_5 estimation.



(a) *(b)*

Figure 6.6 *OMBRE. (a) Optimised profile of insulin infusion rate and (b) profiles predicted by a redesign (broken line) and after identification (solid line); the subject actual response is indicated by diamonds. The bars on the collected samples represent the maximum error on the blood glucose measurements.*

Table 6.6 *Parameter estimation after an OMBRE designed test with 4 updates (the reference t-value is equal to 1.701; asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.3107	0.2848	0.062	4.969	0.031
Θ_2	1.7472	2.0855	0.666	2.625	0.333
Θ_3	0.0010	0.0015	0.01	**0.051 ***	0.009
Θ_4	1.0122	0.9830	0.0126	80.55	0.063
Θ_5	0.3242	0.4081	1.2080	**0.268 ***	0.604

The third parameter is still poorly estimated, but that has a limited impact on the variability of the predicted glucose response as shown in Figure 6.7 where the effect of the uncertainty on Θ_3 is displayed (the variability of the predicted glucose concentration in the postprandial glucose peaks is around 5 mg/dL).

Table 6.7 *Parameter estimation after an OMBRE designed test with 7 updates (the reference t-value is equal to 1.691; asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.3149	0.3107	0.1258	2.503	0.062
Θ_2	1.7487	1.7472	0.6333	2.761	0.312
Θ_3	0.0009	0.0010	0.0188	**0.052 ***	0.009
Θ_4	1.0083	1.0122	0.0121	82.990	0.006
Θ_5	0.3353	0.3242	0.1093	3.068	0.054

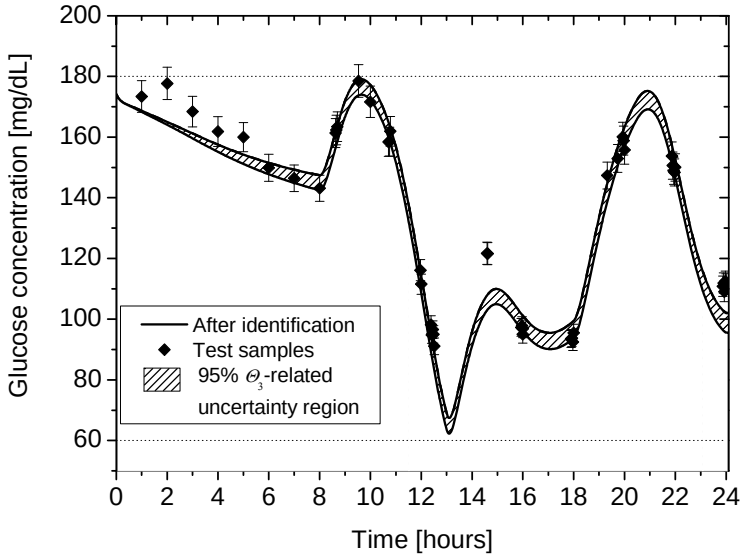


Figure 6.7 *OMBRE: uncertainty on glucose concentration as predicted by the model for the estimated 95% confidence on Θ_3.*

The incapability of estimating Θ_3 in a sound way is related to the effect of the model mismatch, which determines the impossibility of a full matching between the subject and the model responses; in fact, if only a parametric mismatch is considered, then the identification of all the model parameters is feasible (see Chapter 5). As a matter of clarification, Figure 6.8 shows that, even if the (statistically sound) parameterisation of Table 6.7 is adopted, the responses of model and subject after a meal of 10 g of carbohydrates taken in conjunction with an insulin bolus of 523 mU are sensibly different, thus demonstrating that CM and HM are indeed characterised by a diverse model structure.

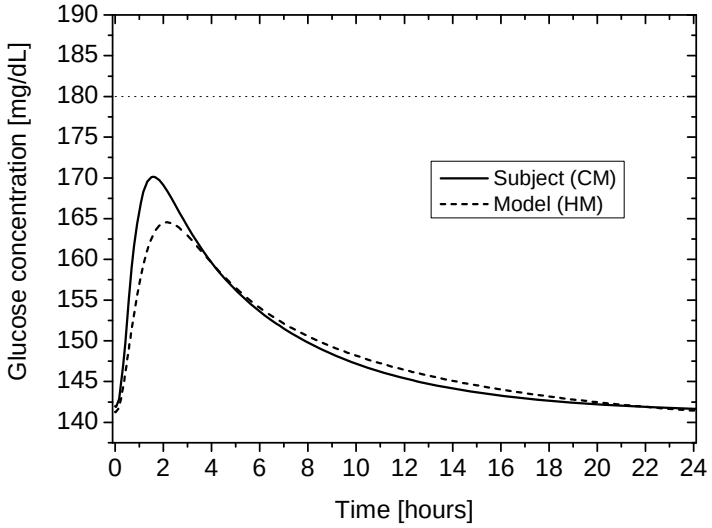


Figure 6.8 *Profile of the subject (simulated with CM) and the model (simulated with HM) after a meal of 10 g of carbohydrates taken in conjunction with a 523 mU insulin bolus.*

However, the results clearly show that a redesign approach may offer several advantages. First of all, the test is safer for the subject in presence of both model and parametric mismatch. Secondly, the parameter estimation is more precise than the one provided by a standard MBDoE. The initial uncertainty and the fact that the design pushes the glycaemic level towards both the upper and the lower bounds, may still lead the clinical experimenter towards a more conservative approach where uncertainty is explicitly taken into account within the design procedure. The results are illustrated and discussed in the next section.

6.6.2 OMBRE-based design of the clinical test including backoff (OMBRE-B)

A backoff strategy is introduced within the redesign procedure, where the generalised backoff vector $\beta'(t) = \beta(t) + \varepsilon^{MM}(t)$ of (6.6) is evaluated according to the following assumptions:

1. the bias $\varepsilon^{MM}(t)$ is set assuming a deviation from the model predicted response of 5%;

2. the backoff $\beta(t)$ is evaluated from a 95% confidence uncertainty region of model responses provided by a stochastic simulation procedure involving $N' = 200$ simulations at perturbed values of model parameters (sampled from an expected uncertainty region **T** of model parameters).

The expected uncertainty region of model parameters ***T*** is defined by a family of uniform distributions R_{Θ_i} centred on the actual values of model parameters

$$\boldsymbol{T} = \left[\Theta_{ij} \left| \Theta_{ij} \in R_{\Theta_i} \left(\hat{\Theta}_i - 0.3\hat{\Theta}_i, \hat{\Theta}_i + 0.3\hat{\Theta}_i \right), \quad i = 1...N_\theta, j = 1...N' \right. \right] \tag{6.10}$$

considering a 30% deviation on the estimated values of model parameters. After the second phase of the experiment, the uniform distributions are adjusted according to the *a-posteriori* variance covariance matrix of model parameters $\mathbf{V}_\theta$ as evaluated by the maximum likelihood estimator. The profile of insulin infusion rate, the subject response, the glucose profiles as dictated by OMBRE-B and as predicted by the model at the end of the test are shown in Figure 6.9. Note that the backoff is also updated after each new estimation of the parametric uncertainty. After 8 hours the backoff takes into account the uncertainty on predicted responses constraining the designed test within the 80-170 mg/dL range, thus ensuring the feasibility of the test. The excitation pattern, and so the distribution of information along the test duration, is very different from that obtained by a simple redesign approach. The amount of the boluses is given by $\mathbf{u}_{bol}^T = [4.6 \quad 1300.0 \quad 78.9]$ [mU] while the glucose amount of the three meals is given by $\mathbf{D}_g^T = [6.6 \quad 32.9 \quad 15.0]$ [g_{CHO}]. The design is constrained within the 80-160 mg/dL range of glycaemia to keep the subject in a safe region in presence of uncertainty. During the lunch period a high amount of insulin bolus is released and the model, even if able to capture the qualitative dynamic behaviour of the subject, fails to predict the subject response. As expected, the parameter estimation after the second phase of the test is definitely not as good as the one provided by OMBRE (Table 6.8), with the last three parameters that are estimated with a large uncertainty.

Table 6.8 *Parameter estimation after an OMBRE-B designed test with 4 updates (the reference t-value is equal to 1.701; asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.2955	0.2853	0.111	2.649	0.054
Θ_2	2.4121	2.3644	0.943	2.558	0.460
Θ_3	0.0001	0.0010	0.884	**0.001 ***	0.432
Θ_4	1.6580	1.6400	10.900	**0.152 ***	5.319
Θ_5	0.1783	0.1771	1.824	**0.098 ***	0.890

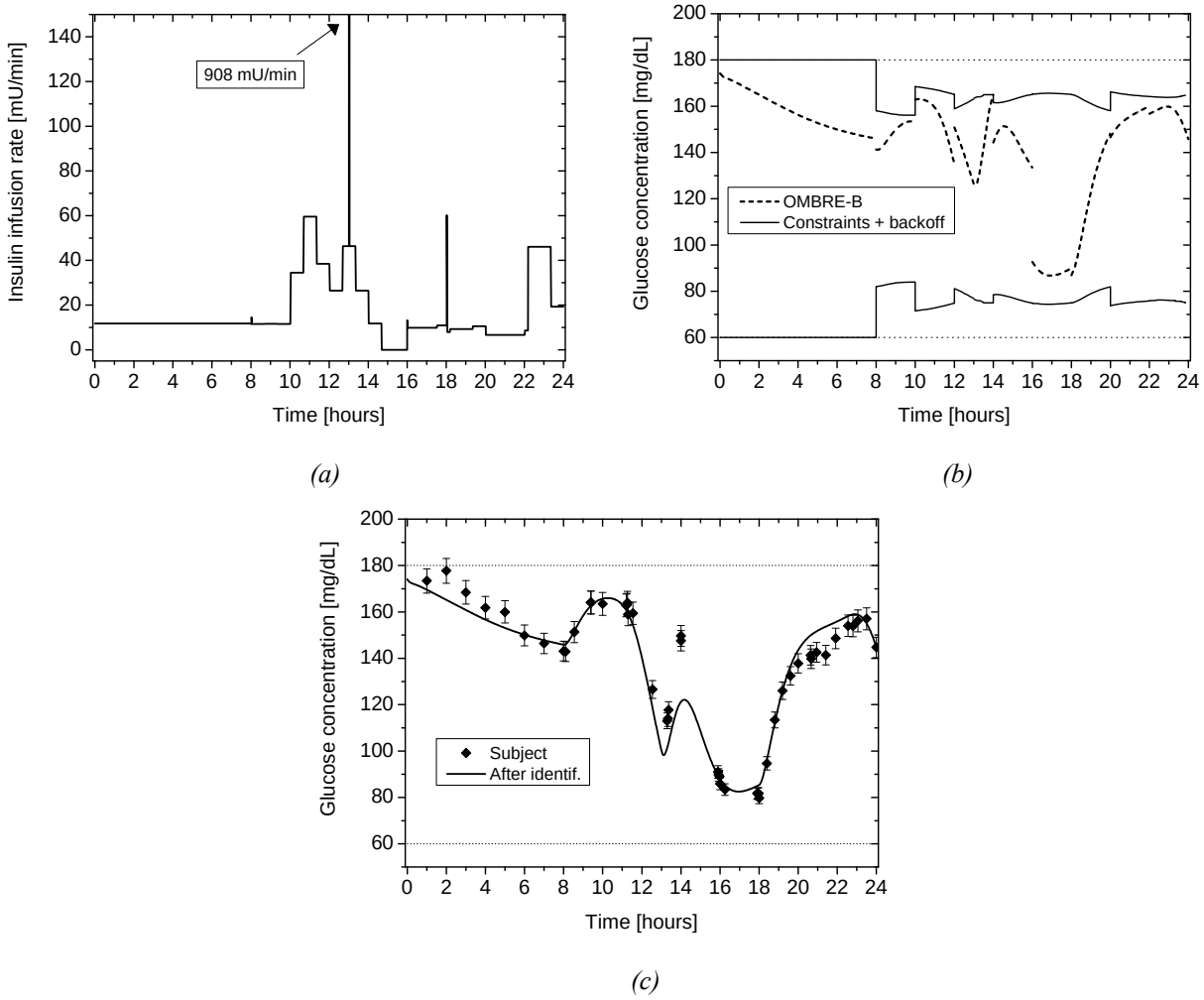


Figure 6.9 *OMBRE-B. (a) Optimised profile of insulin infusion rate and (b) profiles predicted by a redesign (broken line) including the backoff effect on constraints. (c) Profile predicted by the model after identification (solid line); the subject actual response is indicated by diamonds.The bars on the collected samples represent the maximum error on the blood glucose measurements.*

Table 6.9 *Parameter estimation after an OMBRE-B designed test with 7 updates (the reference t-value is equal to 1.691; asterisks denote t-values failing the t-test).*

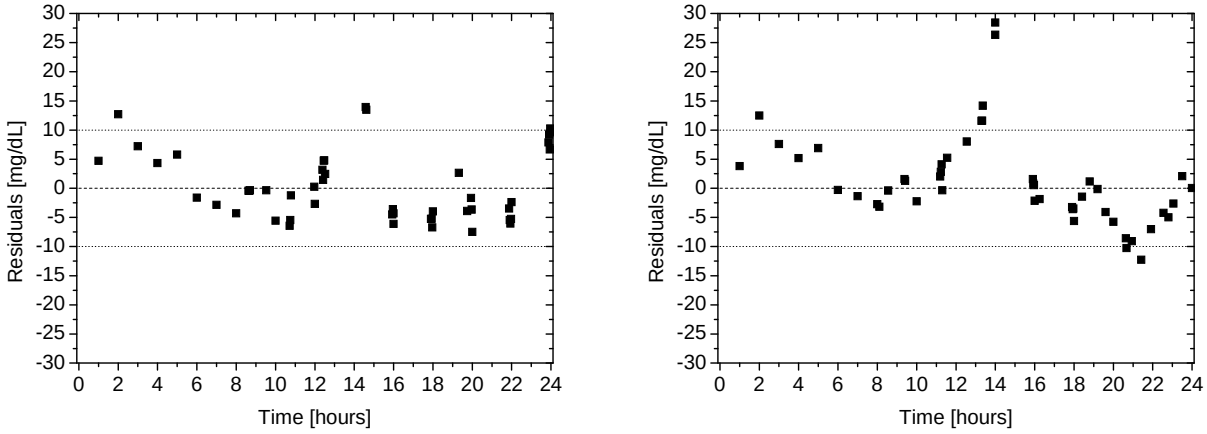
Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.3289	0.3284	0.071	4.643	0.035
Θ_2	1.8980	1.9055	0.471	4.028	0.234
Θ_3	9.91E-5	0.0001	0.668	**1.0E-4***	0.331
Θ_4	1.5851	1.5849	0.020	79.170	0.010
Θ_5	0.1562	0.1567	0.020	7.693	0.011

However, by adding three more updates in the last phase of the test, the parameter estimation is greatly improved (Table 6.9) and is statistically comparable to the one obtained by OMBRE. Results indicate that, even if in general the backoffs shrink the available

experimental space, the possibility to update the design and the parameters estimation allows to decrease the uncertainty region, and to deliver the information content required for a good estimation of the model parameters in a safe manner. The drawback is that a significantly higher computational effort is needed (although mainly at the beginning of the test in order to map the uncertainty region).

6.6.3 Residuals analysis

The residuals distributions from the different redesign configurations OMBRE and OMBRE-B are compared in Figure 6.10 and Table 6.10. Both distributions show a high correlation between residuals, but OMBRE is globally more efficient to fit the test data, with all the absolute residuals contained within the ±14 mg/dL interval. The insulin administration policy has a significant impact on the capability of the model to fit the data as the model shows a limited capability of predicting the subject's response when the insulin bolus is managed. Note that OMBRE provides a better prediction of the glucose concentration also because the insulin infusion profile is managed in a less intrusive way, avoiding significant releases of insulin in the short period (thus keeping the test in a region where the model response is not so different from the subject's). On the contrary, it can be observed that the model identified through the OMBRE-B is not able to fit the data precisely when a high bolus amount is administered (where the deviation is close to 30 mg/dL).



(a) *(b)*

Figure 6.10 *Distribution of residuals (black squares). (a) OMBRE designed test and (b) OMBRE-B designed test.*

Table 6.10 *Statistics on distributions of absolute residuals for the OMBRE and OMBRE-B configurations.*

Redesign configuration	**Mean value** [mg/dL]	**Standard deviation** [mg/dL]	**Maximum value** [mg/dL]	**Minimum value** [mg/dL]
OMBRE	0.29	5.90	13.9	-7.5
OMBRE-B	1.21	8.00	28.5	-12.3

The residuals are neither independent nor normally distributed, but the OMBRE-B distribution shows a higher mean (i.e, the subject response is underestimated) and a higher dispersion around the mean value, when compared to the distribution obtained in the OMBRE approach with no backoff.

6.7 Summary of results and final remarks

Table 6.11 summarises the results obtained in the current study through the adoption of different strategies of model-based design of experiments for the identification of a complex model of glucose homeostasis (HM) when a structural subject-model mismatch is present.
When a day-long identification test can be designed through a model-based strategy, a standard MBDoE approach cannot ensure a feasible test, leading the subject to a state of prolonged hyperglycaemia. In addition to that, after 18 hours the test is still scarcely informative and the parameter estimation is not statistically satisfactory. Conversely, a redesign approach (OMBRE) is capable of planning a test that is both informative and feasible even in the presence of model mismatch so that a statistically sound estimation of all but one (Θ_3) parameters is eventually obtained. When a backoff from active constraints is realised and embedded within an OMBRE framework (OMBRE-B), the information is extracted in a slower way from the test as the subject's glycaemic response is constrained within a narrow range of variability. However, the test turns out to be safe by design for the patient and still sufficiently informative.

Table 6.11 *Summary of the results obtained by different protocols for HM identification.*

Design strategy	Parameters failing t-test after 18 hours	Parameters failing t-test after 24 hours	Feasibility
Standard MBDoE	$\Theta_2\ \Theta_3\ \Theta_4\ \Theta_5$	$\Theta_3\ \Theta_5$	NO
OMBRE	$\Theta_3\ \Theta_5$	Θ_3	YES
OMBRE-B	$\Theta_3\ \Theta_4\ \Theta_5$	Θ_3	YES

To summarise, it has been shown that integrating the use of advanced MBDoE techniques can be a very effective way to tackle the issue of structural system/model mismatch in the parameter identification of a complex physiological model of type 1 diabetes mellitus. The adoption of an online redesign strategy allows exploiting the collected information while a clinical test is still running and makes it possible to reduce the initial uncertainty and to tune the model parameters according to the actual subject's response, thus improving both test safety and test feasibility. Safety for the subject can be further guaranteed by taking into account the system uncertainty through some backoffs from the hyperglycaemic and

hypoglycaemic bounds. It has been shown that in this way a still effective online re-design procedure can be set up so that the clinical test is safe by design.

Chapter 7

Towards the optimisation of dynamic information*

Following a conventional MBDoE procedure, the maximisation of the information content of an experiment is performed under the assumption that the samples are collected in a discrete way during the trial. Each collected sample usually adds a novel (and different) contribution to the overall expected information that is maximised by design before the experiment is carried out, while a time dependent profile of the actual information is obtained only afterwards. As discussed in the previous Chapters, the formulation of the optimal design problem is generally based on the maximisation of a global measurement function of the expected information, evaluated from discrete forms of the Fisher information matrix. This Chapter illustrates the possibility to manage the dynamic profile of information of the experiment adopting advanced MBDoE techniques. A novel MBDoE approach termed dynamic model-based design of experiment (DMBDoE), particularly suitable if a continuous measurement system is available, is here presented. The novel design strategy aims at optimising a continuous measurement of the Fisher information matrix, and allows taking into account the specificity of the measurement system withinin the design framework. The effect of sampling frequency and experimental duration on the rate of information acquisition is discussed in this preliminary study, where the benefits of the proposed strategy are assessed by means of two distinct case studies by comparison to a standard MBDoE approach.

7.1 Introduction

A significant result obtained in Chapter 5, when planning a MPGT or a MOGTT test for the identification of a model of T1DM (§5.9-5.10), was that, even adopting an optimised experimental protocol, a minimum number of samples was required to estimate the set of model parameters with a sufficient degree of precision.

On the one side, such a result is quite expected as the number of samples collected in a single test may be insufficient to estimate the set of parameters, in spite of the optimal experimental conditions determined by design. The effect of sampling rate and measurement precision on information evaluation and design effectiveness has been extensively studied in the literature

* Portions of this Chapter have been published in Galvanin *et al.* (2009b) and Galvanin *et al.* (2010d).

(Emery *et al.*, 2002). Usually the sampling rate, and thus the rate of information acquisition, is strictly limited by the experimental budget (e.g., number and duration of experiments, number and type of measurements) and/or by the specific choices and possibilities set by the experimenter. Accordingly, the experimental design activity usually takes into account the limitations on laboratory facilities and is managed accordingly.

However, there is an additional and subtler cause for the design inefficiency when the number of samples is limited. If the duration of the test is assigned, the design procedure manages the experimental settings in such a way that the expected information is distributed along the entire experiment duration so that an *overall* metric for the Fisher information matrix is maximised (Zullo, 1991). In fact, although each sample eventually acquired will add a novel (and different) component to the overall expected information, the design does not consider the way in which the information evolves continuously in time.

Standard MBDoE techniques have been originally developed considering a discrete acquisition of information. In their original formulation (i.e. §2.2) they do not consider the possibility that the information on the system itself could, in principle, be acquired in a very frequent way if there was the possibility to record the system responses in a continuous way. Usually when monitoring a process several responses, typically concentration measurements, can only be acquired by discrete sampling at a significantly reduced sampling frequency. However, a number of system outputs (e.g. temperatures and pressures) can be measured (in practice) in a continuous way. Moreover, recent advances in sensors technology allow for the development of continuous monitoring systems that are suitable even for concentration measurements. For example, continuous measurement systems have been developed for monitoring concentrations in biological processes adopting near-infrared spectroscopy (Tosi *et al.*, 2008) or online respirometry techniques (Dias *et al.*, 2009). Additionally, as anticipated in Chapter 5, continuous glucose monitoring systems (CGMS) have been recently proposed for diabetes care: these devices can record the glycaemic levels over a continuous 24 hour period in a very frequent way (i.e. 5-10 minutes the frequency of blood glucose display), although they measure the glucose level of the interstitial fluid and a lag time between blood and interstitial reading is therefore always present (Cengiz and Tarborlane, 2009). The glucose concentration measurements usually exhibit accuracy and precision that are significantly lower than the ones provided by the standard (discrete) off-line sampling techniques (Mazze *et al*., 2009); nonetheless, they are expected to provide a substantial support to diabetes management and care in order to tailor the therapy to patients needs (Garg, 2009).

In such a perspective, it may be convenient to tailor the experiment design formulation to the specificity of the sampling system. Features like sampling frequency, measurements accuracy and precision should be embodied in the mathematical formulation of the design problem.

For instance, in the optimal design of a clinical test, it may be convenient to maximise the information since the very beginning of the trial, even if the information content at the beginning of the experiment is very low, with the purpose to shorten the experiment duration. To maintain the optimality of a test, and thus to guarantee a certain level of information with the minimum experiment duration, the rate by which information can be acquired needs to be increased and, in the experimental practice, the frequency and/or the precision of the measurements must be managed accordingly. The need for a different approach to experiment design allowing for the optimisation of the information dynamics of the test is explained by mean of an example in the following section.

7.2 A motivating example: optimal design of clinical tests for the identification of HWM

As previously seen in Chapter 5, the MBDoE approach is applied to a diabetic subject modelled using HWM both for simulating the subject and as identification model. The purpose is to modify the usual protocol of standard tests such as PGT (postprandial glucose test) and OGTT (oral glucose tolerance test) so as to increase the overall information content of the test after a preliminary reference test. The goal is to estimate precisely, with only one properly designed experiment, the set of metabolic parameters $\boldsymbol{\Theta}$ describing the insulin sensitivity of a specific subject (Θ_1, Θ_2, Θ_3) and his/her endogenous glucose production (Θ_4). Here the focus is to assess the effect of the sampling frequency and test duration on the dynamics of the actual information evaluating: *i*) the impact of the design variables on the final parameter estimation; *ii*) the ability to meet critical safety constraints on the subject response within a specified degree of confidence, and *iii*) the minimal experimental budget required to get a satisfactory parameter estimation from the planned test without upsetting the subject excessively.

The design vector is expresses in the form (5.1), where the time-dependent inputs $\mathbf{u}(t)$ that can be manipulated for design purpose comprise the insulin subcutaneous infusion and the insulin subcutaneous bolus, whereas the glucose intake is represented as a time-invariant control variable w. There is only one measurable output $y(t)$ given by the blood glucose concentration G. The optimal test settings are chosen to minimise a measurement function ψ of $\mathbf{V}_\theta$ following (2.14) under the following constraints in the form (4.1):

- interior constraints on the glycaemic curve to ensure normoglycaemia at all times (60-170 mg/dL);
- end point constraint (i.e. constraint at $t = \tau$) on the glucose concentration (80 mg/dL);
- constraint on the final derivative of the glucose concentration to ensure steady glycaemia at the end of the test;
- constraint on the test duration.

Safe conditions must be guaranteed at all times during the clinical test; furthermore, the test should be completed within a specified time interval. It must be also guaranteed that after the test the subject returns to and remains at the basal settings. The designed test formally ends with the last sampling point (which defines the duration of the experiment). The (simulated) glucose measurements are available with a constant relative variance of 0.033 and the elapsed time between two consecutive measurements cannot be shorter than 5 minutes. To improve numerical robustness, parameters are normalised with respect to the true values describing the subject. Thus, the diabetic subject is identified by the parametric set $\boldsymbol{\Theta}$ = [1.000 1.000 1.000 1.000], while the initial guess on model parameters is given by the set $\boldsymbol{\Theta}^0$ = [1.592 0.819 1.375 1.268].

The following protocols are proposed and assessed:

1. MPGT-n_{sp}: modified postprandial glucose test with n_{sp} = 5, 10, 20 (τ = 600 min);
2. MOGTT-n_{sp}: modified OGTT with n_{sp} = 5, 10, 20 (τ = 840 min);
3. MPGT-opt: modified postprandial glucose test with n_{sp} = 20 and τ optimised;
4. MOGTT-opt: modified OGTT with n_{sp} = 20 and τ optimised.

A variable number of samples is chosen in protocols 1. and 2. to evaluate the impact of the sampling frequency on the quality of the final estimate, while in 3. and 4. the goal is to assess whether a test duration could be shortened by increasing the sampling frequency.

The optimal settings determined by design maximise the expected information content of the test, expressed by the dynamic information matrix

$$\mathbf{H}_\theta\left(\boldsymbol{\theta},\boldsymbol{\varphi}\right)=\sum_{k=1}^{n_{sp}}\mathbf{M}_k+\mathbf{H}_\theta^0\,. \tag{7.1}$$

The $\mathbf{M}_k$ matrix represents the contribution of the k-th sample to the overall predicted information content $\mathbf{H}_\theta$. This information is deeply affected by the frequency of sampling (in terms of n_{sp}/τ ratio) and by the excitation pattern of the manipulated inputs; thus, the choice of the sampling protocol has a significant impact on the effectiveness of test in terms of information availability. The expected information dynamics can be evidenced by considering the trace of the information matrix (7.1) where each sample (whose collecting time is optimised) will provide a different (expected) amount of information (given by each step in Figure 7.1). After the experiment is performed, information will be updated, thanks to the parameter estimation, and the profile of the actual information can be obtained (solid line in Figure 7.1).

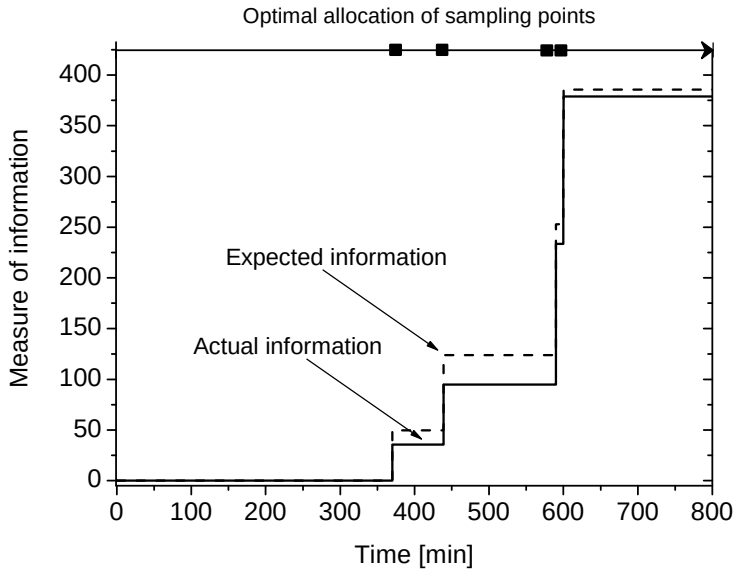


Figure 7.1 *Dynamics of the expected information and of the actual information for a standard MBDoE. The optimal allocation of sampling points is indicated by black squares.*

Note that the actual information is available only *a-posteriori*, after an experiment is executed. In the presence of parametric and/or structural model mismatch, a mismatch between the actual and the expected information is realised such that the two profiles of information do not overlap. This information mismatch is always present during the experiment design procedure, unless the design efficiency (see §2.6) is close to unity.

7.2.1 Modified Postprandial Glucose Test (MPGT)

The purpose is to identify the model set of parameters with a single experiment comprising two meals (breakfast and lunch, scheduled at 8:00 AM and 1:00 PM). The variables being optimised are: the CHO content of the meals, $D_{g,1}$ and $D_{g,2}$ (bounds on breakfast: 5 – 40 g CHO; bounds on lunch: 30 – 70 g CHO); the glucose-dependent insulin infusion rate $u_s(t)$ (parameterised as a piecewise constant function, with n_z = 9 levels and n_{sw} = 8 switching times to optimise), the amount of insulin of the boluses $u_{bol,1}$ and $u_{bol,2}$ and the sampling times. The last sampling point can be taken not later than 600 min (10 h) from the beginning of the experiment (the end of the experiment is scheduled at 6:00 PM). The time interval between consecutive meals is not optimised, and the insulin bolus amount is not constrained to an insulin/CHO ratio. The end point constraints on the glucose concentration and on the derivative of the glucose concentration must be reached within 600 min. As can be seen from Table 7.1 at least 10 samples are necessary to perform a statistically sound parameter estimation.

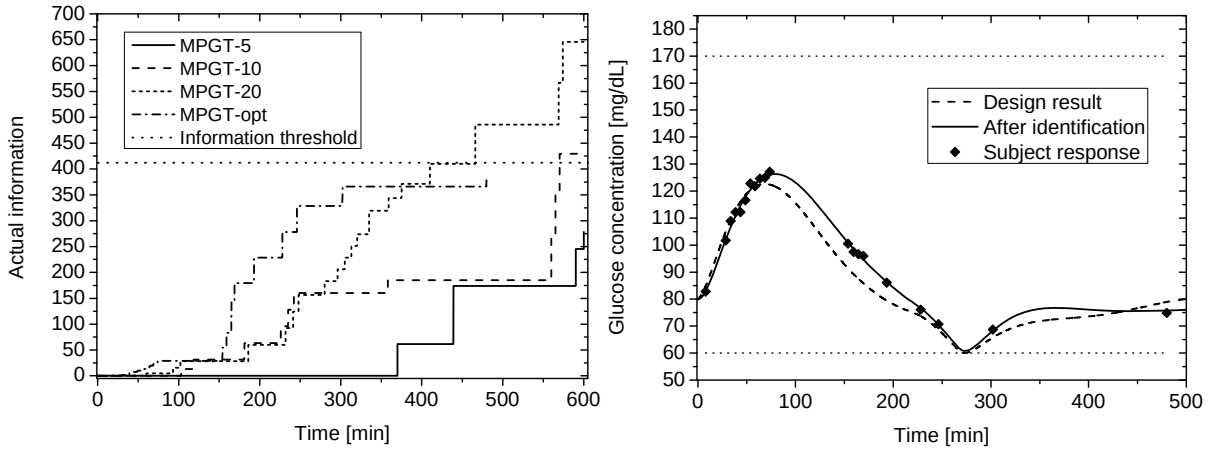
Figure 7.2a shows the contribution of each sample to the overall information (7.2) given by the trace of $\mathbf{H}_\theta$. The information threshold refers to a mean standard deviation of 10% on the

final estimate. When the test duration is also optimised (MPGT-opt), the samples are concentrated at the very beginning of the test, where the test is scarcely informative. However, the optimal settings determined by MPGT-opt allow for a significant increment on the information level of the samples acquired during the time interval $150 < t < 300$ min. As illustrated in Figure 7.2b, this test is safe (even if the profile of glycaemia approaches the lower constraint on hypoglycaemia at $t = 270$ min) and sufficiently short to be carried out ($\tau = 480$ min = 8 h) but the estimation is not statistically satisfactory (although just marginally).

Table 7.1 *Comparison of different MPGT protocols. Superscript * indicates t-values failing the t-test (t_{ref} is the reference t-value and $\boldsymbol{\Theta} = [1.000\ 1.000\ 1.000\ 1.000]^T$).For protocol MPGT-opt $\tau = 8$ h.*

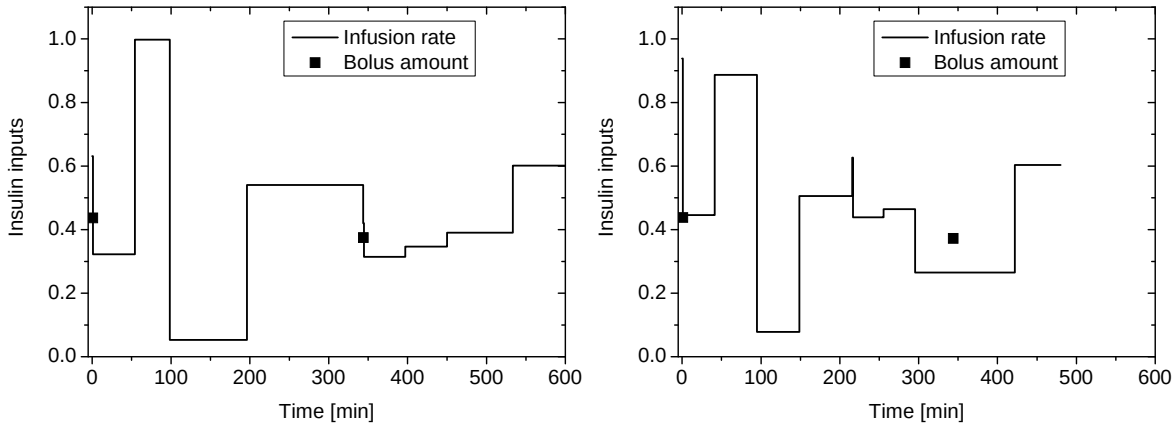
Design	Parameter Estimate $\hat{\Theta}$	Conf. Interval (95%)	*t*-values	t_{ref}
MPGT-5	[1.045 0.729 1.222 1.043]^T	[±0.3665 ±1.2940 ±1.1300 ±0.2341]	[2.85 0.56* 1.08* 4.45]	1.795
MPGT-10	[0.997 0.915 1.059 1.007]^T	[±0.2955 ±0.5136, ±0.3217 ±0.0514]	[3.37 1.78 3.29 19.58]	1.745
MPGT-20	[1.008 0.808 1.114 1.015]^T	[±0.1878 ±0.4276, ±0.2603 ±0.0430]	[5.37 1.89 4.28 23.60]	1.705
MPGT-opt	[0.944 0.826 1.147 1.020]^T	[±0.2235 ±0.7305, ±0.4295 ±0.0713]	[4.23 1.12* 2.67 14.3]	1.705

It is interesting to notice how the MPGT-opt protocol is able to shift the information dynamics by managing the administration of a higher CHO content on breakfast ($\mathbf{D}_{g,i}$ = [30.8, 21.4] g_{CHO}) than in the MPGT-20 test protocol ($\mathbf{D}_{g,i}$ = [21.2, 23.8] g_{CHO}). Moreover, the two tests are characterised by a similar amount of insulin released with the boluses but a completely different policy in the insulin infusion rate (Figure 7.3).



(a) *(b)*

Figure 7.2 *(a) Contribution to the actual information as evaluated by (7.1) for different MPGT protocols and (b) glucose response modeled by design (broken line), after identification (solid line) and subject response (indicated by diamonds) for protocol MPGT-opt. In the time scale, 0 represents 8 AM.*



(a) *(b)*

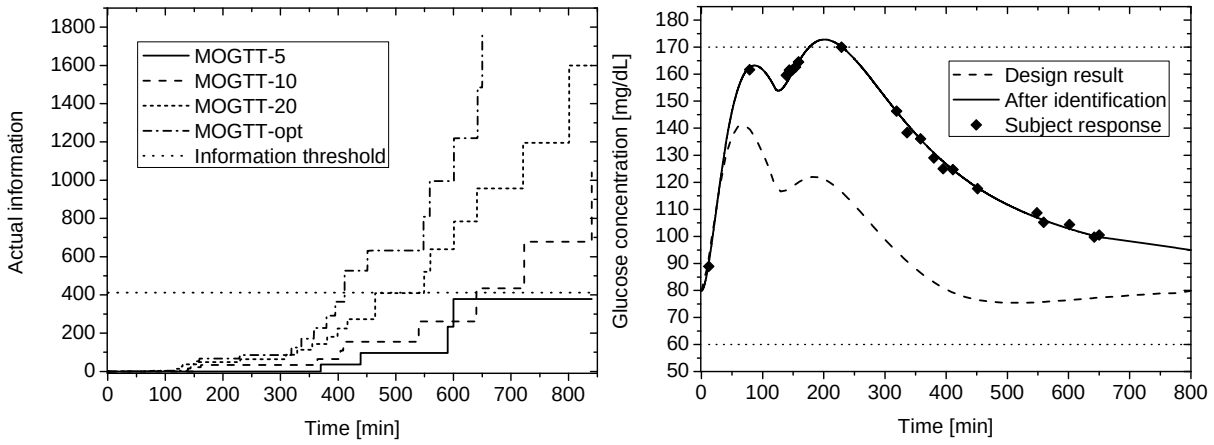
Figure 7.3 *Optimal insulin infusion profile (solid line) and bolus administration (boxes) for protocols (a) MPGT-20 and (b) MPGT-opt.*

7.2.2 Modified Oral Glucose Tolerance Test (MOGTT)

The MOGTT identification test involves multiple glucose solution and insulin bolus intakes. The optimisation variables are: the glucose content of the four meals (glucose solution drink); the time interval between consecutive meals (acceptable range 15-840 min); the sampling times, the amount of each insulin bolus and duration not greater than 840 min (14 h). An additional constraint was imposed on the total amount of CHO ingested (acceptable range: 75-156 g CHO). The end point constraints on blood glucose concentration and its derivative must be fulfilled within 840 min from the last meal. The amount of bolus per meal was modelled adopting equation (5.9). As underlined in Chapter 5, this test is more informative (compare the *y*-axis scale of Figure 7.2a and 7.4a), but a longer experiment duration has to be adopted since the four meals need to be spaced over a sufficiently long period of time. When τ = 840 h (14 h) the estimate is statistically satisfactory only with more than 5 samples (Table 7.2), but, interestingly, the MOGTT approach allows shortening the test duration from 14 to 10.8 h without much affecting the quality of the final estimate, while ensuring a safe and informative test (Figure 7.4b).

Table 7.2 *Comparison of different MOGTT protocols. Superscript * indicates t-values failing the t-test (t_{ref} is the reference t-value and $\boldsymbol{\Theta} = [1.000\ 1.000\ 1.000\ 1.000]^T$). For protocol MOGTT-opt τ = 10.8 h.*

Design	Parameter Estimate $\hat{\Theta}$	Conf. Interval (95%)	*t*-values	t_{ref}
MOGTT-5	$[1.096\ \ 0.800\ \ 1.231\ 1.024]^T$	[±0.2437 ±0.4978 ±0.3028 ±0.1088]	[4.49 1.61* 4.06 9.41]	1.795
MOGTT-10	$[0.902\ \ 1.007\ \ 1.089\ 1.022]^T$	[±0.2139 ±0.1593, ±0.3054 ±0.1018]	[4.22 6.32 3.57 10.04]	1.745
MOGTT-20	$[0.957\ \ 0.975\ \ 1.077\ 1.021]^T$	[±0.1634 ±0.1176, ±0.2447 ±0.0817]	[5.86 8.29 4.40 12.49]	1.705
MOGTT-opt	$[0.906\ \ 0.953\ \ 1.131\ 1.035]^T$	[±0.1813 ±0.2277, ±0.3138 ±0.1014]	[5.00 4.19 3.61 10.22]	1.705



(a) *(b)*

Figure 7.4 *(a) Contribution to the actual information as evaluated by (7.2) for different MOGTT protocols and (b) glucose response modeled by design (broken line), after identification (solid line) and subject response (indicated by diamonds) for protocol MOGTT-opt. In the time scale, 0 represents 8 AM.*

To achieve the information profile illustrated in Figure 7.4a, the MOGTT-opt test protocol manages the assumption of a lower CHO amount in the first two meals (Table 7.3) and a lower bolus administration than in the MOGTT-20 test, in order to keep the feasibility conditions imposed on glycaemia at the end of the test.

Table 7.3 *Comparison of the optimal settings as given by MOGTT-20 and MOGTT-opt test protocols.*

Optimised Design Variables	MOGTT-20	MOGTT-OPT
$\mathbf{t}^{meals}$ [min]	[0, 118, 134, 148]	[0, 120, 138, 154]
$\mathbf{D}_g$ [g]	[59.3, 60, 1.0, 0.9]	[48.7, 24.3, 1.0, 1.0]
k	[0.97, 0.00, 0.06, 0.01]	[0.80, 0.01, 0.06, 0.01]

7.2.3 Additional discussion: the optimisation of dynamic information

Results from the previous Sections show how it is possible to characterize the time dependent profile of the actual information during MPGT and MOGTT clinical tests. In particular, it clearly appears that there exists a close relationship between the dynamics of the actual information, the number of samples acquired and the duration of the test. A standard MBDoE approach can be successfully adopted to shift the dynamic of the actual information, by modifying the number of samples being collected and/or by optimising the duration of the clinical test. However, MBDoE does not allow to optimise the entire time-dependent profile of the actual information, but only the concentration of the information within a prescribed time window. As an attractive alternative, it may be worth maximising the profile of the

actual information from the very beginning of the test by optimising the entire set of design variables.

Following this premise, a novel design criterion involving a dynamic MBDoE approach (DMBDoE) has been formulated and is presented in the next Section. The proposed design technique is suitable for systems in which continuous (or highly frequent) measurements are available. In fact, if the samples are collected very frequently, the measure of the actual information gained from the experiment can be approximated by a continuous profile over the experimental horizon. The optimal design problem is formulated by optimising a continuous dynamic measurement function of the Fisher information matrix with the purpose of reaching a statistically satisfactory estimation of model parameters in the easiest and quickest way.

7.3 The optimisation of dynamic information: DMBDoE

Standard model-based experiment design procedures aim at decreasing the model parameter uncertainty region predicted by a deterministic model as the solution to the optimisation problem (2.14) subject to a set of constraints on the state variables (4.1) and on the design variables (4.2). The experimental settings are chosen to minimise a measurement function ψ of $\mathbf{V}_\theta$ which maximises the global expected information content of the experiment, expressed by the dynamic information matrix (7.1). Formally, the design criteria (§2.2.3) act on the sum of the $\mathbf{M}_k$ contributions to the overall $\mathbf{H}_\theta$, without focusing *on the rate* at which the information is increased. When the experiment is performed, assuming that no sampling scheduling needs to be optimised, the rate of acquisition of the actual information is evidently defined by the features of the measurement system. In particular it is important to know exactly:

1. the sampling frequency (i.e. number of samples per unit time);
2. the measurements precision (i.e. repeatability) and accuracy (dispersion around the "true value" characterising the system response).

From the experiment design perspective, the first factor affects the number of contributions to the overall information, while the second one, under the assumption of randomly distributed measurements errors, deeply affects the formulation (2.10) of the dynamic information matrix (through the definition of the variance-covariance matrix of measurement errors $\mathbf{\Sigma}$).

Considering an A-optimal design criterion (i.e. focusing on the trace *tr* of the dynamic information matrix), an upper limit curve on the expected information (Figure 7.5) can be characterized as the number of samples tends to infinity:

$$\lim_{n_{sp}\to\infty} tr\left(\sum_{k=1}^{n_{sp}}\left[\mathbf{M}_k\right]+\mathbf{H}_\theta^0\right)=\lim_{n_{sp}\to\infty}\sum_{k=1}^{n_{sp}} tr\left[\mathbf{M}_k\right]+K=\int_0^\tau tr\left[\mathbf{M}(t)\right]\mathrm{d}t+K\,. \tag{7.2}$$

In (7.2) K is a constant term quantifying the prior information, while the trace of $\mathbf{M}(t)$ allows for the dynamic evaluation of the expected information (note that the trace is a linear map and for this reason has been considered as a suitable measurement function). This new metric of the expected information is suitable for systems where the measurements can be deemed continuous (i.e., where information can be gathered at a frequency that is much higher than the dominant frequency of the process).

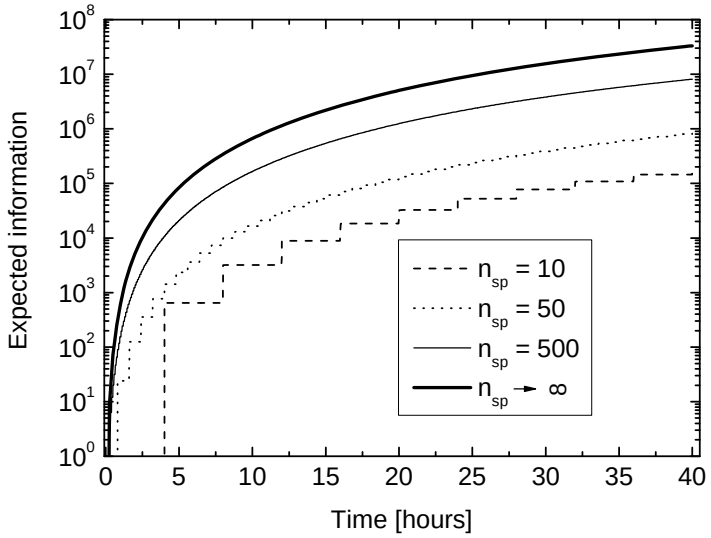


Figure 7.5 *Effect of the number of samples on the evaluation of the expected information.*

A novel design criterion for the dynamic model based design of experiments (DMBDoE) can thus be introduced:

$$\varphi = \arg\max\left[\int_{\tau} tr\left[\mathbf{M}(t)\right]\mathrm{d}t\right] \quad . \tag{7.3}$$

Basically, the DMBDoE criterion aims at maximising the area underneath the curve of the dynamic expected information, while a standard A-optimal MBDoE criterion aims at maximising the sum of the information content of each single sampling point (Figure 7.6).

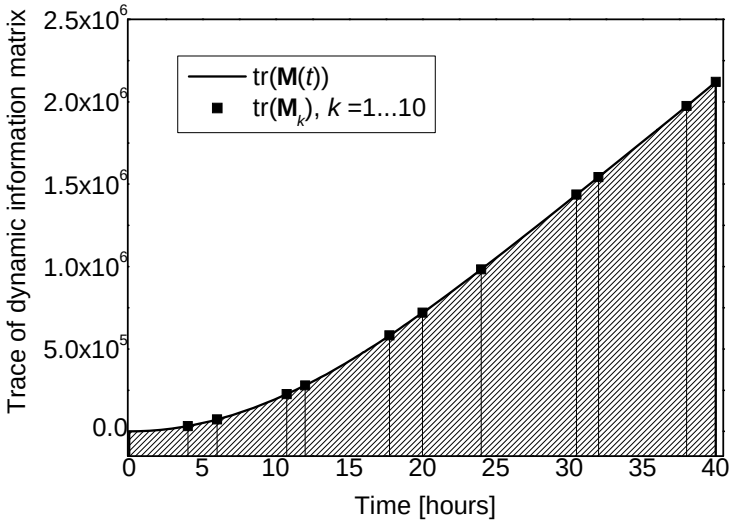


Figure 7.6 *Dynamic evaluation of expected information.*

The benefit of adopting (7.3) as a design objective function comes from the fact that the information is maximised starting from the very beginning of the experiment. This design criterion can be usefully exploited in both a sequential MBDoE framework or by adopting a redesign strategy (see Chapter 3) within a proper time window. After maximising the expected information with (7.1) or (7.3) by acting on the components of the design vector $\boldsymbol{\varphi}$, the experiment is performed and the actual information is evaluated by carrying out a parameter estimation on the collected data. A new information profile will be generated (the "actual information" profile), usually different from the expected profile maximised by design. If the model is a reliable representation of the process, the gap between expected and actual information can be exclusively attributed to the parametric mismatch between the model and the real system.

Note that (7.1) and (7.3) allow to tune the MBDoE activity to the specificity of the measurement system. Moreover, these equations could be used, in perspective, to guide the experimenter on the choice of a proper measurement system. In fact, as previously introduced, the possibility of a quick gain of information has a dramatic impact on the global amount of information, and thus on the effectiveness of the whole identification procedure.

The effectiveness the proposed DMBDoE technique is illustrated and discussed through two simulated case studies. The first one is concerned with the optimal design of a MOGTT for the identification of HWM. The second one is related to the biomass fermentation process for baker's yeast previously presented in §3.4.

7.4 Case study 1: comparing DMBDoE and MBDoE for a modified oral glucose tolerance test

Previous results show that a modified OGTT protocol is more effective than a modified PGT protocol when higher sampling frequencies are adopted. The results also demonstrate the flexibility of this protocol, which is simpler to be carried out and allows achieving a statistically sound parameter estimation in a shorter time. Moreover, the test is not invasive or harmful to the subject. A standard MBDoE approach with the optimisation of the time duration (protocol MOGTT-opt) allows shortening the experimental duration to 10.8 h. We will show that the duration of the MOGTT test can be further be reduced by adopting a DMBDoE approach where the test is optimised by design adopting (7.4) as objective function. It is assumed that a continuous measurements system is available and thus a very frequent sampling (1 sample every 10 minutes) which is quite a standard frequency for CGM systems) can be realised, where the measurements can be obtained with a constant relative variance of 0.03. The maximum experimental duration is set to $\tau = 10$ h.

The management of dynamic information with DMBDoE allows concentrating the actual information at the beginning of the test (Figure 7.8a), ensuring an optimally informative test (Table 7.4). Thanks to the exploitation of the information dynamics, the test can be shortened to $\tau = 480$ min = 8 h without much affecting the quality of the final estimate (Table 7.5).

Table 7.4 *Case study 1: parameter estimation after the experiment designed by DMBDoE where the test duration is set to $\tau = 600$ min. The measurements relative variance is 0.03 and the reference t-value is equal to 1.795 (asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.9180	1.5924	0.1217	7.541	0.0610
Θ_2	0.8042	0.8187	0.2692	2.987	0.1349
Θ_3	1.2581	1.3755	0.2778	4.530	0.1392
Θ_4	1.0779	1.2677	0.0948	11.370	0.0475

Table 7.5 *Case study 1: parameter estimation after the experiment designed by DMBDoE where the test duration is set to $\tau = 480$ min. The measurements relative variance is 0.03 and the reference t-value is equal to 1.795 (asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.9255	1.5924	0.1286	7.196	0.0642
Θ_2	0.7949	0.8187	0.3309	2.403	0.1652
Θ_3	1.2593	1.3755	0.3087	4.079	0.1541
Θ_4	1.0787	1.2677	0.1063	10.140	0.0531

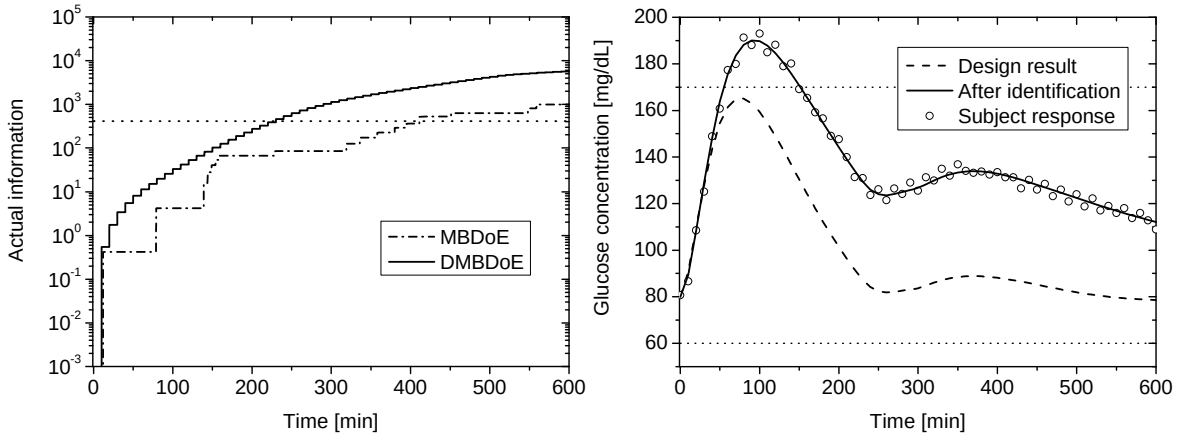
Table 7.6 compares the optimal design settings provided by MBDoE (protocol MOGTT-opt) with the ones provided by a DMBDoE optimisation. In order to exploit the information during

the initial dynamics of the test, the DMBDoE tends to concentrates the CHO administration on the first meal while a standard MBDoE approach would distribute the CHO administration on the first two meals and thus along the first hours of the test.

Table 7.6 *Case study 1: comparison of the optimal settings of the MOGTT test as given by MBDoE and DMBDoE.*

Optimised Design Variables	MBDoE	DMBDoE
$\mathbf{t}^{meals}$ [min]	[0, 120, 138, 154]	[0, 231, 251, 294]
$\mathbf{D}_g$ [g]	[48.8, 24.3, 1.0, 0.9]	[58.4, 7.7, 1.0, 0.9]
k	[0.80, 0.01, 0.06, 0.01]	[0.64, 0.12, 0.00, 0.01]

The slight hyperglycaemic condition achieved (as an effect of the parametric mismatch between the subject and the model, Figure 7.8b) can be tolerated in the clinical practice (only the lower bound on glycaemia is a hard constraint). If measurements are available with a significantly higher measurements error (0.07 the relative variance) as it happens by adopting the actual CGMS devices, the parameter estimation is not statistically satisfactory adopting a 8 hours test (Table 7.7). Even if not shown it has been verified that under these measurement settings a statistically satisfactory parameter estimation can be ensured only if the test is at least 9 hours long. This preliminary result shows the interesting impact of the measurements quality (i.e. not only the frequency) on the design effectiveness, and opens new possibility for designing a clinical test adopting continuous measurement systems.



(a) *(b)*

Figure 7.8 *Case study 1. (a) Actual information as evaluated by (7.2) for MBDoE and DMBDoE planned MOGTT and (b) glucose response modeled by design (broken line), after identification (solid line) and subject response (indicated by circles) for protocol MOGTT-D.*

Table 7.7 *Case study 1: parameter estimation after the experiment designed by DMBDoE where the test duration is set to τ = 480 min and the measurements are available with relative variance 0.07. The reference t-value is equal to 1.795 (asterisks denote t-values failing the t-test).*

Model Parameter	Final Value	Initial Guess	Confidence Interval 95%	95% t-value	Standard Deviation
Θ_1	0.9917	1.5924	0.2519	3.936	0.1257
Θ_2	0.7658	0.8187	0.4837	1.583*	0.2414
Θ_3	1.2358	1.3755	0.3879	3.186	0.1936
Θ_4	1.0727	1.2677	0.1349	7.954	0.0673

7.5 Case study 2: biomass fermentation process

The novel DMBDoE methodology discussed in the previous section is applied to the biomass fermentation process described by the set of differential and algebraic equations (3.6) and detailed in §3.4. The experimental conditions that characterise an experiment are the dilution factor u_1 (range 0.05-0.20 h^{-1}) and the substrate concentration in the feed u_2 (range 5-35 g/L), mathematically approximated through piecewise constant profiles over 8 switching intervals (the duration of each interval is allowed to be between 1 and 20 h). The initial biomass and substrate concentration $x_1(0)$ and $x_2(0)$ are set to 1.4 g/L and 0 g/L, respectively. In the system both x_1 and x_2 can be measured during the experiment. The final objective is to design a single experiment (lasting $\tau = 40$ h) to yield the best possible information for the estimation of the four parameters θ_i.

Two experiment design configurations are considered and compared in the study:

1. MBDoE: a standard E-optimal designed experiment with (7.1) as the objective function; the design also optimises the collocation in time of $n_{sp} = 10$ samples (the elapsed time between any two sampling points is allowed to be between 1 and 20 h);
2. DMBDoE: a dynamic experiment design is performed by adopting (7.4) as the objective function; it is supposed that the measurements are available very frequently (every 10 min).

The E-criterion was used in the standard MBDoE approach because it was proven as the most effective design approach for this case study (Asprey and Macchietto, 2000). Even if not shown here for sake of brevity, it has nonetheless been verified that an A-optimal design criterion would provide very similar optimal excitation patterns. Synthetic experimental data are obtained by simulation with $\boldsymbol{\theta} = [0.310, 0.180, 0.550, 0.050]^T$ as the "true" parameters and are available with a constant relative variance of 0.03 (case A, "noise-free measurements") and 0.20 (case B, "noisy measurements"). These two distinct cases have been chosen to assess the impact of the measurements accuracy on DMBDoE effectiveness.

The initial guess for the model parameters' values is set to $\boldsymbol{\theta}^0 = [1.000, 1.000, 1.000, 1.000]^T$. Since $\boldsymbol{\theta}$ is obviously unknown in practice, results of the parameter estimation are given in terms of the *a-posteriori* statistics obtained after performing a maximum likelihood parameter

estimation. The quality of the final estimates is assessed by observing for each parameter the interval of estimation confidence and the *t*-value statistics obtained after the optimally designed experiments have been executed and model parameters re-estimated with the new data.

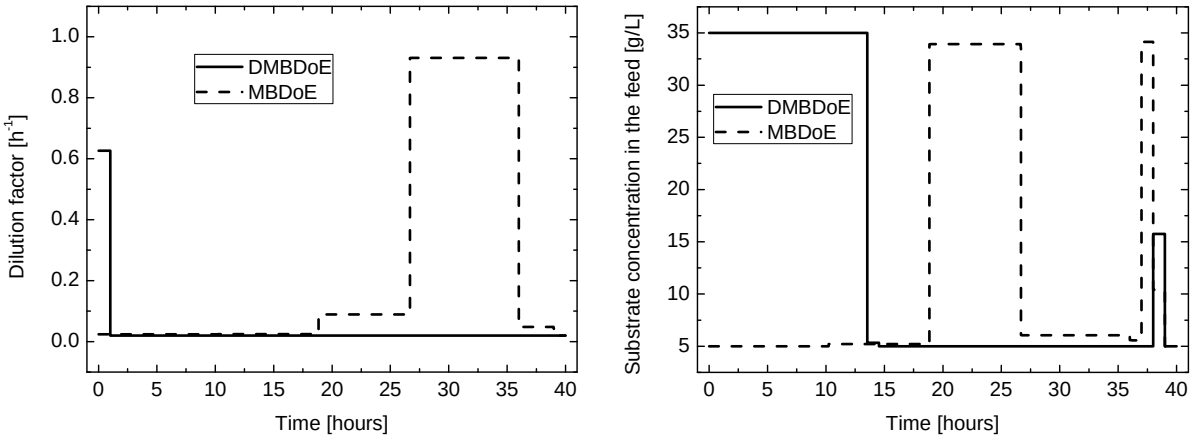
7.5.1 Case A: noise-free measurements

When (almost) noise-free measurements are available, both MBDoE approaches allow reaching a statistically satisfactory parameter estimation (Table 7.8), but DMBDoE ensures a dramatically better confidence on the final estimate, thanks to the higher rate of information acquisition.

Table 7.8 *Case study 2.A: comparison of parameter estimations for different design configurations (the reference t-value is 1.74 for MBDoE and 1.65 for DMBDoE estimation).*

	MBDoE	**DMBDoE**
Estimate	$[0.3064\ 0.2015\ 0.4955\ 0.0448]^T$	$[0.3154\ 0.1762\ 0.5792\ 0.0520]^T$
Conf. Interval (95%)	[±0.0118 ±0.0540 ±0.1250 ±0.0134]	[±0.0010 ±0.0014 ±0.0048 ±0.0005]
***t*-values**	[26.04 3.73 3.96 3.350]	[297.20 125.10 119.80 103.50]

Interestingly (Figure 7.9), in a DMBDoE approach the design is such that the system is excited at the very beginning of the experiment in order to increase the information content of the samples being acquired as soon as the experiment starts. On the contrary, the excitation pattern provided by MBDoE is mainly concentrated in the second half of the trial.



(a) *(b)*

Figure 7.9 *Case study 2.A. Profiles of the manipulated inputs as optimised by the two different design strategies: (a) dilution factor and (b) substrate concentration in the feed for DMBDoE (solid line) and MBDoE (broken line).*

This clear difference on the excitation policy has a significant effect on the distribution of information along the experimental horizon. In fact, the dynamics of the actual information are completely different for the two design configurations (Figure 7.10). A minimum required information limit based on the A-optimal design criterion can be defined by considering a mean standard deviation of 10% on the final estimate of model parameters. It can be noticed that the second half of the experiment as planned by DMBDoE does not deliver an appreciable contribution to the overall information, which is fully exploited at the very beginning of the trial. A maximum on the actual information is reached around t = 11 h, and subsequently the increment on information is negligible. As a result, the experiment planned by DMBDoE could be stopped before the end as a statistically satisfactory parameter estimation would be reached already. On the contrary, the experiment planned by a standard MBDoE technique requires approximately the full length of the experiment for a statistically sound parameter estimation.

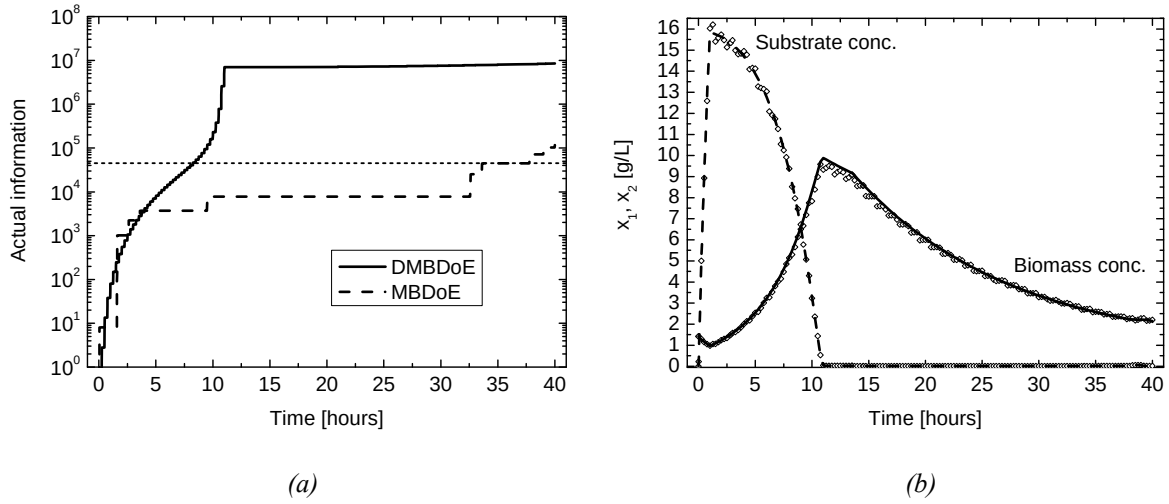


Figure 7.10 *Case study 2.A. (a) Profiles of actual information for a standard MBDoE and for DMBDoE as given by the summation term of (7.2); the dotted line represents the A-optimal information limit for a 10% deviation on the final estimate. (b) Biomass and substrate concentration profiles as predicted by the model after the parameter identification of the DMBDoE planned experiment; biomass and substrate concentration measurements are indicated by diamonds.*

7.5.2 Case B: noisy measurements

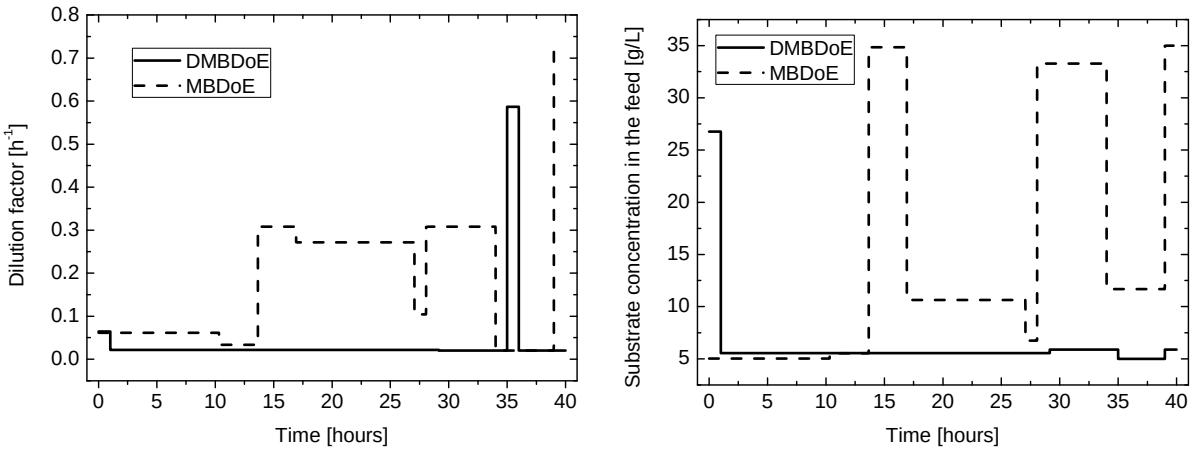
When quite noisy measurements are available, a standard MBDoE approach is not sufficient to provide a statistically sound parameter estimation (Table 7.9) with a single experiment. On the contrary, the DMBDoE strategy appears to be less sensitive to the entity of the measurement noise and provides a statistically satisfactory estimation for all parameters.

The level of excitation provided by MBDoE is significantly higher than the one provided by DMBDoE (Figure 7.11), but it is still concentrated (as in case A) in the second part of the experiment (after 10 h). Analysing the actual information profiles (Figure 7.12a) it can be

noticed how the information acquired through discrete samples is not sufficient to guarantee a statistically sound parameter estimation. Conversely, when a dynamic design is carried out, the information exploited at the very beginning of the experiment is sufficient to reach a statistically sound parameter estimation in the first half of the experiment.

Table 7.9 *Case study 2.B: comparison of parameter estimations for different design configurations. Superscript * indicates t-values failing the test (reference t-value is 1.74 for MBDoE and 1.65 for DMBDoE estimation).*

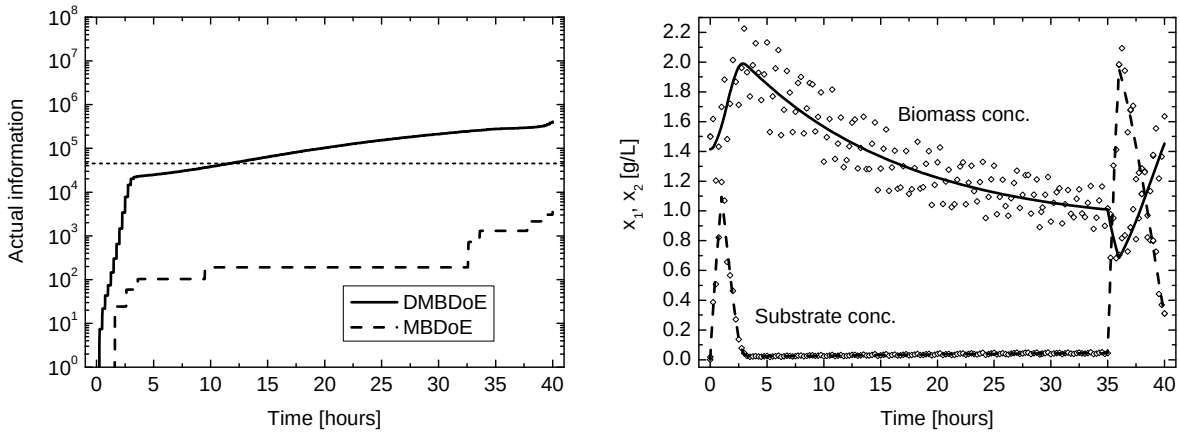
	MBDoE	**DMBDoE**
Estimate	$[0.3047\ 0.1970\ 0.5099\ 0.0436]^T$	$[0.3040\ 0.1757\ 0.5327\ 0.0491]^T$
Conf. Interval (95%)	[±0.2000 ±0.3369 ±0.8502 ±0.1903]	[±0.0292 ±0.0137 ±0.0745 ±0.0087]
***t*-values**	$[1.52^*\ \ 0.58^*\ 0.59^*\ 0.23^*]$	[10.40 12.85 7.15 5.62]



(a) *(b)*

Figure 7.11 *Case study 2.B. Profiles of the manipulated inputs as optimised by the two different design strategies: (a) dilution factor and (a) substrate concentration in the feed for DMBDoE (solid line) and MBDoE (broken line).*

It can be noticed the relevant effect of the measurements error on the information dynamics: the profile still exhibits a peak at the beginning of the experiment at t = 3 hours (and this guarantees a substantial benefit on the parameter estimation), but after that point the increment on information is even lower than the one provided by MBDoE. However, it can be observed that even if measurements are very noisy, the new approach (Table 7.9) can provide a sounder parameter estimation of θ_2, θ_3 and θ_4 than the one provided by a standard MBDoE with noise-free measurements (Table 7.8). Thus, particular attention should be made by the experimenter on choosing the proper measurement system. A continuous measurement system, even if providing noisy data, could be more suitable for model development and validation than a more precise but discrete approach.



(a) *(b)*

Figure 7.12 *Case study 2.B. (a) Profiles of actual information for a standard MBDoE and for DMBDoE as given by the summation term of (7.2); the dotted line represents the A-optimal information limit for a 10% deviation on the final estimate. (b) Biomass and substrate concentration profiles as predicted by the model after the parameter identification of the DMBDoE planned experiment; biomass and substrate concentration measurements are indicated by diamonds.*

7.5.3 Additional discussion

As already mentioned, from the analysis of the dynamics of the actual information when a DMBDoE approach is pursued (Figure 7.10 and Figure 7.12) it seems that the experiment can be stopped well before its planned duration, while maintaining at the same time a satisfactory parameter estimation.

Table 7.10 *Case study 2: comparison of parameter estimations for DMBDoE planned minimal-length experiments for different scenarios: noise-free measurements (the reference t-value is 1.74) and noisy measurements (the reference t-value is 1.66).*

	Noise free measurements	***Noisy measurements***
Estimate	$[0.3022\ 0.1809\ 0.5359\ 0.0423]^T$	$[0.2872\ 0.1762\ 0.4999\ 0.0457]^T$
Conf. Interval (95%)	[±0.0208 ±0.0050 ±0.0410 ±0.0200]	[±0.0643 ±0.0217 ±0.1381 ±0.0192]
t-values	[14.48 35.59 13.33 2.115]	[4.464 8.118 3.619 2.381]
Duration (h)	12.75	14.50

This behaviour is confirmed by performing an additional parameter estimation on two DMBDoE experiments (Table 7.12) where the trial is stopped as soon as the *t*-test is satisfied for the entire parametric set. The results show significant benefits in terms of time saving. For both experiments the precise estimation of θ_4 is critical. When noise-free measurements are available, the approach allows to reduce the experiment duration from 40 to 12.75 hours.

When only noisy measurements are available a slightly longer experiment is required (14.5 h), but still the experiment length can be significantly reduced.

7.6 Final remarks

Each experiment performed exhibits a time dependent profile of the actual information that can be easily handled by standard or advanced MBDoE techniques. On the other hand, these techniques are based on the optimisation of a global measurement of the expected information, where the dynamics of the information itself (i.e. the evolution of the expected information in time) are not considered in the formulation of the optimal design problem. The information dynamics are influenced not only by the excitation pattern, but also by the features of the measurement system. Sampling frequency and measurements quality (in terms of precision and accuracy) deeply affects the availability of information and the way in which information can be increased thanks to the design procedure. As a result, the mathematical formulation of the design problem should take into account the specificity of the measurement system. A novel design criterion (DMBDoE), particularly suitable for systems where continuous measurements are available, has been proposed and analysed in order to optimise the information dynamics of the experiments. DMBDoE allows exploiting different information patterns where the information is always maximised, since the very beginning of the trial.

An MBDOE approach has been applied to a complex model of glucose homeostasis with the purpose of evaluating the impact of sampling frequency and test duration on the information dynamics of a modified post prandial glucose test (MPGT) and a modified oral glucose tolerance test (MOGTT). The information dynamics can be managed by MBDoE in such a way to ensure shorter and easier tests to perform. MOGTT test protocol proved to be a more informative and shorter test than a MPGT, and can be further reduced adopting a DMBDoE strategy. The novel approach allows to drastically reduce the duration of the test without affecting the quality of the final estimates.

Results from the analysis of a bioreactor model show that the parametric identification is significantly improved when DMBDoE is used. A clear benefit of adopting the novel technique is given by the fact that it is possible to reduce the overall duration of the experiment in a substantial way. A significant result was that a continuous measurement system, even if providing noisy data, could be more suitable for model development and validation than a more precise but discrete approach.

Conclusions and perspectives

Model-based design of experiments (MBDoE) techniques represent a valuable tool for the rapid assessment and development of dynamic deterministic models, allowing for the maximisation of the information content of an experimental trial in order to assist the model parameter identification task. Also due to the fact that they can handle constraints both in the system inputs and in the system outputs, MBDoE techniques have become an established tool within the process engineering community, where dynamic first-principles models of complex nonlinear chemical processes often need to be identified.

Although MBDoE turns out to be a standard approach to parametric identification of dynamic systems, conventional MBDoE techniques still suffer from some limitations. In fact, their effectiveness is deeply affected by such factors as parameter uncertainty on prior estimates coupled to hard constraints on design and/or state variables, structural system/model mismatch, and frequency at which the measurements are made available. The first objective of the Thesis was the development of new advanced MBDoE techniques to address the aforementioned issues of standard MBDoE approaches.

A second goal was to demonstrate the usefulness and effectiveness of MBDoE techniques within scientific domains other than the process engineering one. In particular, within the biomedical area there are a number of important applications and critical issues, which could benefit from an MBDoE methodology. Two identification problems have been considered: one related to the optimal drug administration in cancer chemotherapy, and one related to glucose homeostasis models for subjects affected by type 1 diabetes mellitus (T1DM).

With reference to the first topic, the main scientific contributions of this research have been related to the development of:

1. an online strategy for the optimal redesign of experiments (OMBRE);
2. a backoff-based strategy for MBDoE;
3. a dynamic model-based design of experiments (DMBDoE) technique, particularly suitable when continuous measurement systems are available;

These achievements are briefly recollected and discussed in the following.

Standard MBDoE involves a sequential procedure (experiment design; experiment execution; parameter estimation) where the information within the collected samples can be exploited only after the experiment is concluded. Conversely, the proposed OMBRE approach allows maximising and exploiting the information as soon as it is generated by the experiment thanks to intermediate parameter estimations, with great benefit in terms of precision and accuracy of the final estimation. Accordingly, the experimental settings (comprising the time-dependent

profiles of the manipulated inputs and the allocation of sampling points in time) are updated (formally a “redesign”) as the experiment is running. The results have clearly shown the powerful feature of OMBRE of being less sensitive to the quality of the initial parameter estimation. Additionally, the proposed approach allows splitting the whole optimisation problem into a number of smaller problems with great benefit in terms of computational time. Furthermore, this is an important feature to consider when large optimisation problems are carried out, in order to reduce the risk of incurring in suboptimal solutions.

In a large of variety of problems, experiment feasibility can be even more important than optimality. Following this motivation, a novel backoff-based MBDoE strategy has been proposed where the effect of model mismatch and parametric uncertainty is accounted for by means of a constrained formulation. Formally, a backoff from active constraints is evaluated by performing a stochastic simulation over the entire domain of variability of the model parameters. That allows for the definition of a (reduced) feasible design space within which the MBDoE optimisation may be safely carried out. The results have clearly shown that the proposed backoff-based strategy outperforms a standard one whenever hard constraints are present in the system outputs and the parametric uncertainty in the model is significant.

The mathematical formulation of a standard optimal experiment design problem is usually carried out under the assumption that the measurements are acquired in a discrete way. However, the current evolution of measurement systems makes the continuous acquisition of measurements a reality. If measurements are available in a continuous way, so is information as well, and the formulation of the MBDoE problem should be modified accordingly. A novel “dynamic” MBDoE strategy (DMBDoE) has been developed that takes into account the specificity of continuous measurement systems. The proposed approach allows optimising and exploiting the whole dynamic evolution of the actual information. Although still at a preliminary stage, the results have shown how an DMBDoE approach is capable of shortening the length of an identification experiment, considerably.

As for the extension of MBDoE to biomedical systems, this research has demonstrated the potential of conventional and advanced MBDoE strategies for the parametric identification of complex physiological models. The most advanced physiological models are characterised by structural complexity and by the existence of hard constraints on the system, which are inherently related to the metabolic activity of the subject whose physiology is represented by the model. In addition, poor system observability and controllability usually make the parametric identifiability procedure a very complicated and challenging task.
Particular attention has been drawn to the problem of identifying complex physiological models of T1DM, where system/model structural mismatch can exacerbate the adverse effect

of hitting the constraints on the blood glucose concentration. The research has shown that, by adopting conventional and advanced MBDoE techniques, the model parameters can be identified for a single individual in a statistically sound way through safe and moderately invasive clinical tests of prescribed length. In this perspective, this research also represents a process systems engineering contribution to the development of an artificial pancreas for people affected by T1DM.

Some considerations about future research directions are in order at this point. Following the structure of this Thesis, two broad research areas can be identified: the improvement of conventional and advanced MBDoE techniques for process engineering systems, and the extension of these techniques to address the model identification challenges of the biomedical community.

As for the improvement of MBDoE techniques, it should be noted that a general methodology for selecting the most appropriate experiment design technique (including a design criterion) to be used for planning a series of experiments given a model structure is missing at present. A systematic selection procedure should therefore be developed, and possibly implemented in a comprehensive and user-friendly software environment, to assist the industrial practitioner when he/she needs to face the issue of selecting which technique is more appropriate for the model he/she needs to identify.
Traditionally, the optimal design of experiments has been carried out with the control loops open (unless for the lower-level loops ensuring the system stability). However, in order to minimise the plant upsets, it would be desirable that the control loops remain closed, so as to guarantee that the product quality is kept within the desired standards even during the experimentation, an issue that may be particularly significant if the (parametric or structural) uncertainty of the model is high. Therefore, a research effort should be directed to addressing the problem of optimal experiment design in a closed-loop system environment. Additionally, the control system could be possibly exploited to “steer” the information profile generated by an experiment in such a way as to track a user-defined information profile.
This research has shown that there are close relationships between a redesign of experiments approach like OMBRE and a model-based control approach like model-predictive control (MPC). These similarities should be identified in a formal way, possibly recognizing whether an OMBRE task can be actually cast as an MPC problem.

The study on the identification of physiological models of T1DM should be extended to more complex models where other factors affecting the glycaemic response of the subject are taken into account (i.e. stress, physical exercise, diet). Emerging sampling techniques such as continuous glucose measuring systems should be considered in the clinical test design

scheme, also accounting for the technical limitations of the currently available devices. Particularly, the impact of blood sampling frequency and measurement error (both systematic and random) on the test safety should be carefully investigated. At a more mature stage of the research, *in vivo* experimentation will be definitely needed to further assess the potential of conventional and novel MBDoE strategies. In this perspective, close interaction with clinicians is definitely a must for any subsequent step of the research in this area.

Finally, the development of a new general methodology for MBDoE may prove useful for the parametric identification of other physiological models, for example in the care of diseases like cancer or H.I.V. Complex models have been proposed in the literature for these systems that are difficult (or perhaps impossible) to identify through unplanned experiments.

Appendix A

Models of glucose homeostasis

The Appendix contains the details on the models of glucose homeostasis adopted in the Thesis. The Hovorka model (§A.2) with the insulin infusion submodel by Wilinska (§A.3.2) is used in Chapter 5 and Chapter 7 and in the Thesis it is denoted as HWM. The Hovorka model (§A.2) and the Cobelli model (§A.1) with the Nucci infusion submodel (§A.3.1) are used in Chapter 6 and are denoted in the text as HM and CM respectively.

A.1 Cobelli model of glucose homeostasis

The system of equations of the Cobelli model as presented in Dalla Man *et al.* (2007) are here summarised. Fig. A.1 shows a schematic representation of the model.

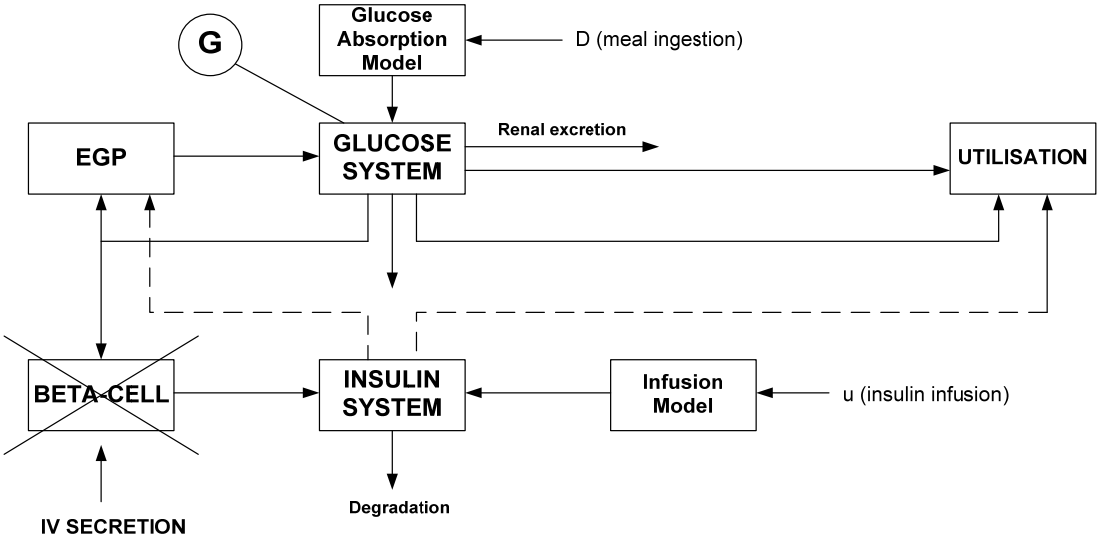


Figure A.1 *Schematic representation of the Cobelli model (CM). Renal excretion, utilisation, endogenous glucose production (EGP), glucose absorption units as well as glucose and insulin systems are described by systems of differential and algebraic equations. In order to simulate a patient affected by type 1 diabetes mellitus, the secretion model has been removed and an insulin infusion model has been added to the system.*

Note that insulin concentration is always expressed in the previous sections as mU/L, while in the present section and in the original paper it is expressed in pmol/L (the conversion is 1 mU/L = 7.175 pmol/L). The entire set of model parameters defining a healthy subject is reported in Table A.1.

Table A.1 *Parameters of Cobelli model for a healthy subject.*

Subsystem	Parameter	Value	Unit
Glucose	V_G	1.88	dl/kg
	k_1	0.065	min^{-1}
	k_2	0.079	min^{-1}
Insulin	V_I	0.05	l/kg
	m_1	0.19	min^{-1}
	m_2	0.484	min^{-1}
	m_4	0.194	min^{-1}
	m_5	0.0304	min . kg/pmol
	m_6	0.6471	dimensionless
	HE_b	0.6	dimensionless
Rate of appearance	k_{max}	0.0558	min^{-1}
	k_{min}	0.0080	min^{-1}
	k_{abs}	0.057	min^{-1}
	k_{gri}	0.0558	min^{-1}
	f	0.9	dimensionless
	a	0.00013	mg^{-1}
	b	0.82	dimensionless
	c	0.00236	mg^{-1}
	d	0.010	dimensionless
Endogenous production	k_{p1}	2.7	mg/kg/min
	k_{p2}	0.0021	min^{-1}
	k_{p3}	0.009	mg/kg/min per pmol/L
	k_{p4}	0.0618	mg/kg/min per pmol/kg
	k_i	0.0079	min^{-1}
Utilisation	F_{cns}	1	mg/kg/min
	V_{m0}	2.5	mg/kg/min
	V_{mx}	0.047	mg/kg/min per pmol/L
	K_{m0}	225.59	mg/kg
	p_{2U}	0.0331	min^{-1}
Renal excretion	k_{e1}	0.0005	min^{-1}
	k_{e2}	339	mg/kg

The glucose masses in plasma (G_p) and tissues (G_t) are represented by the following set of equations:

$$\frac{dG_p(t)}{dt} = EGP(t) + R_a(t) - U_{ii}(t) - E(t) - k_1 G_p(t) + k_2 G_t(t) \tag{A.1}$$

$$\frac{dG_t(t)}{dt} = -U_{id} + k_1 G_p(t) - k_2 G_t(t) \tag{A.2}$$

and are expressed in [mg/kg], while R_a [mg/kg/min] is the rate of appearance of glucose in plasma, E is the renal excretion [mg/kg/min], EGP is the endogenous glucose production [mg/kg/min], U_{ii} and U_{id} are the insulin dependent and independent glucose utilizations [mg/kg/min], V_g is the glucose distribution volume [dL/kg], k_1 and k_2 are rate parameters [min^{-1}]. The measured plasma glucose concentration is

$$G(t) = \frac{G_p}{V_G}. \tag{A.3}$$

The insulin subsystem is described by the following equations:

$$\frac{dI_l(t)}{dt} = -(m_1 + m_3(t))I_l(t) + m_2 I_p(t) \tag{A.4}$$

$$\frac{dI_p(t)}{dt} = -(m_2 + m_4)I_p(t) + m_1 I_l(t) + R_i(t) \tag{A.5}$$

where I_l and I_p are the insulin masses in the liver and in plasma respectively [pmol/kg], and R_i is the rate of appearance of insulin in plasma [pmol/kg/min] as defined by the insulin infusion subsystem (see §A.3). The rate parameters are m_1, m_2, m_4 and m_3, which is related to hepatic extraction *HE* (i.e. the relative time-varying fraction of insulin leaving the liver)

$$HE(t) = -m_5 S + m_6 \tag{A.6}$$

with $HE(0) = HE_b$ and

$$m_3(t) = \frac{HE(t)m_1}{1 - HE(t)}. \tag{A.7}$$

The secretion *S* is absent for a subject affected by type 1 diabetes ($S = 0$) and insulin can enter the insulin subsystem only through R_i. The insulin concentration in plasma is

$$I(t) = \frac{I_p}{V_I} \tag{A.8}$$

where V_I is the insulin distribution volume [L/kg]. The rate of appearance of glucose in plasma R_a is described by the complex sub-model presented by Dalla Man et al. (2006):

$$Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t) \tag{A.9}$$

$$\frac{dQ_{sto1}(t)}{dt} = -k_{gri} Q_{sto1}(t) + D\delta(t) \tag{A.10}$$

$$\frac{dQ_{sto2}(t)}{dt} = -k_{empt}(Q_{sto}) Q_{sto2}(t) + k_{gri} Q_{sto1}(t) \tag{A.11}$$

$$\frac{dQ_{gut}}{dt} = -k_{abs}Q_{gut}(t) + k_{empt}(Q_{sto})Q_{sto2}(t) \tag{A.12}$$

$$R_a(t) = \frac{fk_{abs}Q_{gut}(t)}{BW} \tag{A.13}$$

where Q_{sto} and Q_{gut} are the amount of glucose in the stomach (solid phase Q_{sto1} , and liquid phase Q_{sto2}) and in the intestine respectively [mg], k_{gri} [min^{-1}] is the rate constant of grinding, k_{empt} is the rate constant of gastric emptying (which is a non linear function of Q_{sto}) and k_{abs} [min^{-1}] is the rate constant of intestinal absorption; f is the fraction of intestinal absorption which actually appears in plasma, D is the amount of ingested glucose [mg] and BW is the body weight [kg].
Glucose utilisation is made up of two components:

$$U(t) = U_{ii}(t) + U_{id}(t) \tag{A.14}$$

the insulin-independent utilisation $U_{ii}(t) = F_{cns}$ taking into account the glucose uptake by the brain and erytrocytes, and the insulin-dependent utilisation U_{id}

$$U_{id}(t) = \frac{V_m(X(t))G_t(t)}{K_m(X(t)) + G_t(t)} \tag{A.15}$$

depending nonlinearly from glucose in the tissues. V_m and K_m are assumed to be linearly dependent from the insulin in the interstitial fluid [pmol/L] X

$$V_m(X(t)) = V_{m0} + V_{mx}X(t) \tag{A.16}$$

$$K_m(X(t)) = K_{m0} + K_{mx}X(t) \tag{A.17}$$

$$\frac{dX}{dt} = -p_{2U}X(t) + p_{2U}[I_t(t) - I_b] \tag{A.18}$$

with p_{2u}, K_{m0}, V_{m0} parameters of the utilisation subsystem. Endogenous glucose production is defined by the equation

$$EGP(t) = k_{p1} - k_{p2}G_p(t) - k_{p3}I_d(t) \tag{A.19}$$

where I_d is a delayed insulin signal [pmol/L], obtained by a chain of two compartments

$$\frac{dI_1(t)}{dt} = -k_i\left[I_1(t) - I(t)\right] \tag{A.20}$$

$$\frac{dI_d(t)}{dt} = -k_i\left[I_d(t) - I_1(t)\right] \tag{A.21}$$

and k_i, k_{p1}, k_{p2}, k_{p3} are parameters of the *EGP* subsystem.
The renal excretion E occurs when plasma glucose exceeds a threshold and it is defined by the following equations:

$$E(t) = \begin{cases} k_{e1}\left[G_p(t) - k_{e2}\right] & if \quad G_p(t) > k_{e2} \\ 0 & if \quad G_p(t) \le k_{e2} \end{cases} \tag{A.22}$$

where k_{e1} is the glomerular filtration rate [min^{-1}] and k_{e2} is the renal threshold of glucose in [mg/kg]).

A.2 Hovorka model of glucose homeostasis

The system of equations defining the Hovorka model as presented in Hovorka *et al.* (2002) are here summarised. Fig. A.2 shows a schematic representation of the model.

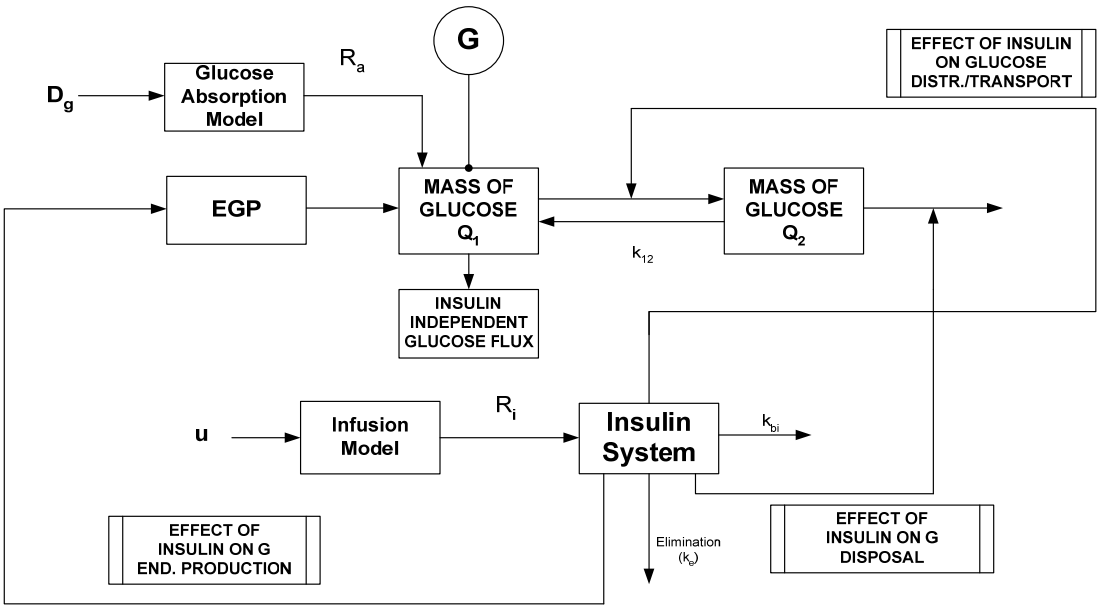


Figure A.2 *Schematic representation of the Hovorka model. The insulin compartment (I) affects the accessible (Q1) and non accessible (Q2) compartments of glucose mass through a three-compartmental subsystem controlling glucose distribution/transport, disposal (glucose hold-up) and endogenous glucose production (EGP). Glucose can also be consumed through an insulin independent stand-alone channel. The system inputs are the bolus/infusion of insulin (insulin administration) through the insulin infusion model, and the measured variable is the blood glucose concentration (G).*

Please note that while in the previous section of this work the glucose concentration is always expressed as mg/dL, here, as in the original paper (Hovorka *et al.*, 2002), it is expressed in mmol/L. The insulin concentration is expressed in mU/L. The glucose accessible and non-accessible compartments are represented by the following set of equations:

$$\frac{dQ_1(t)}{dt} = -\left[\frac{F_{01}^c}{V_G G(t)} + x_1(t)\right]Q_1(t) + k_{12}Q_2(t) - F_R + U_G(t) + EGP_0\left[1 - x_3(t)\right] \tag{A.23}$$

$$\frac{dQ_2(t)}{dt} = x_1(t)Q_1(t) - \left[k_{12} + x_2(t)\right]Q_2(t) \tag{A.24}$$

$$G(t) = Q_1(t)/V_G \tag{A.25}$$

where EGP_0 is the endogenous glucose production extrapolated to 0 insulin concentration, while F_{01}^c is the total non-insulin dependent glucose flux (corrected for the ambient concentration):

$$F_{01}^c = \begin{cases} F_{01} & \text{if} \quad G > 4.5 mmol/L \\ F_{01}G/4.5 & \text{otherwise} \end{cases} \tag{A.26}$$

and F_R is the renal clearance rate above the glucose threshold of 9 mmol/L, given by:

$$F_R = \begin{cases} 0.003(G-9)V_G & \text{if} \quad G > 9 mmol/L \\ 0 & \text{otherwise} \end{cases} \tag{A.27}$$

The insulin action subsystem is modelled through a three-compartment structure

$$\frac{dx_1}{dt} = -k_{a1}x_1(t) + k_{b1}I(t) \tag{A.28}$$

$$\frac{dx_2}{dt} = -k_{a2}x_2(t) + k_{b2}I(t) \tag{A.29}$$

$$\frac{dx_3}{dt} = -k_{a3}x_3(t) + k_{b3}I(t) \tag{A.30}$$

while the gut absorption rate is described by an exponential function of the following form:

$$U_G(t) = \frac{D_G A_G t e^{-\frac{t}{t_{\max,G}}}}{t_{\max,G}^2}. \tag{A.31}$$

where $t_{\max,G}$ is the time of maximum appearance rate of glucose (so that the $U_G(t)$ is modelled as a two-compartment chain with identical transfer rate $1/t_{max,G}$). The A_G parameter takes into account the fact that only a fraction of the whole CHO content of the meal (D_G) appears in plasma while the remaining part is extracted by the liver. In the current study the digesting dynamics were not modelled, and the focus is on the representation of insulin-dependent glucose flux. The insulin absorption sub-model is characterised by the following equations:

$$\frac{dS_3}{dt} = BW.R_i \tag{A.32}$$

$$I = \frac{S_3}{V_I} \tag{A.33}$$

where R_i is the rate of appearance of insulin in plasma provided by the subcutaneous insulin infusion submodel (see §A.3) and here expressed in [mU/kg/min] and BW is the body weight of the subject [kg]. The insulin and glucose distribution volumes, the insulin elimination rate constant and the transfer rate contributions are also kept constants (Table A.2).

Table A.2 *Parameters of model that are kept constants as reported in Hovorka et al.(2002) and following amendments (Hovorka, 2007).*

Constants	Description	Value
k_{12}	Transfer rate	0.066 min-1
k_{a1}	Deactivation Rate	0.006 min-1
k_{a2}	Deactivation Rate	0.06 min-1
k_{a3}	Deactivation Rate	0.03 min-1
k_e	Insulin elimination from plasma	0.138 min-1
V_I	Insulin Distribution Volume	0.12 L/Kg
V_G	Glucose Distribution Volume	0.16 L/Kg
A_G	Carbohydrate (CHO) bioavailability	0.8 (unitless)
$T_{max,G}$	Time-to-maximum of CHO absorption	40 min

As suggested by the authors themselves (Hovorka *et al.*, 2002), a new parameterisation is considered allowing to split the insulin sensitivity into three terms (insulin sensitivity of distribution/transport, disposal and endogenous glucose production respectively):

$$S_{IT}^f = \frac{k_{b1}}{k_{a1}} \tag{A.34}$$

$$S_{ID}^f = \frac{k_{b2}}{k_{a2}} \tag{A.35}$$

$$S_{IE}^{f} = \frac{k_{b3}}{k_{a3}} \quad . \tag{A.36}$$

In this way the k_{ai} parameters are also treated as constants. The values of the parameters are valid for a healthy male subject. With the alternative parameterisation given by Eqs. (A.34)-(A.36) the vector of model parameters is the set $\boldsymbol{\theta} = \left[S_{IT}^{f} \quad S_{IT}^{d} \quad S_{IT}^{e} \quad EGP_0 \quad F_{01}\right]$, whose nominal values are shown in Table A.3.

Table A.3 *Nominal values of the Hovorka model parameters for a healthy male subject, as reported in (Hovorka et al., 2002).*

Model Parameters	Description	True Values
S_{IT}^{f}	Insulin sensitivity of distribution/transport	51.2E-4
S_{ID}^{f}	Insulin sensitivity of disposal	8.2E-4
S_{IE}^{f}	Insulin sensitivity of EGP	520E-4
EGP_0	EGP extrapolated to zero insulin concentration	0.0161 mmol/kg min
F_{01}	Non-Insulin dependent flux	0.0097 mmol/kg min

A.3 Insulin infusion submodels

Two distinct insulin infusion submodels have been analysed throughout the Thesis, whose details are exhaustively presented in the following sections.

A.3.1 Nucci and Cobelli submodel of insulin infusion

The insulin infusion model adopted in this study is a modification of a model described in Nucci and Cobelli (2000) and recently applied to the original Cobelli model in a simulation study (Dalla Man *et al.*, 2007). The subcutaneous insulin infusion is modeled through a double compartmental channel described by the following equations:

$$\frac{dI_{sc1}(t)}{dt} = -\left(k_d + k_{a1}\right) I_{sc1}(t) + u(t) \tag{A.37}$$

$$\frac{dI_{sc2}(t)}{dt} = k_d I_{sc1}(t) - k_{a2} I_{sc2}(t) \tag{A.38}$$

where I_{sc1} is the amount of nonmonomeric insulin in the subcutaneous space, I_{sc2} is the amount of monomeric insulin in the subcutaneous space and $u(t)$ is the exogenous insulin infusion rate (here expressed in [pmol/min/kg]). The values of model parameters k_d, k_{a1}, k_{a2} are kept fixed at the values reported in Table A.4.

Table A.4 *Parameters of the subcutaneous insulin infusion model.*

Parameter	Value	Unit
k_d	0.0164	min^{-1}
k_{a1}	0.0018	min^{-1}
k_{a2}	0.0182	min^{-1}

The rate of appearance of insulin in plasma $R_i(t)$ is

$$R_i(t) = k_{a1} I_{sc1}(t) + k_{a2} I_{sc2}(t) \tag{A.39}$$

and is expressed in [pmol/kg/min].

A.3.2 Wilinska submodel of insulin infusion

The Wilinska insulin infusion submodel (Wilinska *et al.*, 2005) aims at modeling the dynamics of absorption of the subcutanous short-acting insulin and is characterised by the following equations:

$$\frac{dS_{1a}}{dt} = ku - k_{a11} S_{1a} - LDA \tag{A.40}$$

$$\frac{dS_{1b}}{dt} = (1-k)u - k_{a22} S_{1b} - LDB \tag{A.41}$$

$$\frac{dS_2}{dt} = k_{a11} S_{1a} - k_{a11} S_2 \tag{A.42}$$

$$\frac{dS_3}{dt} = k_{a11} S_2 + k_{a22} S_{1b} - k_e' I \tag{A.43}$$

$$I = \frac{S_3}{V_I} \tag{A.44}$$

$$LDA = V_{MAX,LD} \frac{S_{1a}}{(K_{m,LD} + S_{1a})} \tag{A.45}$$

$$LDB = V_{MAX,LD} \frac{S_{1b}}{(K_{m,LD} + S_{1b})} \tag{A.46}$$

where *LDA* is the local degradation at the injection site for continuous infusion, while *LDB* is the local degradation at the injection site for insulin bolus. For our purposes, the parameters of Wilinska sub-model are not estimated and are kept constants at the value reported in Table A.1 (where a brief description of their physical meaning is included, too). The insulin and

glucose distribution volumes, the insulin elimination rate constant and the transfer rate contributions are also kept constants (Table A.2).

Table A.1. *Parameters of Wilinska submodel for insulin absorption as reported in Wilinska et al. (2005).*

Constants	***Description***	***Value***
V_I	insulin distribution volume	42.01 x 10^{-2} L/Kg
k_{a11}	slow channel transfer rate	0.011 1/min
k_{a22}	fast channel transfer rate	0.021 1/min
k_e	Insulin elimination transfer rate	3.68 x 10^{-2} 1/min
k	proportion in slow channel	0.67 (unitless)
$V_{MAX,LD}$	saturation level	1.93 mU/min
$K_{m,LD}$	half-concentration constant	62.6 mU

In this model the rate of appearance of insulin in plasma [mmol/min] is

$$R_i(t) = k_{a11} S_2(t) + k_{a22} S_{1b}(t) \tag{A.47}$$

and is modeled through a three compartments chain represented by equations (A.40)-(A.42).

References

Albisser, A. M., B. S. Leibel, T. G. Ewart, Z. Davidovac, C. K. Botz, W. Zingg (1974). An artificial endocrine pancreas. *Diabetes*., **23**, 389-396.

Altekar, M., C. A. Homon, M. A. Kashem, S. W. Mason, R. M. Nelson, L. A. Patnaude, J. Yingling, P. B. Taylor (2007). Assay optimization: a statistical design of experiments approach. *Clin. Lab. Med.,* **27**, 139-154.

Anderson, V. L., R. A. McLean (1974). Design of experiments: a realistic approach. Marcel Dekker Inc., New York (U.S.A).

Apley, D. W., J. Liu, W. Chen (2006). Understanding the effects of model uncertainty in robust design with computer experiments. *ASME J. Mech. Des.*, **128**, 945-958.

Asprey S. P., S. Macchietto (2002). Designing robust optimal dynamic experiments. *J. Process Contr.*, **12**, 545-556.

Asprey, S. P., S. Macchietto (2000). Statistical tools for optimal dynamic model building, *Computers Chem. Eng.*, **24**, 1261-1267.

Atkinson, A. C., A. N. Donev (1992). *Optimum experiment designs*. Oxford University Press, Oxford (U.K.).

Atkinson, A. C., V. V. Fedorov (1975). Optimal design: experiments for discriminating between several models. *Biometrika*, **62**, 289-303.

Bahri, P. A., J. A. Bandoni, G. W. Barton, J. A. Romagnoli (1995). Backoff calculations on optimising control: a dynamic approach. *Computers Chem. Eng.*, **19**, S699-S710.

Bahri, P. A., J. A. Bandoni, J. A. Romagnoli (1996). Effect of Disturbances in Optimizing Control: Steady-State Open-Loop Back-Off Calculation. *AIChE J*., **42**, 983-999.

Bahri, P. A., J. A. Bandoni, J. A. Romagnoli (1997). Integrated Flexibility and Controllability Analysis in Design of Chemical Processes. *AIChE J.*, **43**, 997-1007.

Balsa-Canto, E., A. A. Alonso, J. R. Banga (2008). Computing optimal dynamic experiments for model calibration in predictive microbiology. *Journal of Food Process Engineering*, **31**, 186-206.

Balsa-Canto, E., M. Rodriguez-Fernandez, J. R. Banga (2007). Optimal design of dynamic experiments for improved estimation of kinetic parameters of thermal degradation. *Journal of Food Process Engineering*, **82**, 178-188.

Baltes, M., R. Schneider, C. Sturm, M. Reuss (1994). Optimal experiment design for parameter estimation in unstructured growth models. *Biotechnol. Prog.*, **10**, 480-488.

Banga, J. R., E. Balsa-Canto, C. G. Moles, A. A. Alonso (2005). Dynamic optimisation of bioprocesses: Efficient and robust numerical strategies. *J. Biotechnol*., **117**, 407-419.

Banga, J. R., W. D. Seider (1996). Global optimization of chemical processes using stochastic algorithms. In: *Nonconvex Optimization and its Applications-State of the Art of Global Optimization-Computational Methods and Applications*, Kluwer Academic Publ., Dordrecht, The Netherlands.

Bansal, V., J. D. Perkins, E. N. Pistikopoulos (2000). Flexibility analysis and design of linear systems by parametric programming. *AIChE J*., **46**, 335-346.

Bard, Y. (1977). *Nonlinear parameter estimation.* Academic Press, New York (U.S.A.).

Bardow, A. W. Marquardt (2004). Incremental and simultaneous identification of reaction kinetics: methods and comparison. *Chem. Eng. Sci.*, **59**, 2673-2684.

Bardow, A., V. Goke, H. J. Koss, K. Lucas, W. Marquardt (2005). Concentration dependent fluid diffusion coefficients from a single experiment using model-based Raman spectroscopy. *Fluid Phase Equilibria*, **228**, 357-366.

Bartlett, J. E, J. W. Kotrlik, C. Higgins (2001). Organizational research: Determining appropriate sample size for survey research. *Information Technology, Learning, and Performance Journal*, **19**, 43-50.

Barz, T., V. Loffler, H. Arellano-Garcia, G. Wozny (2009). Optimal experimental design for the determination of protein ion-exchange equilibrium parameters. In: *Computer-Aided Chemical Engineering 27, 10th International Symp. on Process Systems Engineering*, (R.M. Brito-Alves, C.A. Oller do Nascimento, E.C. Biscaia Jr., Eds.), Elsevier, Amsterdam (The Netherlands), 309-314.

Bauer, I., H. G. Bock, S. Körkel, J. P. Schlöder (2000). Numerical methods for optimum experimental design in DAE systems. *J. Comput. Appl. Mathem.*, **120**, 1-25.

Bellazzi, R., G. Nucci, C. Cobelli (2001). The subcutaneous route to insulin-dependent diabetes therapy. *IEEE Eng. Med. Biol.*, **20**, 54-64.

Bellman, R., K. J. Aström (1970). On structural identifiability. *Math. Biosci.*, **7**, 329-339.

Benabbas, L., S.P. Asprey, S. Macchietto (2005). Curvature-based methods for designing optimally informative experiments in multiresponse nonlinear dynamic situations. *Ind. Eng. Chem. Res.* **44**, 7120-7131.

Bequette, B. W. (2005). A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. *Diabetes Technol. Ther.*, **7**, 28-47.

Bergman, R. N. (2007). Orchestration of glucose homeostasis – From a small acorn to the California oak. *Diabetes*., **56**, 1489-1501.

Bergman, R. N., L. S. Phillips, C. Cobelli (1981). Physiologic evaluation of factors controlling glucose tolerance in man. *J. Clin. Invest.*, **68**, 1456-1467.

Bernaerts, K, J. F. Van Impe (2004). Data-driven approaches to the modeling of bioprocesses. *Transactions of the Institute of Measurement and Control*, **26**, 349-372.

Bernaerts, K., J. F. Van Impe (2005). Optimal dynamic experiment design for estimation of microbial growth kinetics at sub-optimal temperatures: Modes of implementation. *Sim. Mod. Pract. Th.*, **13**,129-138.

Bernardo, F. P., P. M. Saraiva (1998). A robust optimization framework for process parameter and tolerance design. *AIChE J.*, **44**, 2007-2019.

Bernardo, F. P., P. M. Saraiva, E. N. Pistikopoulos (2000). Inclusion of information costs in process design optimization under uncertainty. *Computers Chem. Eng.*, **24**, 1695.

Bilodeau, M., D. Brenner (1999). *Theory of Multivariate Statistics (2nd ed.)*. Springer, Berlin (Germany).

Bischof, C. H., H. M. Bücker, B. Lang, A. Rasch (2003). Solving large-scale optimization problems with EFCOSS. *Advances in engineering software*, **34**, 633-639.

Blau, G., M. Lasinski, S. Orcun, S. Hsu, J. Caruthers, N. Delgass, V. Venkatasubramanian (2008). High fidelity mathematical model building with experimental data: A Bayesian approach. *Comput. Chem. Eng.*, **32**, 971-989.

Bock, H. G. (1983). Recent advances in parameter identification techniques for O.D.E. In: *Progress in Scientific Computing 2*, Deuflhard and Hairer Eds., Boston.

Bock, H., E. Kostina, H. X. Phu, R. Rannacher (2003). *Modeling, simulation and optimization of complex processes.* Springer, Berlin (Germany).

Boston, R., D. Stefanovski, P. Moate, A. E. Sumner, R. M. Watanabe, R. N. Bergman (2003). MINMOD Millennium: a computer program to calculate glucose effectiveness and insulin sensitivity from the frequently sampled intravenous glucose tolerance test. *Diabetes Technol. Ther.*, **5**, 1003-1015.

Bowden, R (1973). The theory of parametric identification. *Econometrica*, **41**, 1069-1074.

Box, G. E. P., H. L. Lucas (1959). Design of experiments in non-linear situations. *Biometrika*, **46**, 77-90.

Box, G. E. P., K. B. Wilson (1951). On the experimental attainment of optimum conditions (with discussion). *Journal of the Royal Statistical Society*, **13**, 1-45.

Box, G. E. P., N. R. Draper (1987). *Empirical model-building and response surfaces*. John Wiley & Sons, New York (U.S.A).

Box, G. E. P., W. G. Hunter, J. S. Hunter (1978). *Statistics for experimenters. An introduction to design, data analysis and model building.* John Wiley & Sons, New York.

Box, G. E. P., W. J. Hill (1966). Discrimination Among Mechanistic Models. *Technometrics*, **9**, 57-69.

Brendel, M., D. Bonvin, W. Marquardt (2006). Incremental identification of kinetic models for homogeneous reaction systems. *Chem. Eng. Sci.*, **61**, 5404-5420.

Brun, R., M. Kühni, H. Siegrist, W. Gujer, P. Reichert (2002). Practical identifiability of ASM2d parameters-systematic selection and tuning of parameter subsets. *Water Research*, **36**, 4113-4127.

Bruwer, M. J., J. F. MacGregor (2006). Robust Multi-Variable Identification: Optimal Experimental Design with Constraints. *J. Process Control*, **16**, 581-600.

Buchberger, B. (1998). An algorithmical criterion for the solvability of algebraic systems of equation. *Aequationes Mathematicae*, **4**, 45-50.

Buzzi-Ferraris G., P. Forzatti (1983). Sequential Experimental Design Procedure for Discriminating Among Rival Models. *Chem. Eng. Sci.*, **38**, 225-238.

Buzzi-Ferraris G., P. Forzatti (1984). Sequential Experimental Design for Model Discrimination in the Case of Multiple Responses. *Chem. Eng. Sci.*, **39**, 81-96.

Camacho, E. F., C. Bordons, C. (2004). *Model Predictive Control*. Springer-Verlag, London (U.K.).

Carson, E., C. Cobelli (2001). *Modelling methodology for physiology and medicine*. Academic Press, San Diego (U.S.A.).

Caumo, A., P. Vicini, J. J. Zachwieja, A. Avogaro, K. Yarasheski, D. M. Bier, C. Cobelli, (1999). Undermodeling affects minimal model indexes: insights from a two-compartmental model. *Am. J. Physiol. Endocrinol. Metab.*, **276**, 1171-1193.

Cengiz, E., W. V. Tamborlane (2009). A tale of two compartments: interstitial versus blood glucose monitoring. *Diabetes Technol. Ther*., **11**, S11-S16.

Chachuat, F., B. Srinivasan, D. Bonvin (2008). Model Parameterisation Tailored to Real Time Optimization. In: *Proc 18th European Symposium on Computer Aided Process Engineering* (ESCAPE), Bertrand Braunschweig and Xavier Joulia (Editors), Lyon (France), June 1-4, 1-13.

Chaloner, C., I. Verdinelli (1995). Bayesian experimental design: a review. *Statistical Science*, **10**,273-304.

Chao, C. T. (2004). Selection of Sampling Units under a Correlated Population Based on the Eigensystem of the Population Covariance Matrix. *Environmetrics*., **15**, 757-775.

Chen, B. H., S. Bermingham, A. H. Neumann, H. J. M. Kramer, S. P. Asprey (2004). On the Design of Optimally Informative Experiments for Dynamic Crystallization Process Modeling. *Ind. Eng. Chem. Res.*, **43**, 4889-4902.

Chen, C. L., S. Macchietto, B. J. Stenhouse (1988). Application of an improved SQP method to the optimisation of process flowsheets. In: *Proceedings of the Annual AIChE Meeting*, Washington (U.S.A.).

Chu, Y., J. Hahn (2008). Integrating parameter selection with experimental design under uncertainty for nonlinear dynamic systems. *AIChE J.*, **54**, 2310-2320.

Chung S. H., D. L. Ma, R. D. Braatz (1999). Optimal model-based experimental design in batch crystallization. *Chemometrics and Intelligent Laboratory Systems*, **50**, 83-90.

Clarke, W. L., S. Anderson, L. Farhy, M. Breton, L. Gonder-Frederick, B. Cox, B. Kovatchev (2005). Evaluating the clinical accuracy of two continuous glucose sensors using continuous glucose–error grid analysis. *Diabetes Care*, **28**, 2412-2417.

Clemens, A. H. (1979). Feedback control dynamics for glucose controlled insulin infusion systems. *Med. Prog. Technol.*, **6**, 91-98.

Cobelli, C., K. Thomaseth (1986). The minimal model of glucose disappearance: optimal input studies. *Math. Biosci.*, **83**, 127–155.

Cochran, W. G. (1977). *Sampling Techniques*. Wiley, New York (U.S.A.).

Dalla Man C., R. A. Rizza, C. Cobelli (2007). Meal simulation model of the glucose insulin system. *IEEE. Trans. Biomed. Eng.*, **54**, 1741-1749.

Dalla Man, C., C. Cobelli (2006). A system model of oral glucose absorption: Validation on gold standard data. *IEEE Trans. Biomed. Eng.*, **53**, 2472-2478.

Darlington, J., C. C. Pantelides, B. Rustem, B. A. Tanyi (1999). An algorithm for constrained nonlinear optimisation under uncertainty. *Automatica*, **35**,217-228.

Davidescu, F. P., S. B. Jorgensen (2008). Structural parameter identifiability analysis for dynamic reaction networks. *Chem. Eng. Sci.*, **63**, 4754-4762.

Davies, O. L. D. (1954). *The design and analysis of industrial experiments*. Oliver & Boyd, Edinburgh (U.K.).

Davis, D. D., C. Holt (1993). *Experimental economics*. Princeton University Press, New Jersey (U.S.A.).

De Fronzo, R. A., D. T. Jordan, A. Aundreb (1979). Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am. J. Physiol*., **237**, E214-E223.

Dette, H., F. Bretz, A. Pepelyshev, J. Pinheiro (2008). Optimal designs for dose-finding studies. *Journal of the American Statistical Association*, **103**, 1225-1237.

Dias, J. M. L., F. Pardelha, M. Eusebio, M. A. M. Reis, R. Oliveira (2009). On-line monitoring of PHB production by mixed microbial cultures using respirometry, titrimetry and chemometric modelling. *Process Biochem.*, **44**, 419-427.

Dirion, J. L., C. Reverte, M. Cabassud (2008). Kinetic parameters estimation from TGA: optimal design of TGA experiments. *Chem. Eng. Res. Des*, **86**, 618-625.

DiStefano, J. J. (1981). Optimized blood sampling protocols and sequential design of kinetic experiments. *American Journal of Physiology*, **9**, 259-265.

DiStefano, J. J. (1982). Algorithms, software and sequential optimal sampling schedule design for pharmacokinetic and physiologic experiments. *Math. Comp. Sim.*, **24**, 531-534.

Donckels, B. M. R., D. J. W. De Pauw, P. A. Vanrolleghem, B. De Baets (2009). A kernel-based method to determine optimal sampling times for the simultaneous estimation of the parameters of rival mathematical models. *Journal of Computational Chemistry*, **30**, 2064-2077.

Doran, C. V., J. G. Chase, G. M. Shaw, K. T. Moorhead, N. H. Hudson (2005). Derivative weighted active insulin control algorithms and intensive care unit trials. *Contr. Eng. Pract.*, **13**, 1129-1137.

Doyle III, F. J., L. Jovanovic, D. E. Seborg, R. S. Parker, B. W. Bequette, A. M. Jeffrey, X. Xia, I. K. Craig, T. McAvoy, T. (2007). A tutorial on biomedical process control. *J. Process Control*, **17**, 571-594.

Dragalin, V., V. Fedorov (2006). Adaptive design for dose-finding based on efficacy-toxicity response. *Journal of Statistical Planning and Inference*, **136**, 1800-1823.

Draper, N. R., W. G. Hunter (1966). Design of experiments for parameter estimation in multiresponse situations. *Biometrika*, **53**, 525-533.

Dua, P., V. Dua, E. N. Pistikopoulos (2008). Optimal delivery of chemotherapeutic agents in cancer. *Computers Chem. Eng.*, **32**, 99-107.

El-Khatib, F. H., J. Jiang, E. R. Damiano (2007). Adaptive closed-loop control provides blood-glucose regulation using dual subcutaneous insulin and glucagon infusion in diabetic swine. *J. Diabetes Sci. Technol.*, **1**, 181-192.

Emery, A. F. (2001). Using the concept of information to optimally design experiments with uncertain parameters. *ASME J. Heat Transfer*, **123**, 593-600.

Emery, A. F., A. V. Nenarokomov (1998). Optimal experiment design. *Meas. Sci. Technol.*, **9**, 864-876.

Emery, A. F., A. V. Nenarokomov, T. D. Fadale (2000). Uncertainties in parameter estimation: the optimal experiment design. *International Journal of Heat and Mass Transfer*, **43**, 3331-3339.

Emery, A. F., B. F. Blackwell, K. J. Dowding (2002). The relationship between information, sampling rates, and parameter estimation models. *Journal of heat transfer*, **124**, 1192-1199.

Espie, D., S. Macchietto (1989). The Optimal Design of Dynamic Experiments. *AIChE J.*, **35**, 223-229.

Fabietti, P. G., V. Canonico, M. Orsini Federici, M. Massi Benedetti, E. Sarti (2006). Control oriented model of insulin and glucose dynamics in type 1 diabetics. *Med. Biol. Comput.*, **44**, 69-78.

Farmer, T. G., T. F. Edgar, N. A. Peppas (2009). Effectiveness of intravenous infusion algorithms for glucose control in diabetic patients using different simulation models. *Ind. Eng. Chem. Res.*, **48**, 4402-4414.

Farmer, T. G., T. F. Edgar, N. A. Peppas (2009). Effectiveness of Intravenous Infusion Algorithms for Glucose Control in Diabetic Patients Using Different Simulation Models. *Ind. Eng. Chem. Res.*, **48**, 4402-4414.

Fedorov, V., S. L. Leonov (1997). Optimal design of dose response experiments: a model-oriented approach. *Drug Information Journal*, **35**, 1373-1383.

Finan, D. A., H. Zisser, L. Jovanovich, W. Bevier, D. E. Seborg (2006). Identification of linear dynamic models for type 1 diabetes: a simulation study. In: Proceedings of the International Symposium on Advanced Control of Chemical Processes, Gramado (Brazil), 503-508.

Fisher, M. E. (1991). A semiclosed-loop algorithm for the control of blood glucose levels in diabetics. *IEEE Trans. Biomed. Eng.*, **38**, 57-61.

Fisher, R. A. (1935). *The design of the experiments*. Oliver & Boyd, Edinburgh (U.K.).

Floudas, C. A., P. M. Pardalos (2003). *Frontiers in global optimization*. Kluwer Academic Publ., Norwell, Massachussets (U.S.A.).

Foracchia, M., A. Hooker, P. Vicini, A. Ruggeri (2004) POPED, a software for optimal experiment design in population kinetics. *Comput. Meth. Prog. Biol.*, **74**, 29-46.

Forcolin, A (2007). Optimal design of experiments for parameter identification in physiological models of diabetes. *Master's Thesis in Chemical Engineering*. Dipartimento di Principi e Impianti di Ingegneria Chimica, Università di Padova (Italy).

Ford, I., D. M. Titterington, C. P. Kitsos (1989). Recent advances in nonlinear experimental design. *Technometrics*, **31**, 49-60.

Franceschini, G. (2007). *New formulations for model-based experiment design and application to a biodiesel production process*, Imperial College of London, London (U.K.).

Franceschini, G., S. Macchietto (2007). Anti-correlation approach to model based experiment design: application to a biodiesel production process. *Ind. Eng. Chem. Res.*, **47**, 2331-2348.

Franceschini, G., S. Macchietto (2007). Validation of a model for biodiesel production through model-based experiment design. *Ind. Eng. Chem. Res.*, **46**, 220-232.

Franceschini, G., S. Macchietto (2008). Model-based Design of Experiments for Parameter Precision: State of the Art. *Chem. Eng. Sci.*, **63**, 4846-4872.

Franceschini, G., S. Macchietto (2008). Novel anti-correlation criteria for model-based experiment design: algorithm and application. *AIChE J.*, **54**, 3221-3238.

Frederiksen, P. S. (1998). Parameter uncertainty and design of optimal experiments for the estimation of elastic constants. *Int. J. Solids Structures*, **35**, 1241-1260.

Furler, S. M., E. W. Kraegen, R. H Smallwood, D. J. Chilsom (1985). Blood glucose control by intermittent loop closure in the basal mode: Computer simulation studies with a diabetic model. *Diabetes Care*., **8**, 553-561.

Gadkar, K. G., R. Gunawan, F. J. Doyle III (2005). Iterative approach to model identification of biological networks. *Bioinformatics*, **6**, 155-175.

Galvanin, F., S. Macchietto, F. Bezzo (2007). Model-based design of parallel experiments. *Ind. Eng. Chem. Res.*, **46**, 871-882.

Galvanin, F., M. Barolo, F. Bezzo. (2008). Towards on-line model-based design of experiments. In: Proceedings of the 18th European Symposium on Computer Aided Process Engineering (B. Braunschweig and X. Joulia, Eds.), Elsevier, Amsterdam (The Netherlands), 349-354.

Galvanin, F., M. Barolo, F. Bezzo (2009a). Online model-based re-design of experiments for parameter estimation in dynamic systems. *Ind. Eng. Chem. Res.*, **48**, 4415-4427.

Galvanin, F., S. Macchietto S., M. Barolo, F. Bezzo (2009b). Optimal design of clinical tests for the identification of physiological models of type 1 diabetes mellitus. *Ind. Eng. Chem. Res.*, **48**, 1989-2002.

Galvanin, F., M. Barolo, F. Bezzo, S. Macchietto (2009c). A backoff-based strategy to improve robustness in model-based experiment design under parametric uncertainty. In: Proceedings for FOCAPD 2009, Colorado (U.S.A.), 7-12 June.

Galvanin, F., M. Barolo, S. Macchietto, F. Bezzo (2009d). On the optimal design of clinical tests for the identification of physiological models of type 1 diabetes mellitus. In: *Computer-Aided Chemical Engineering 27, 10th International Symp. on Process Systems Engineering*, (R.M. Brito-Alves, C.A. Oller do Nascimento, E.C. Biscaia Jr., Eds.), Elsevier, Amsterdam (The Netherlands), 183-188.

Galvanin, F., M. Barolo, F. Bezzo, S. Macchietto (2010a). "A backoff based strategy for model-based experiment design under parametric uncertainty". *AIChE J.*, in press. doi: 10.1002/aic.12138.

Galvanin, F., M. Barolo, S. Macchietto, F. Bezzo (2010b). A process systems engineering approach to the development of an artificial pancreas for subjects with type-1 diabetes mellitus. In: *Process Systems Engineering series (Vol. 7): Dynamic Process Modelling*, Pistikopoulos et al. (Eds.), Wiley-VCH Verlag GmbH & Co., Weinheim.

Galvanin, F., M. Barolo, F. Bezzo, S. Macchietto (2010c). Optimal design of clinical tests for the identification of physiological models of type 1 diabetes mellitus in the presence of model mismatch. (*Submitted*).

Galvanin, F., M. Barolo, F. Bezzo (2010d). A framework for model based design of experiments in the presence of continuous measurement systems. *Submitted to the 2010 IFAC International Symposium on Dynamics and Control of Process Systems (DYCOPS 2010).*

Garg, S. K. (2009). The future of continuous glucose monitoring. *Diabetes Technol. Ther.*, **11**, S1-S4.

Geuten, K., T. Massingham, P. Darius, E. Smets, N. Goldman (2007). Experimental design criteria in phylogenetics: where to add taxa. *Systematic Biology*, **56**, 609-622.

Gevers, M. (2005). Identification for control: from the early achievements to the revival of experiment design. *European Journal of Control*, **11**, 335-352.

Goodwin, G. C., R. L. Payne (1973). Optimal test signal design for linear single input-single output system identification. *International Journal of Control*, **17**, 45-55.

Goodwin, G. C., R. L. Payne (1977). *Dynamic system identification: experiment design and data analysis*. Academic Press, New York (U.S.A.).

Grijspeerdt, K., P. Vanrolleghem (1999). Estimating the parameters of the Baranyi model for bacterial growth. *Food microbiology*, **16**, 593-605.

Grossmann, I. E., M. Morari (1984). Operability, Resiliency and Flexibility-Process Design Objectives for a Changing World. In: *2nd Int. Conf. Foundations Comput. Aided Process Des.*, 931-1010.

Grossmann, I. E., R. W. H. Sargent (1978). Optimum Design of Chemical Plants with Uncertain Parameters. *AIChE J.*, **37**, 517-525.

Halemane, K. P., I. E. Grossmann (1983). Optimal Process Design under Uncertainty. *AIChE J.*, **29**, 425-436.

Harold W. Sorenson, (1980). *Parameter Estimation: Principles and Problems*, Marcel Dekker, New York (U.S.A.).

Heine, T., M. Kawohl, R. King (2008). Derivative-free optimal experiment design. *Chem. Eng. Sci.*, **63**, 4873-4880.

Hinkelmann, K., O. Kempthorne (1994). *Design and analysis of experiments: introduction to experimental design.* John Wiley & Sons, New York (U.S.A).

Hirsch, I.B., D. Armstrong, R. M. Bergenstal, B. Buckingham, B. P. Childs, W. L. Clarke, A. Peters, H. Wolpert (2008). Clinical application of emerging sensor technologies in diabetes management: consensus guidelines for continuous glucose monitoring (CGM). *Diabetes Technol. Ther.*, 232-246.

Hjalmarsson, H. (2005). Adaptive input design in system identification. In: *Proc. 44 th IEEE Conference on Decision and Control*, Seville, Spain.

Hjalmarsson, H. (2005). From experiment design to closed-loop control. *Automatica*, **41**, 393-438.

Hjalmarsson, H. (2008). System identification of complex and structured systems. *European Journal of Control*, **15**, 275-310.

Hjalmarsson, H., M. Gevers, F. De Bruyne (1996). For model-based control design, closed-loop identification gives better performance. *Automatica*, **32**, 1659-1673.

Hochwald, B., A. Nehorai (1997). On identifiability and information-regularity in parameterized normal distributions. *Circuits Systems Signal Processing*, **16**, 83-89.

Hovorka, R. (2005). Management of diabetes using adaptive control. *Int. J. Adapt. Control Signal Process.*, **19**, 309-325.

Hovorka, R. Personal communication. 2007.

Hovorka, R., F. Shojaee-Moradie, P. V. Carroll, L. J. Chassin, I. J. Gowrie, N. C. Jackson, R. S. Tudor, A. M Umpleby, R. H. Jones (2002). Partitioning glucose

distribution/transport, disposal, and endogenous production during IVGTT. *Am. J. Physiol. Endocrinol. Metab.*, **282**, E992–E1007.

Hovorka, R., V. Canonico, L. J. Chassin, U. Haueter, M. Massi-Benedetti, M. O. Federico, T. R. Pieber, H. C. Schaller, L. Schaupp, T. Vering, M. E. Wilinska (2004). Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol. Meas.*, **25**, 905-920.

Hsiang, T., P. M. Reilly (1971). A practical method for discriminating among mechanistic models. *Can. J. Chem. Eng.*, *49*, 865-878.

Hunter, W. G., A. M. Reiner (1965). Designs for discriminating between two rival models. *Technometrics*, **7**, 307-323.

Ierapetritou, M. G., E. N. Pistikopoulos (1994). A Novel Optimization Approach of Stochastic Planning Models. *Ind. Eng. Chem. Res.*, **33**, 1930-1944.

Issanchou, S., P. Cognet, M. Cabassud (2005). Sequential experimental design strategy for rapid kinetic modeling of chemical synthesis. *AIChE J.*, **51**, 1773-1781.

Isukapalli, S. S., A. Roy, P. G. Georgopulos (1998). Stochastic response surface methods (SRSMs) for uncertainty propagation: application to environmental and biological systems. *Risk Analysis*, **18**, 351-363.

Jansson, H (2004). Experiment design with applications in identification for control. *PhD Thesis*, Royal Institute of Technology, Stockholm, Sweden.

Jarvis R. B., C. C. Pantelides (1992). A differentiation-free algorithm for solving high-index systems. In: *AIChE 1992 Annual Meeting*, Miami Beach, Florida (U.S.A).

Joshi, M., A. Seidel-Morgenstern, A. Kremling (2006). Exploiting the bootstrap method for quantifying parameter confidence intervals in dynamical systems. *Metab. Eng.*, **8**, 447-553.

Kalicka, R., D. Bochen (2006). A new OSS design based on parameter sensitivity to changes in measurements. *Control and Cybernetics*, **35**, 387-406.

Keeping, B. R., C. C. Pantelides (1998). A distributed parallel memory algorithm for the efficient computation of sensitivities of differential-algebraic systems. *Mathematics and Computers in Simulation*, **44**, 545-558.

Kevitzky, L. (1975). Design of experiments for the identification of linear dynamic systems. *Technometrics*, 17, 303-308.

Kiefer, J. (1959). Optimum experimental design. *Journal of the Royal Statistical Society*, **21**, 272-319.

King, G., E. Gakidou, N. Ravishankar, R. T. Moore, J. Lakin, M. Vargas, M. M. Téllez-Rojo, J. E. Hernández Ávila, M. Hernández Ávila, H. H. Llamas (2007). A "politically robust" experimental design for public policy evaluation, with application to the mexican universal health insurance program. *Journal of Policy Analysis and Management*, **26**, 479-506.

Kiparissides, A., S. Kucherenko, A. Mantalaris, E. N. Pistikopoulos (2009). Global sensitivity analysis challenges in biological systems analysis. *Ind. Eng. Chem. Res.*, **44**, 868-878.

Kittrell, J. R., W. G. Hunter, C. C. Watson (1966). Obtaining precise parameter estimates for nonlinear catalytic rate models. *AIChE J.,* **12**, 5-10.

Kontoravdi, C., S.P. Asprey, E.N. Pistikopoulos, A. Mantalaris (2005). Application of global sensitivity analysis to determine goals for design of experiments: an example study on antibody-producing cell cultures. *Biotechnology Progress*, **21**, 1128-1135.

Körkel, S. (2002). Numerische Methoden für optimale Versuchs-planungsprobleme bei nichtlinearen DAE-Modellen. *PhD Thesis*, University of Heidelberg.

Körkel, S., E. Kostina, H. G. Bock, J. P. Schlöder (2004). Numerical methods for optimal control problems in design of robust optimal experiments for nonlinear dynamic processes. *Opt. Methods and Software*, **19**, 327-338.

Körkel, S., I. Bauer, H. G. Bock, J. P. Schlöder (1999). A sequential approach for nonlinear optimum experimental design in DAE systems. In: *Proc. Int. Workshop on Scientific Computing in Chemical Engineering, May 26-28*, TU Hamburg-Harburg, Germany.

Kreutz, C., J. Timmer (2009). Experimental design in systems biology. *FEBS Journal*, **276**, 923-942.

Krishnan, S., Barton, G. W., Perkins, J. D. (1992). Robust parameter estimation in on-line optimization-part I. Methodology and simulated case study. *Comput. Chem. Eng.*, **16**, 545.

Kucherenko, S., M. Rodriguez-Fernandez, C. Pantelides, N. Shah (2009). Monte Carlo evaluation of derivative-based global sensitivity measures. *Reliab. Eng. Syst. Saf.,* **94**, 1135-1148.

Landersdorfer, C. B., W. J. Jusko (2008). Pharmacokinetic/Pharmacodynamic Modelling in Diabetes Mellitus. *Clin. Pharmacokinet.*, **47**, 417-448.

Lazic, Z. R. (2004). *Design of experiments in chemical engineering*. Wiley-VCH, Weinheim (Germany).

Lear, J. B., G. W. Barton, J. D. Perkins (1995). Interaction between process design and process control: the impact of disturbances and uncertainty of the estimates of achievable economic performance. *J. Process Control*, **18**, 244-257.

Leineweber, D. B., I. Bauer, H. G. Bock,; J. P. Schlöder (2008). An efficient multiple shooting based reduced SQP strategy for large-scale dynamic process pptimization. Part 1: theoretical aspects. *Comput. Chem. Eng.*, **27**, 157-166.

Li, P., H. Arellano-Garcia, G. Wozny (2008). Chance constrained programming approach to process optimization under uncertainty. *Computers Chem. Eng.*, **32**, 25-45.

Liang, Y., K. Fang, Q. Xu (2001). Uniform design and its applications in chemistry and chemical engineering. *Chemometrics and Intelligent Laboratory Systems*, **58**, 43-57.

Lindley, D. V. (1956). On a measure of information provided by an experiment. *Ann. Math. Statist.*, **27**, 986-1005.

Lindqvist, K., H. Hjalmarsson (2001). Identification for control: adaptive input design using convex optimisation. In: *Proc. 40th IEEE Conference on Decision and Control*, Orlando, Florida (U.S.A.).

Linusson, A., J. Gottfries, F. Lindgren, S. Wold (2000). Statistical molecular design of building blocks for combinatorial chemistry. *J. Med. Chem.*, **43**, 1320-1328.

Ljung, L. (1987). *System identification: theory for the user*. Prentice-Hall Inc., Engiewood Cliffs, New Jersey (U.S.A.).

Ljung, L., Gevers, M. (1986). Optimal experiment designs with respect to the intended model application. *Automatica*, **22**, 543-554.

Ljung, L., T. Glad (1994). On global identifiability for arbitrary model parametrizations. *Automatica*, **30**, 265-276.

Loeblein, C., J. D. Perkins (1998). Economic analysis of different structures of on-line process optimisation systems. *Computers Chem. Eng.*, **22**, 1257-1269.

Loeblein, C., J. D. Perkins, B. Srinivasan, D. Bonvin (1999). Economic performance analysis in the design of on-line batch optimisation systems. *J. Process Control*, **9**, 61-78.

Lohmann, T., H. G. Bock, J. Schlöder (1992). Numerical methods for parameter estimation and optimal experiment design in chemical reaction systems. *Ind. Eng. Chem. Res.*, **31**, 54-57.

Lynch, S. M., B. W. Bequette (2002). Model predictive control of blood glucose in type I diabetics using subcutaneous glucose measurements. *Proc. ACC.*, 4039-4043.

Makroglou, A., J. Li, Y. Kuang (2006). Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview. *Applied Num. Mathem.*, **56**, 559-573.

Marchetti, G., M. Barolo, L. Jovanovich, H. Zisser, D. E. Seborg (2008). An inproved PID switching strategy for type 1 diabetes. *IEEE Trans. Biomed. Eng.*, **55**, 857-865.

Martin, R. B. (1992). Optimal control drug scheduling of cancer chemotherapy. *Automatica*, **28**, 1113-1123.

Martinez, E. C., M. D. Cristaldi, R. J. Grau (2009). Design of dynamic experiments in modeling for optimisation of dynamic experiments. *Ind. Eng. Chem. Res.*, **48**, 3453-3465.

Mazze, R. S., E. Strock, S. Borgman, D. Wesley, P. Stout, J. Racchini (2009). Evaluating the accuracy, reliability and clinical applicability of continuous glucose monitoring (CGM): is CGM ready for real time? *Diabetes Technol. Ther.*, **11**, 11-18.

Mehra, R. K. (1974). Optimal input signals for parameter estimation in dynamic systems: survey and new results. *IEEE Transactions on Automatic Control*, **19**, 753-768.

Meiler, M., D. Andre, A. Perez, O. Schmid, E. P. Hofer (2009). Nonlinear D-optimal design of experiments for polymer-electrolyte-membrane fuel cells. *Journal of Power Sources*, **190**, 48-55.

Micchi, A., G. Pannocchia (2008). Comparison of input signals in subspace identification of multivariable ill-conditioned systems. *J. Proc. Contr.*, **18**, 582-593.

Minitab Inc. (2000). MINITAB User Guide 2.

Mohideen, M. J., J. D. Perkins, E. N. Pistikopoulos (1996). Optimal design of dynamic systems under uncertainty. *AIChE J.*, **42**, 2251-2272.

Mönnigmann, M., W. Marquardt (2003). Steady-state process optimization with guaranteed robust stability and feasibility. *AIChE J.*, **49**, 3110-3126.

Munack, A., C. Posten (1989). Design of optimal dynamical experiments for parameter estimation. In: *Proceedings of the 1989 American Control Conference*, Pittsburgh (U.S.A.).

Nomura, M., M. Shichiri, R. Kawamori, Y. Yamasaki, N. Iwama, H. A. Abe. (1984). A mathematical insulin-secretion model and its validation in isolated rat pancreatic islets perfusion. *Comput. Biomed. Res.*, **17**, 570-579.

Nucci, S., C. Corbelli (2000). Models of subcutaneous insulin kinetics. A critical review. *Comput. Methods Progr. Biomed.*, **62**, 249-257.

Nyberg, J., M. O. Karlsson, A. C. Hooker (2009). Simultaneous optimal experimental design on dose and sample times. *J. Pharmacokinet. Pharmacodyn.*, **36**, 125-145.

Ollerton, R. L. (1989). Application of optimal control theory to diabetes mellitus. *Int. J. Control*, **50**, 2503-2522.

Ossenbruggen, P. J., H. Spanjers, A. Klapwik (1996). Assessment of a two-step nitrification model for activated sludge. *Water research*, **30**, 939-953.

Panjarnpornporn, C., M. Saroush (2007). On-line parameter estimation through dynamic inversion: a real time study. *Ind. Eng. Chem. Res.*, **39**, 2503-2507.

Parker, R. S., F. J. Doyle III, J. H. Ward, N. A. Peppas (2000). Robust H_∞ glucose control in diabetes using a physiological model, *AIChE J.*, **46**, 2537-2549.

Parker, R. S., F.J. Doyle III (2001). Control-relevant modeling in drug delivery. *Advanced Drug Delivery Reviews.*, **48**, 211-228.

Parker, R.S., F. J. Doyle III, N. A. Peppas (1999). A model-based algorithm for blood glucose control in type 1 diabetic patients. *IEEE Trans. Biomed. Eng.*, **46**, 148-157.

Percival, M. W., E. Dassau, H. Zisser, L. Jovanovic, F. J. Doyle III (2009). Practical approach to design and implementation of a control algorithm in an artificial pancreatic beta cell. *Ind. Eng. Chem. Res.*, **48**, 6059-6067.

Pillonetto, G., G. Sparacino, C. Cobelli (2003). Numerical non-identifiability regions of the minimal model of glucose kinetics: superiority of Bayesian estimation. *Math. Biosci.*, **184**, 53-67.

Pistikopoulous, E. N. (1995). Uncertainty in process design and operations. *Comput. Chem. Eng.*, **19**, 553-563.

Pohjanpalo, H. (1978). System identifiability based on the power series expansion of the solution. *Math. Biosci.*, **41**, 21-33.

Prasad, V., D. G. Vlachos (2008). Multiscale model and informatics-based optimal design of experiments: application to the catalytic decomposition of ammonia on ruthenium. *Ind. Eng. Chem. Res.*, **47**, 6555-6567.

Pritchard, D. J., D. W. Bacon (1975). Statistical assessment of chemical kinetic models. *Chem. Eng. Sci.*, **30**, 567-575.

Pritchard, D. J., D. W., Bacon (1978). Prospects for reducing correlations among parameter estimates in kinetic models. *Chem. Eng. Sci.* **33**, 1539-1543.

Process Systems Enterprise (2004). *gPROMS Introductory User Guide*, Process Systems Enterprise Ltd., London (U.K.).

Pukelsheim, F. (1993). *Optimal Design of Experiments*. J. Wiley & Sons, New York (U.S.A.).

Queipo, N. V., R. T. Haftka, W. Shyy, T. Goel, R. Vaidyanathan, P. K. Tucker (2005). Surrogate-based analysis and optimization. *Progress in Aerospace Sciences*, **41**, 1-28.

Rasch, A., H. M. Bücker, A. Bardow (2009). Software supporting optimal experimental design: a case study of binary diffusion using EFCOSS. *Computers and Chemical Engineering*, **33**, 838-849.

Raspanti, C. G., J. A. Bandoni, L. T. Biegler (2000). New strategies for flexibility analysis and design under uncertainty. *Computers Chem. Eng.*, **24**, 2193-2209.

Ray, W. H. (1980). *Advanced Process Control*. McGraw-Hill, New York (U.S.A.).

Reverte, C., J. L. Dirion, M. Cabassud (2007). Kinetic model identification and parameters estimation from TGA experiments. *J. Anal. Appl. Pyrolysis*, **79**, 297-305.

Rojas, C. R., J. S. Welsh, G. C. Goodwin, A. Feuer (2007). Robust optimal experiment design for system identification. *Automatica*, **43**, 993-1004.

Rooney, W. C., L. T. Biegler (2001). Design for Model Parameter Uncertainty Using Nonlinear Confidence Regions. *AIChE J.*, **47**, 1794-1804.

Rothenberg, T. J. (1971). Identification in Parametric Models. *Econometrica*, **39**, 577-592.

Rustem B, S. Zakovic (2003). Semi-infinite programming and application to min-max problems. *Annals of Operation Research*., **124**, 81-110.

Saccomani, M. P., S. Audoly, G. Bellu, L. D'Angiò, C. Cobelli (1997). Global identiability of nonlinear model parameters. In: *Proceedings of the SYSID '97 11th IFAC Symposium on System Identification.*, **3**, 219-224.

Saccomani, M. P., S. Audoly, L. D'Angiò (2003). Parameter identifiability of nonlinear systems: the role of initial conditions. *Automatica*, **39**, 619-632.

Saltelli, A., S. Tarantola (2002). On the relative importance of input factors in mathematical models: safety assessment for nuclear waste disposal. *Journal of American Statistical Association*, **97**, 702-709.

Saltelli, A., S. Tarantola, K. P. S. Chan (1999). A quantitative model-independent method for global sensitivity analysis of model output. *Technometrics*., **41**, 39-56.

Schaller, H. C., L. Schaupp, M. Bodenlenz, M. E. Wilinska, L. J. Chassin, P. Wach, T. Vering, R. Hovorka, T. R. Pieber (2006). On-line adaptive algorithm with glucose prediction capacity for subcutaneous closed loop control of glucose: evaluation under fasting conditions in patients with type 1 Diabetes. *Diabetic Med.*, **23**, 90-93.

Schittkowski, K. (2008). Parameter identification and model verification in systems of partial differential equations applied to transdermal drug delivery. *Mathematics and Computers in Simulation*, **79**, 521-538.

Schöneberger, J. C., H. Arellano-Garcia, G. Wozny, S. Körkel, H. Thielert (2009). Model-based experimental analysis of a fixed bed reactor for catalytic SO_2 oxidation. *Ind. Eng. Chem. Res.*, **48**, 5165-5176.

Schwaab, M., E. C. Biscaia Jr., J. L. Monteiro, J. C. Pinto (2008). Nonlinear parameter estimation through particle swarm optimization. *Chem. Eng. Sci.*, **63**, 1542 1552.

Schwaab, M., J. C. Pinto (2007). Optimum reference temperature for reparameterization of the Arrhenius equation. Part 1: problems involving one kinetic constant. *Chem. Eng. Sci.*, **62**, 2750-2764.

Schwaab, M., L. P. Lemos, J. C. Pinto (2008). Optimum reference temperature for reparameterization of the Arrhenius equation. Part 2: problems involving multiple reparameterisations. *Chem. Eng. Sci.*, **63**, 2895-2906.

Seborg, D. E., T. F. Edgar, D. A. Mellichamp (2004). *Process Dynamics and Control*, 2nd ed., Wiley, New York (U.S.A.).

Shannon, C. E. (1948). A mathematical theory of communication. *Bell. System Tech. J.*, **27**, 379-423.

Shirt, R. W., T. J. Harris, D. W. Bacon (1994). Experimental design considerations for dynamic systems. *Ind. Eng. Chem. Res.*, **33**, 2656-2667.

Sidoli, F.R., A. Mantalaris, S. P. Asprey (2004). Modelling of mammalian cells and cell culture processes. *Cytotechnology*, **44**, 27-46.

Sidoli, F.R., A. Mantalaris, S. P. Asprey (2005). Toward global parametric estimability of a large-scale kinetic single-cell model for mammalian cell cultures. *Ind. Eng. Chem. Res.*, **44**, 868-878.

Silber, H. E., J. Nyberg, A. C. Hooker, M. O. Karlsson (2009). Optimization of the intravenous glucose tolerance test in T2DM patients using optimal experimental design. *J. Pharmacokinet. Pharmacodyn.*, **36**, 281-295.

SimLab User Manual (release 3.2.5), Joint Research Centre (European Commission), Brussels, 2008. Available at: http://simlab.jrc.ec.europa.eu/docs/index.htm [accessed July 15, 2009].

Simpson, T. W., J. Peplinski, P. N. Koch, J. K. Allen (2001). Metamodels for computer based engineering design: survey and recommendations. *Eng. Comput.*, **17**, 129-150.

Sjöblom, J., Creaser, D. (2008). Latent variable projections of sensitivity data for experimental screening and kinetic modeling. *Comput. Chem. Eng.*, **32**, 3121.

Sjöstrand, M., A. Holmäng, P. Lönnroth (1999). Measurement of interstitial insulin in human muscle. *Am. J. Physiol. Endocrinol. Metab.*, **276**, 151-154.

Sobol, I. M. (2001). Global sensitivity indices for nonlinear mathematical models and their Monte Carlo estimates. *Mathematics and Computers in Simulation*, **55**, 271-280.

Söderström, T., P. Stoica (1989). *System identification*. Prentice Hall, New York (U.S.A.).

Solvason, C. C., N. G. Chemmangattuvalappil, F. T. Eljack, M. R. Eden (2009). Efficient visual mixture design of experiments using property clustering techniques. *Ind. Eng. Chem. Res.*, **48**, 2245-2256.

Sorensen, J.T. (1985). *A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes*, Massachusetts Institute of Technology, Cambridge (U.S.A.).

Stanfelj, N., T. E. Marlin, J. F. MacGregor (1993). Monitoring and diagnosis process control performance: the single-loop case. *Ind. Eng. Chem. Res.*, **32**, 301-314.

Steil, G. M., M. F. Saad (2006). Automated insulin delivery for type 1 diabetes. *Diabetes and the endocrine pancreas, Current Opinion in Endocrinology & Diabetes*, **13**, 205-211.

Stein, M. L. (1999). Interpolation of spatial data: some theory for kriging. Springer-Werlag, New York (U.S.A).

Stigter, J. D., D. Vries, K. J. Keesman (2006). On adaptive optimal input design: a bioreactor case study. *AIChE J.*, **52**, 3290-3296.

Swaney, R. E., I. E. Grossmann (1985). An Index for Operational Flexibility in Chemical Process Design. *AIChE J.*, **31**, 621-629.

Tosi, S., M. Rossi, E. Tamburini, G. Vaccari, A. Amaretti, D. Matteuzzi (2008). Assessment of In-line Near-infrared Spectroscopy for Continuous Monitoring of Fermentation Processes. *Biotechnol. Prog.*, **19**, 1816-1821.

Vajda, S., P. Valkó, T. Turanyi (1985). Principal component analysis of kinetic models. *International Journal of Chemical Kinetics*, **17**, 55-81.

Valdramidis, V.P., A. H. Geeraerd, J. E. Gaze, A. Kondjoyan, A. R. Boyd, H. L. Shaw, J. F. Van Impe (2006). Quantitative description of *Listeria monocytogenes* inactivation kinetics with temperature and water activity as the influencing factors: model prediction and methodological validation on dynamic data. *Journal of Food Engineering*, **76**, 79-88.

Vassiliadis V.S., R. W. H. Sargent, C. C. Pantelides (1994). Solution of a class of multistage dynamic optimizations problems. 1-Problems without path constraints. *Ind. Eng. Chem. Res.*, **33**, 2111-2122.

Vassiliadis, V. S., E. Balsa-Canto, J. R. Banga (1999). Second order sensitivities of general dynamic systems with application to optimal control problems. *Chem. Eng. Sci.*, **54**, 3851-3860.

Versyck, K. J., J. E. Claes, J. F. Van Impe (1998). Optimal experimental design for practical identification of unstructured growth models. *Math. Comp. Sim.*, **46**, 621-629.

Versyck, K.J., J. F. Van Impe (1998). Trade-offs in design of fedbatch experiments for optimal estimation of biokinetic parameters. In: Proceedings of the 1998 IEEE International Conference on Control Applications, Trieste (Italy), 51-55.

Walter, E., L. Pronzato (1996). On the identifiability and distinguishability of non linear parametric models. *Mathematics and Computers in Simulation*, **42**, 125-134.

Walter, E., Pronzato, L. *Identification of parametric models from experimental data*. Springer-Verlag, Berlin (Germany).

Walter, E., Y. Lecourtier (1981). Unidentifiable compartmental models: What to do? *Math. Biosci.*, **56**, 1-25.

White, L. V. (1975). The optimal design of experiments for estimation in nonlinear model. *PhD Thesis*, University of London.

Wilinska, M. E., L. J. Chassin, H. C. Schaller, L. Schaupp, T. R. Pieber, R. Hovorka (2005). Insulin kinetics in type–1 diabetes: Continuous and bolus delivery of rapid acting insulin. *IEEE Trans. Biomed. Eng.*, **52**, 3-12.

World Health Organisation department of non-communicable disease surveillance (2006). *Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia.*

Yang, Y. J., J. H. Young, R. N. Bergman (1987). Modified protocols improve insulin sensitivity estimation using the minimal model. *Am. J. Physiol.*, **253**, E595-E602

Zhang, Y., T. F. Edgar (2008). PCA combined model-based design of experiments (DOE) criteria for differential and algebraic system parameter identification. *Ind. Eng. Chem. Res.*, **47**, 7772-7783.

Zullo, L. (1991). *Computer Aided Design of Experiments. An Engineering Approach*, The University of London, London (U.K.).

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